Association Between Insulin Resistance and Homeostatic Model Assessment for Insulin Resistance Values: Meta-Analysis and Systematic Review

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Abstract

Insulin resistance is commonly linked with obesity, which is a pathophysiologic factor of type 2 diabetes mellitus. The present study aims to assess the relationship between obesity and insulin resistance by systematic review and meta-analysis. Search methods were conducted using the PubMed database for reports of studies on homeostatic model assessment for insulin resistance (HOMA-IR). Randomized controlled trials were identified through this database and were published between 2012 and 2022. The meta-analysis was performed using Revman 5.4.1 software using a fixed effect model. Continuous variables are reported as the mean difference with a 95% confidence interval. Among the 50 records retrieved, only 9 full-text articles were available for meta-analysis. Data from 580 participants were analysed, 320 in the experimental group and 260 in the control group. The mean difference for HOMA-IR was -0.34 [95% CI -0.51, -0.17]. This systematic review's results with meta-analysis showed evidence for a significant association between insulin resistance and obesity. In conclusion, this systematic review and meta-analysis investigated the relationship between IR and HOMA-IR across various studies and found a strong association.

Keywords: *Homeostatic model assessment for insulin resistance, insulin resistance, randomized controlled trials, type 2 diabetes Mellitus.*

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1. Introduction

Insulin resistance (IR) and Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) are closely related concepts in the context of diabetes and metabolic health. IR is defined as a condition where the body's cells become less responsive to the effects of insulin. Thus, resulting in elevated blood sugar levels due to glucose uptake by cells is impaired. It is a key factor in the development of type 2 diabetes and is often associated with obesity, sedentary lifestyle, and genetic predisposition. [1] The HOMA-IR is a commonly used method to assess insulin resistance in individuals. HOMA method was first described in 1985. It takes into account fasting glucose and insulin levels to calculate a score that indicates the degree of insulin resistance. It provides a valuable tool for monitoring and managing insulin resistance in patients, allowing for early intervention and prevention of complications associated with insulin resistance. HOMA-IR, can accurately assess an individual's IR by considering their fasting glucose and insulin levels, which will be useful to diagnose and control individuals with IR. [2] Threshold levels of HOMA-IR differs on age, gender, race and condition of metabolism. HOMA-IR is a mathematical model used to quantify insulin resistance based on fasting glucose and fasting insulin levels. Higher HOMA-IR values indicate greater insulin resistance and vice versa. [3] The formula for HOMA-IR is:

HOMA-IR = [Fasting plasma insulin (μU/ml) x Fasting Glucose (mmol/L)]/ 22.5

Khalili D et al., has reported an increase in one standard deviation (SD) change in HOMA-IR was associated with an increased risk of isolated impaired fasting glucose (iIFG), isolated impaired glucose tolerance (iIGT), combined impaired fasting glucose & impaired glucose tolerance (CGI) and Diabetes Mellitus (DM). HOMA-B, which assesses beta-cell function, was inversely correlated with iIFG but positively correlated with iIGT incidence. However, neither HOMA-IR nor HOMA-B alone is a perfect predictor of diabetes or pre-diabetes. [4] HOMA-IR provides only an estimate of insulin resistance and may not capture dynamic changes in insulin sensitivity. Monitoring HOMA-IR can help identify individuals at risk of developing diabetes. Lifestyle modifications, including exercise and dietary changes, can improve insulin sensitivity and reduce HOMA-IR values. [1, 5] HOMA-IR was used as an indicator of insulin resistance. It was calculated using fasting insulin and glucose levels, with a HOMA-IR value of less than 2.5 considered normal. A reduction in HOMA-IR indicated an improvement in insulin sensitivity. [6]

Metabolic syndrome, a cluster of conditions linked to insulin resistance, affects approximately 25% of adults worldwide. This syndrome includes obesity, hypertension, dyslipidemia, and high blood glucose levels. [7, 8, 9] In the U.S., 42.4% of adults are obese (as of 2017-2018 data), and obesity is a major driver of insulin resistance. The National Health and Nutrition Examination Survey (NHANES) shows that insulin resistance is more common among obese individuals. Insulin resistance is more prevalent in high-income countries due to higher rates of obesity and sedentary lifestyles. For example, in the U.S. and Europe, insulin resistance and type 2 diabetes are major public health concerns. [10, 20]

