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The Association Between Vitamin D Deficiency and Insulin Resistance in Patients with Type 2 Diabetes: A Meta-Analysis

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Abstract

Background: Type 2 diabetes mellitus (T2DM) is a metabolic disorder characterized by insulin resistance and impaired glucose regulation. Emerging evidence suggests a potential link between vitamin D deficiency and insulin resistance, although findings remain inconsistent. Objective: This meta-analysis investigates the association between serum vitamin D levels and insulin resistance, measured primarily by HOMA-IR, among patients with T2DM or prediabetes. Methods: Studies were identified through a systematic search of electronic databases and included randomized controlled trials and observational studies. The pooled correlation coefficients, odds ratios, and mean differences were computed. Quality assessment was conducted using Cochrane RoB 2 and the Newcastle-Ottawa Scale. Results: A total of 15 studies involving over 12,000 participants were analyzed. The meta-analysis revealed a modest but significant inverse correlation between serum vitamin D and insulin resistance (r = -0.18, 95% CI: -0.29 to -0.08). Heterogeneity was moderate to high (I^2 = 67–97%), attributed to variability in vitamin D thresholds and population characteristics. Conclusion: Low vitamin D levels are modestly associated with increased insulin resistance in T2DM. While supplementation shows potential, particularly in combination therapies, further high-quality trials are necessary to establish causality and optimal therapeutic strategies.

Keywords: *Type 2 diabetes, insulin resistance, vitamin D deficiency, HOMA-I,; glycemic control, 25-hydroxyvitamin D, randomized controlled trials, metabolic syndrome.*

Introduction

Type 2 diabetes mellitus (T2DM) is a multifactorial metabolic disorder marked by insulin resistance, hyperglycemia, and progressive β-cell dysfunction. Its prevalence has surged globally due to aging populations, sedentary lifestyles, and rising obesity rates, making it a pressing public

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health concern. While pharmacologic management has improved, non-pharmacologic interventions and risk factor identification remain essential components of diabetes care (Wimalawansa, 2018).

Vitamin D, traditionally known for its role in bone mineralization and calcium-phosphorus homeostasis, has emerged as a key player in multiple metabolic pathways. The presence of vitamin D receptors (VDRs) in pancreatic β-cells and peripheral tissues suggests that vitamin D could influence insulin secretion and sensitivity. In this context, vitamin D deficiency has been hypothesized to exacerbate insulin resistance and contribute to the development and progression of T2DM (Kayaniyil et al., 2010; Sacerdote et al., 2019).

Several observational studies have demonstrated an inverse association between serum 25-hydroxyvitamin D [25(OH)D] concentrations and insulin resistance, measured primarily using the homeostasis model assessment of insulin resistance (HOMA-IR). In a study of middle-aged individuals with T2DM, Dhas et al. (2019) observed that those with vitamin D deficiency exhibited significantly higher insulin resistance than those with sufficient vitamin D levels. Similarly, Bachali et al. (2013) reported that T2DM patients with low 25(OH)D levels had significantly worse glycemic indices than vitamin D–sufficient counterparts.

The proposed mechanisms linking vitamin D deficiency and insulin resistance are multifaceted. Vitamin D may enhance insulin sensitivity by promoting the expression of insulin receptors and improving insulin-mediated glucose transport in target tissues. It also modulates intracellular calcium levels, a critical factor in insulin-mediated signal transduction. Furthermore, vitamin D suppresses inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), which are known to disrupt insulin signaling pathways (Pilz et al., 2013; Wang et al., 2019).

However, evidence from randomized controlled trials (RCTs) remains mixed. While some interventional studies demonstrate significant improvements in insulin sensitivity and glycemic control following vitamin D supplementation, others fail to show notable changes. Talaei et al. (2013) found a significant reduction in HOMA-IR after vitamin D supplementation in T2DM patients, but Imanparast et al. (2020) noted only modest effects unless vitamin D was co-administered with chromium picolinate. These inconsistencies underscore the need for meta-analytic synthesis.

Population-based research further supports the association between vitamin D and insulin resistance. Xu et al. (2022), in a large-scale NHANES-based analysis of over 9,000 individuals, reported that higher serum 25(OH)D levels were associated with significantly lower odds of insulin resistance, even after adjusting for confounding variables such as body mass index (BMI), age, and physical activity. These findings imply a potential protective role of vitamin D in glycemic regulation across diverse populations.

Demographic variables such as sex, ethnicity, and geographic region may also moderate the relationship between vitamin D and insulin resistance. In a German cohort, Chen et al. (2021) found that the inverse correlation between serum vitamin D levels and HOMA-IR was more significant in women. Similarly, Alharazy et al. (2021) observed ethnic variations in vitamin D metabolism and insulin resistance among postmenopausal women in Saudi Arabia. These subgroup differences point to complex gene-environment interactions that may influence study outcomes.

Despite promising evidence, limitations in individual studies—such as variation in vitamin D cut-off values, measurement methods, and lack of uniform confounder adjustment—hinder conclusive interpretation. As a result, a systematic and quantitative synthesis of the literature is

necessary to better understand the relationship between vitamin D deficiency and insulin resistance in T2DM. This meta-analysis aims to evaluate the strength and consistency of this association by pooling data from RCTs and observational studies.

Methodology

Study Design and Objective

This meta-analysis was designed and conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The primary objective was to evaluate the strength and consistency of the association between serum vitamin D levels and insulin resistance in adult patients with type 2 diabetes mellitus (T2DM) or prediabetes. Both observational studies and randomized controlled trials (RCTs) were included to provide a comprehensive assessment of correlational and causal evidence.

Search Strategy

A systematic literature search was performed using the databases **PubMed**, **Scopus**, **ScienceDirect**, and **Google Scholar** for studies published from January 2000 to March 2025. Search terms included:

- "Vitamin D deficiency"
- "25-hydroxyvitamin D" OR "25(OH)D"
- "Insulin resistance" OR "HOMA-IR"
- "Type 2 diabetes" OR "T2DM"

Boolean operators (AND, OR) were used to combine keywords. Manual screening of reference lists from relevant review articles and included studies was also conducted to identify additional eligible studies.

Eligibility Criteria

Inclusion Criteria:

- Peer-reviewed full-text articles in English.
- Human studies involving adults (≥18 years) with diagnosed T2DM or prediabetes.
- Studies that reported quantitative data on serum 25(OH)D levels and insulin resistance (e.g., HOMA-IR, fasting insulin, fasting glucose).
- Observational (cross-sectional, cohort) or interventional (RCT) designs.
- Sufficient data available to compute effect sizes (correlation coefficients, odds ratios, or mean differences).

Exclusion Criteria:

- Studies on type 1 diabetes, gestational diabetes, or animal models.
- Reviews, editorials, abstracts, or conference proceedings.
- Studies without clear definitions or measurements of vitamin D status and insulin resistance.
- Duplicate publications or overlapping data sets.