Insulin resistance is a significant risk factor for cardiovascular diseases (CVD). People with insulin resistance or type 2 diabetes have a 2-4 times higher risk of developing heart disease compared to the general population. [11, 12] Managing IR, type 2 diabetes, and related complications places a significant burden on healthcare systems. In the U.S., the total cost of diabetes in 2017 was estimated to be $327 billion, which includes direct medical costs and lost productivity. [13, 14]

Patients with sepsis and organ failure have limited tissue glucose utilization due to severe IR. Pancreatic β-cell function and insulin resistance from baseline glucose and insulin or C-peptide levels reflecting the balance of hepatic glucose production and insulin secretion intervals, which are assessed by HOMA method. This balance is maintained through a feedback loop between hepatic β-cells. Levels are significantly higher in patients who have not survived sepsis and septic shock and both stress-induced hyperglycemia and insulin resistance are associated with mortality. [15, 16, 17] The aim of the present systematic review and meta-analysis study is to investigate the association between insulin resistance and homeostasis model assessment of insulin resistance value.

2. Methodology

2.1. Study Design and Search Strategy

The study design was a systematic review of published literature and meta-analysis of data from each selected study. The study question was whether a HOMA-IR values can predict the IR. The relevant data were collected from PUBMED. This study was carried out in accordance with the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement for quality of reporting meta-analysis. [18] An extensive literature search was conducted in the PubMed databases using keywords like insulin resistance, insulin, risk factor and obesity. The relevant literature on insulin resistance and HOMA-IR over the previous ten years (between January 2012 and December 2022). This study using the following filters like free full text, randomized controlled trail, humans, English, both genders, adults and above 19+ years of age. The following were excluded preprint articles and MEDLINE articles. One of the investigators (SPK) was performed literature search and another investigator (SMK) independently assessed the eligibility of the selected studies.

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 HOMA-IR 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) insulin resistance measure (HOMA-IR). In the present the heterogeneity was assessed by using the I^2 (Table 2, Fig. 2). Since the size of sample is small (< 10 studies per covariate), meta-regression analysis was not performed. [19] Publication bias was computed by using funnel plots of Standard Mean Differences (SMD). To test the robustness of our results, conducted sensitivity analysis by removing one study at a time from the pool of studies to assess its impact on the findings. In the present study, publication bias was assessed using funnel plots of SEs (Fig. 1). The Egger test was employed to assess the degree of funnel plot asymmetry. When asymmetry was detected, sensitivity analyses using the trim-and-fill method were performed to further investigate the findings.

2.4. Statistical Analysis

Data analysis was performed by using Revman 5.4.1 software. Continuous outcome variables are expressed as mean difference, 95% confidence intervals were analysed as summary statistics and a fixed effects model was used based on the heterogeneity of outcomes across studies. The p-value indicates the level of statistical significance. If the diamond shape does not touch the line of no effect, the difference found between the two groups was statistically significant. In that case, the p-value is usually <0.01. Statistical heterogeneity among included studies was evaluated by the inconsistency index I^2.

3. Results

A total of 351 records were identified through the original and updated searches (Fig 1). After removing duplicates, 333 records were screened, and one additional record was identified through citation searching. This led to the assessment of 50 full-text records for eligibility, resulting in 11 records describing 9 studies being included in the review.

3.1. Study Characteristics

The characteristics of the included studies are outlined in Tables 1. Studies were predominantly of double blind, with 7 studies following a crossover design and 2 studies following a cluster randomized design. Duration of the interventions ranged between 1 week and 5 years. A range of age were investigated within the studies. The most common were between 45 to 68 years. Dietary interventions were investigated in 3 studies, with exercise interventions used in 6 studies. 7 studies assessed interventions involving multiple components (eg, both diet and exercise), whereas 2 studies involved lifestyle modifications alone.

Table 1: Characteristics of the included studies for IR and HOMA-IR Values

Author Name, Year	Setting	Study Design	Total	Mean Age (years)	HOMA IR [Mean (SD)]	
					Intervention	Control
Brennan AM et al., 2020	Single	RCT	61	68.6	7.028 (6.98)	4.44 (3.24)
Basu A et al., 2021	Multiple	RCT	33	53	2.1 (0.5)	3.5 (1.4)
Hajj CE et al., 2020	Single	RCT	88	66.3	2.51 (2.46)	2.41 (1.92)
Jahansouz C et al., 2018	Multiple	RCT	63	50.5	3.85 (1.85)	12.6 (12.8)
Abbate M et al., 2021	Single	RCT	128	50	4.5 (5.3)	5.9 (3.8)
Umphonsathien M et al., 2022	Single	RCT	40	45	2.5 (0.68)	3.47 (0.74)
Njembe MTN et al., 2021	Single	RCT	24	55	1.68 (0.27)	1.25 (0.14)
Kruschitz R et al., 2020	Single	RCT	50	NR	1.7 (1.3)	6.9 (5.6)
Zhang X et al., 2022	Single	RCT	93	45	2.76 (0.21)	2.83 (0.18)

NR - Reported

3.2. Risk-of-Bias Assessment

The risk-of-bias assessments for the selected studies are summarized in Fig. No. 1 and further detailed, including the rationale for assessing bias in each study. Using the Cochrane Risk of Bias Tool, most studies included in this review were identified as having a low risk of bias (Fig. 1). Low risk of bias has occurred due to the Cochrane Risk of Bias Tool is primarily designed for RCTs. The studies included in this review utilized quasi-experimental designs, which did not involve randomization, allocation concealment, blinding of participants and personnel, or blinding of outcome assessment.

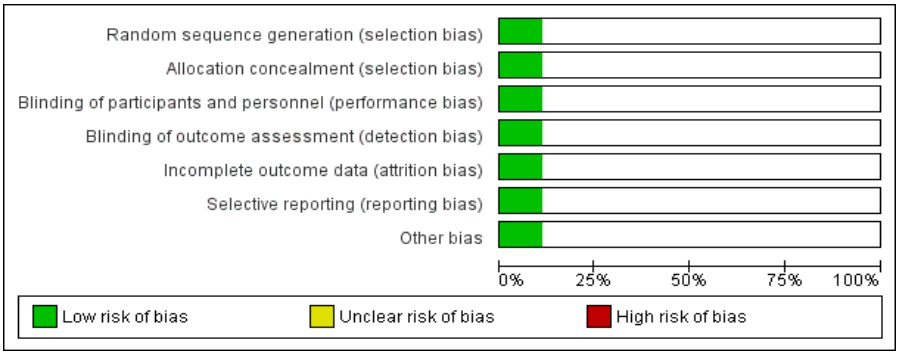

Fig. 1: Risk of bias graph of review authors' judgements about each risk of bias item presented as percentages across all included studies

The PRISMA flowchart (Fig. No. 2) illustrates the process of selecting studies for a systematic review or meta-analysis. 351 records were initially identified through PUBMED database search and after removing duplicates, 333 unique records remained. Followed by identification all 333 records were screened based on their titles and abstracts and 283 records were excluded at this stage, leaving 50 records. Further, 50 full-text articles were thoroughly assessed to determine if they met the inclusion criteria and 39 articles were excluded during this phase, likely due to not meeting the criteria.

The based on inclusion criteria 9 studies were included in the qualitative synthesis and all 9 studies were included in the quantitative synthesis (meta-analysis). PRISMA flowchart effectively summarizes on how the initial pool of 351 records was narrowed down to 9 studies that were included in both qualitative and quantitative analyses. The strong relationship was observed (-2.21 to – 0.70) between IR and HOMA IR [Fig. No. 3].

The meta-analysis estimated a between-study variance (τ^2) of 0.48. This value indicates that there is moderate to substantial heterogeneity in the effect sizes across the included studies. The τ^2 value reflects the extent to which the true effects vary between studies, suggesting that the included studies are not all estimating the same underlying effect size. The meta-analysis yielded a χ^2 value of 63.01, indicating significant heterogeneity among the included studies. This high χ^2 value suggests that the observed differences in effect sizes are unlikely to be due to chance alone, implying that the studies may be estimating different underlying effects. The meta-analysis revealed significant heterogeneity among the included studies, with an I^2 value of 87%. This suggests that 87% of the variability in effect sizes across the studies is due to real differences between studies, rather than sampling error. The high I^2 value indicates substantial inconsistency in the results, suggesting that the studies are not estimating a common effect size. The values are represented in the Fig. 3.

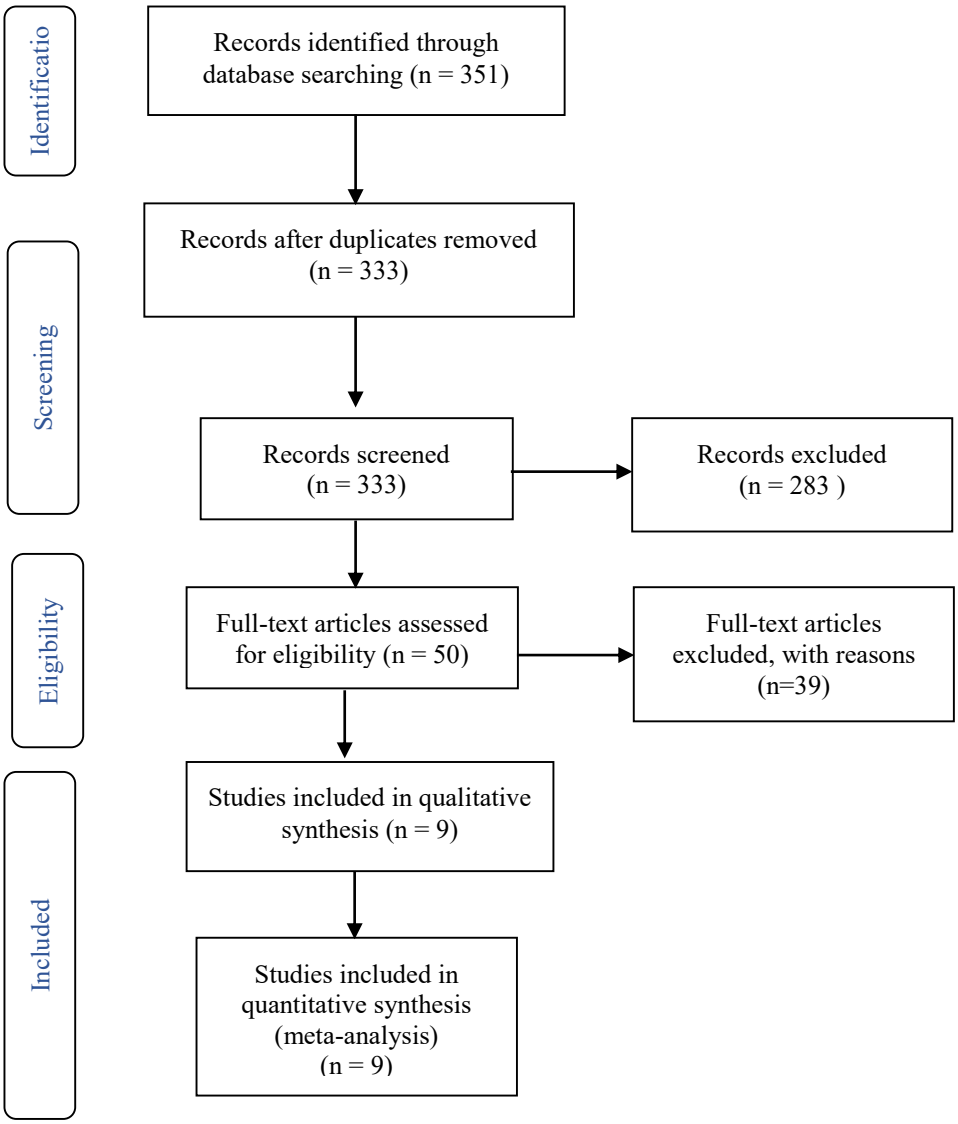

Fig. 2: PRISMA flowchart of the study selection

Funnel plots were created for outcomes with 10 or more effect sizes, and the results of the Egger test. Asymmetry in the funnel plot was observed for body weight, suggesting the presence of small study effects, potentially due to publication bias (bias, −0.501; 95% CI, −0.877 to 0.137; P = 0.006). The use of the trim and fill method revealed a significant effect of lifestyle intervention on HOMA-IR (0.2; 95% CI, 0.1-0.7; P = 0.01), suggesting that estimated unpublished studies may have influenced the effect. No funnel plot asymmetry was detected for the other outcomes.

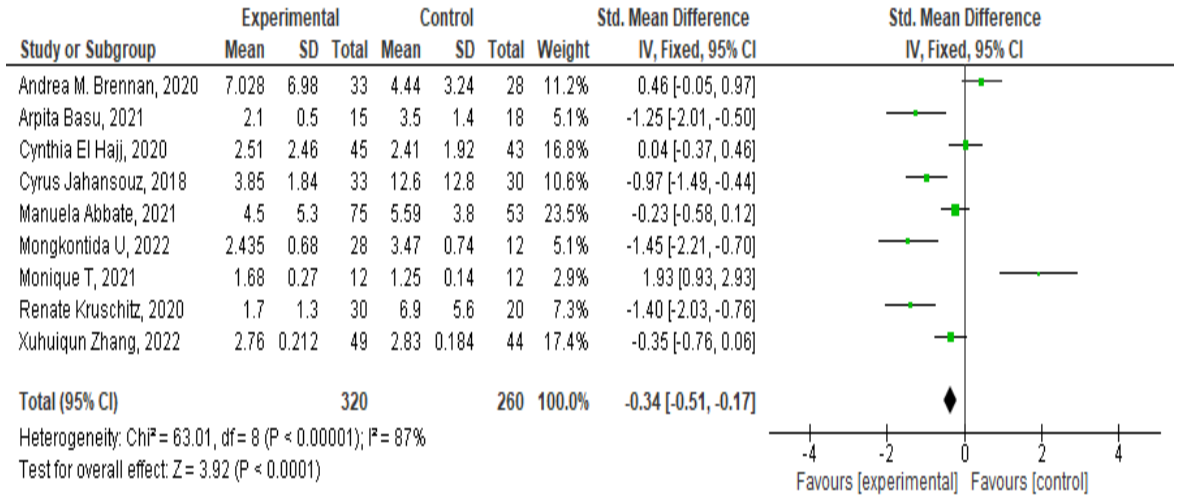

Fig. 3: Forest plot to compare of the association between IR and HOMA-IR value among the two groups

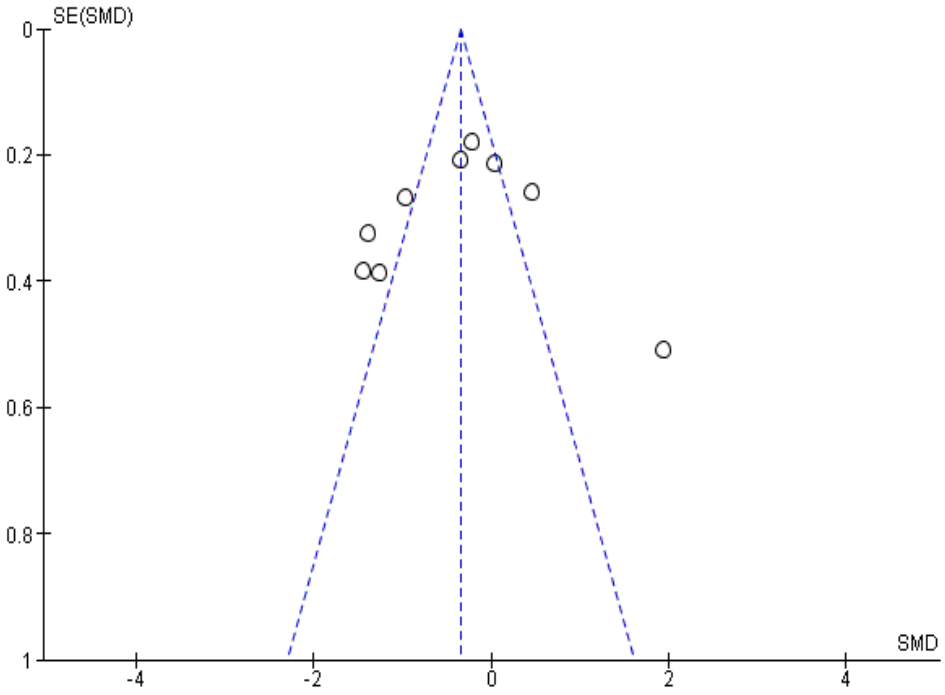

Fig. 4: Funnel Plot of publication bias for the association between IR and HOMA IR Value

4. Discussion

The study summarized the evidence from RCT that have evaluated association between HOMA IR and insulin resistance. The PRISMA flowchart provides the process of selecting studies for a systematic review or meta-analysis. PRISMA flowchart used to (a) identify and remove duplicate records (b) screen for titles and abstracts as well as to exclude the studies which are not meets the criteria (c) check eligibility like full articles and reason for removal of articles and (d) studies included for qualitative and quantitative synthesis for systematic review and meta-analysis respectively. This flowchart effectively summarizes how the initial pool of 351 records was narrowed down to 9 studies that were included in both qualitative and quantitative analyses. IR is a significant public health concern worldwide, which is related to the global epidemic of obesity and type 2 diabetes. [20] Globally, IR prevalence is estimated between 15 and 30% that differs significantly by region, age, and population characteristics. IR is a key factor in the development of type 2 diabetes. In 2021, around 537 million adults (20-79 years old) were living with diabetes globally, and over 90% of these cases are type 2 diabetes, which is primarily driven by insulin resistance. [21, 22, 23]

Tettamanzi. F et al., 2021, reported that a high-protein diet was more effective than a Mediterranean diet in reducing HOMA-IR, thus lowering insulin resistance in insulin-resistant obese women. The HP diet was more effective in reducing insulin levels, with a mean change of -3.50 μIU/mL, compared to an increase of 1.55 μIU/mL for the M diet. HOMA-IR also showed greater improvement with the HP diet, showing a mean change of -0.996 versus 0.32 for the M diet. Statistically significant differences were observed in both insulin and HOMA-IR outcomes between the two diets ($P = 0.01$ and $P = 9 \times 10^{-3}$, respectively). [24] Miazgowski. T et al., 2020, showed that weight loss at modest, was associated with a significant decrease in HOMA-IR, suggesting that reducing body weight improved insulin resistance. Specifically, the study found a 13.8% reduction in HOMA-IR alongside weight loss, reinforcing the link between body weight reduction and improved insulin sensitivity. [6]

Insulin resistance is defined physiologically as a state of reduced responsiveness in insulin-targeting tissues to high physiological insulin levels and is considered the pathogenic driver of many modern diseases, including metabolic syndrome, non-alcoholic fatty liver disease (NAFLD), atherosclerosis, and T2DM. [25] The HOMA-IR is a widely utilized measure of insulin resistance in clinical research. This Meta-analysis was performed to find out association between IR and HOMA-IR using a data from randomized controlled trial. HOMA-IR value was used as an outcome measure in the studies reviewed. This studies by Basu A et al., [26] Jahansouz C et al., [27] Abbate M et al., [28] Umphonsathien M et al., [29] Kruschitz R et al., [30] and Zhang X et al., [31] were reported a significant difference, whereas the Brennan AM et al., Hajj CE et al., and Njembe MTN et al., were reported that no significant relation between IR and HOMA-IR. In the present, the diamond shape represents, from the forest plot, the overall pooled effect from the inclusion studies show statistical significance. [32, 33, 34] Chi square test of heterogeneity, the resulted value $P < 0.00001$, thus null hypothesis was rejected. The magnitude of heterogeneity estimated by the I^2 statistic is 87% represent considerable heterogeneity.

This meta-analysis reported that mean difference value was -0.34 [-0.51, -0.17]. The publication bias evaluation results of this study showed symmetrical pattern which evidence of absence of publication bias. The results of this study showed that significantly association between insulin resistance and HOMA-IR.

Trouwborst. I et al., 2021, reviewed on HOMA-IR and tracked changes in insulin sensitivity following interventions such as weight loss or dietary changes. Lower HOMA-IR values post-intervention reflect improvements in insulin sensitivity, indicating a reduced level of insulin resistance. [35] Maroofi M and Nasrollahzadeh J, 2020, observed that Intermittent calorie restriction ICR led to beneficial modulations in insulin and HOMA-IR, indicating that ICR may improve insulin sensitivity more effectively than continuous calorie restriction (CCR), particularly in insulin-resistant participants. [36] The effectiveness of ICR in improving insulin resistance varied among different populations. Some studies indicated significant improvements in insulin resistance with ICR, while others found no significant differences compared to CCR. In a subgroup analysis, it was noted that ICR reduced insulin resistance (as measured by HOMA-IR) primarily in those individuals categorized in the highest percentile of HOMA-IR, indicating that those with greater insulin resistance may benefit more from ICR. They also suggested that HOMA-IR is a relevant marker for assessing insulin resistance, and intermittent calorie restriction may improve insulin sensitivity, particularly in those with higher levels of insulin resistance, while the relationship between HOMA-IR and insulin resistance is complex and influenced by various factors including dietary intake and weight loss.

In the study of Brennan AM et al., 2020, 61 Sedentary older obese (BMI 36.3 ± 5.0 kg/m^2) adults (68.6 ± 4.7 years) were randomized to one of 3 groups: health education control (HED); diet-induced weight loss (WL); or weight loss and exercise (WL + EX) for 6 months. This trial operations began at the University of Pittsburgh and subsequently moved to AdventHealth Translational Research Institute (AH TRI). [32] With continuous data, the mean difference with standard deviation is 0.46 [-0.05, 0.97] presented in are calculated and presented graphically in column represented as a box along with its 95% confidence interval (95%) cross the line of no effect. This study could not find a significant difference. The size of the box represents the study weight which is 11.2%. [32] In the study of Basu A et al., 2021, 14 week randomized controlled crossover study, 33 participants were assigned to one of the three arms for four weeks separated by a one-week washout period: control powder, one serving (low dose: 13 g strawberry powder/day), or two-and-a -half servings (high dose: 32 g strawberry powder/ day). With continuous data, the mean difference with standard deviation is -1.25 [-2.01, -0.50] presented in are calculated and presented graphically in column represented as a box along with its 95% confidence interval (95%) does not cross the line of no effect. This study found a significant difference. The size of the box represents the study weight which is 5.1%. [26]

Palacios. T et al., 2020, correlated and showed that any changes in certain metabolic parameters, like butyrate and propionate levels, were negatively impact HOMA-IR, suggesting that these metabolites might play a role in improving insulin sensitivity. Maki. KC

et al., 2020, observed that diets high in carbohydrates could increase HOMA-IR, thus indicating higher insulin resistance. Conversely, diets lower in carbohydrates, such as those containing eggs, were found to reduce HOMA-IR, suggesting improved insulin sensitivity. Hence, HOMA-IR serves as an important marker for assessing insulin resistance and the impact of dietary interventions on metabolic health. [37]

In the study of Hajj CE et al., 2020, Non-Obese patients with T2DM (n = 88), deficient/insufficient in vitamin D, were randomly assigned into one of two groups-a treatment group receiving 30,000 IU cholecalciferol/week for a period of six months, and a placebo group. With continuous data, the mean difference with standard deviation is 0.04[-0.37, 0.46] presented in are calculated and presented graphically in column represented as a box along with its 95% confidence interval (95%) cross the line of no effect. This study could not find significant difference. The size of the box represents the study weight which is 16.8%. [33]

Kraus. WE et al., 2019, used HOMA-IR to assess IR among participants undergoing caloric restriction (CR). They may have observed a decrease in HOMA-IR values in the CR group, suggesting improved insulin sensitivity. This finding aligns with the broader conclusion that CR can positively impact various cardiometabolic risk factors, including insulin resistance. It's important to note that while HOMA-IR is a useful tool, it is not a direct measure of insulin resistance. [39] Other methods, such as oral glucose tolerance tests (OGTT) and hyperinsulinemic-euglycemic clamps, can provide more precise assessments. Lerchbaum. E et al., 2019, conducted RCT and they observed vitamin D supplementation was found to have an adverse effect on the fasting glucose/ fasting insulin ratio, which aligns with other observations showing negative effects on insulin sensitivity measures like HOMA-IR. However, in general populations without significant deficiency, the benefits of vitamin D on insulin resistance are not well-supported. Overall, while HOMA-IR remains a valuable tool for assessing insulin resistance, the role of vitamin D in modifying insulin sensitivity requires further investigation, particularly with respect to different doses, baseline vitamin D levels, and study populations. [40]

In the study of Jahansouz C et al., 2018, Participants were randomly assigned to intensive lifestyle modification and medical management protocol (n = 29) or to intensive lifestyle modification and medical management protocol augmented with Roux-en-Y gastric bypass (n = 34), 12-month changes were examined. With continuous data, the mean difference with standard deviation is -0.97 [-1.49, -0.44] presented in are calculated and presented graphically in column represented as a box along with its 95% confidence interval (95%) does not cross the line of no effect. This study found a significant difference. The size of the box represents the study weight which is 10.6%. [27] In the study of Abbate M et al., 2021, randomized controlled trial on 128 participants with MetS and non-alcoholic fatty liver disease (NAFLD), as well as available data on estimated glomerular filtration rate (eGFR) and urinary albumin-to-creatine ratio (UACR). Patients were randomized in 1:1:1 ratio to either Conventional Diet, Mediterranean diet (MD)-high meal frequency, and MD-physical activity groups.

With continuous data, the mean difference with standard deviation is -0.23 [-0.58, 0.12] presented in are calculated and presented graphically in column represented as a box along with its 95% confidence interval (95%) does not cross the line of no effect. This study found a significant difference. The size of the box represents the study weight which is 23.5%. [28]

In the study of Umphonsathien M et al., 2022, 40 Participants with obesity and type 2 diabetes were recruited and randomly assigned to three groups, consisting of control, 2 days/week and 4 days/week of intermittent VLCD. With continuous data, the mean difference with standard deviation is -1.45[-2.21, -0.70] presented in are calculated and presented graphically in column represented as a box along with its 95% confidence interval (95%) does not cross the line of no effect. This study found a significant difference. The size of the box represents the study weight which is 5.1%. [29] In the study of Njembe MTN et al., 2021, 24 women and men were randomly assigned to two groups. Each day, they consumed two eggs enriched with oleic acid (control group) or enriched with ALA, DHA, RmA, and PunA (test group) for 3 months. With continuous data, the mean difference with standard deviation is 1.93[0.93, 2.93] presented in are calculated and presented graphically in column represented as a box along with its 95% confidence interval (95%) cross the line of no effect. This study could not find significant difference. The size of the box represents the study weight which is 2.9%. [34]

Sandberg. JC et al., 2018, reviewed various studies, including dietary interventions, showed that improvements in insulin sensitivity (lower HOMA-IR) were associated with beneficial effects on metabolic health. For example, whole grain rye consumption demonstrated potential anti-diabetic properties by improving insulin sensitivity, as indicated by changes in HOMA-IR values. This relationship underscores HOMA-IR's role as a valuable metric for assessing the degree of insulin resistance in both clinical and research settings. [41]

In the study of Kruschitz R et al., 2020, 50 Vitamin D (VD) deficient (25-hydroxy-vitamin D - (25[OH]D) <75 nmol/l) patients, recruited for a randomized controlled trial of VD supplementation. Divided into patients with 25(OH)D ≥50 nmol/l (adequate VD group; AVD) and into those <50 nmol/l (inadequate VD group; IVD) at 6 and 12 months (T6/12) postoperatively. CVD risk factors, medical history and anthropometric data were assessed. With continuous data, the mean difference with standard deviation is -1.40 [-2.03, -0.76] presented in are calculated and presented graphically in column represented as a box along with its 95% confidence interval (95%) does not cross the line of no effect. This study found a significant difference. The size of the box represents the study weight which is 7.3%. [30] In the study of Zhang X et al., 2022, single-centre, randomized, 2-arm, controlled, 12-wk parallel trial, adults [n = 93; male/female: 39/54; mean ± SD age: 42 ± 12 y; BMI: 32.6 ± 3.9 (in kg/m2); HOMA-IR: 2.7 ± 1.7] were counselled to exchange avocado (AV) or control food (C; low fat, low fibre, energy matched) for carbohydrate food in their usual diet for 12 wk.

With continuous data, the mean difference with standard deviation is -0.35[-0.76, 0.06] presented in are calculated and presented graphically in column represented as a box along with its 95% confidence interval (95%) does not cross the line of no effect. This study found a significant difference. The size of the box represents the study weight which is 17.4%. [31]

The primary strength of this meta-analysis is the extensive and comprehensive literature search but it has several limitations, present study shown considerable heterogeneity. The observed heterogeneity in HOMA-IR was the assessments in three out of nine datasets with a sample size below 50. The random effects model was chosen to account for heterogeneity and the association remained significant in all group analyses. The relationship between insulin resistance and HOMA-IR could not be delineated since the present meta-analysis is only based on randomized controlled trial.

4. Limitations

This meta-analysis identified several limitations and potential biases in the selected studies examining the association between IR and the (HOMA-IR). First, heterogeneity in study, which are the included studies had various designs, including double-blind, crossover and randomized group that could have differences in the methodological rigor and the comparability of the results. Second, duration of Interventions, interventions in the studies ranged widely from 1 week to 5 years, which might influence affect the consistency of the outcomes measured. Third, age range of identified participants, the most common age range investigated was between 45 to 68 years, the variation in age can influence the generalizability of the findings across different age groups. Fourth, types of interventions in the selected studies observed at dietary interventions, exercise interventions, and combinations of both, which can result lead to varied effects on IR and HOMA-IR. Fifth, publication bias, the funnel plot and Egger test indicated asymmetry for body weight outcomes, suggesting the presence of small study effects, potentially due to publication bias. This implies that smaller studies with less significant results might be less likely to be published, skewing the overall findings. Sixth, between study variance, the meta-analysis revealed a between-study variance (τ^2) of 0.48, which indicates moderate to substantial heterogeneity in effect sizes across the studies, suggesting that the true effects vary between studies. Eighth, significant heterogeneity, The high χ^2 value and I^2 value of 87% indicates significant inconsistency in the results across the studies, which may be due to real differences between the studies rather than sampling error. These limitations and potential biases focus the need for caution when interpreting the results of the meta-analysis and underscore the importance of considering the diversity and quality of the included studies when assessing the relationship between IR and HOMA-IR.

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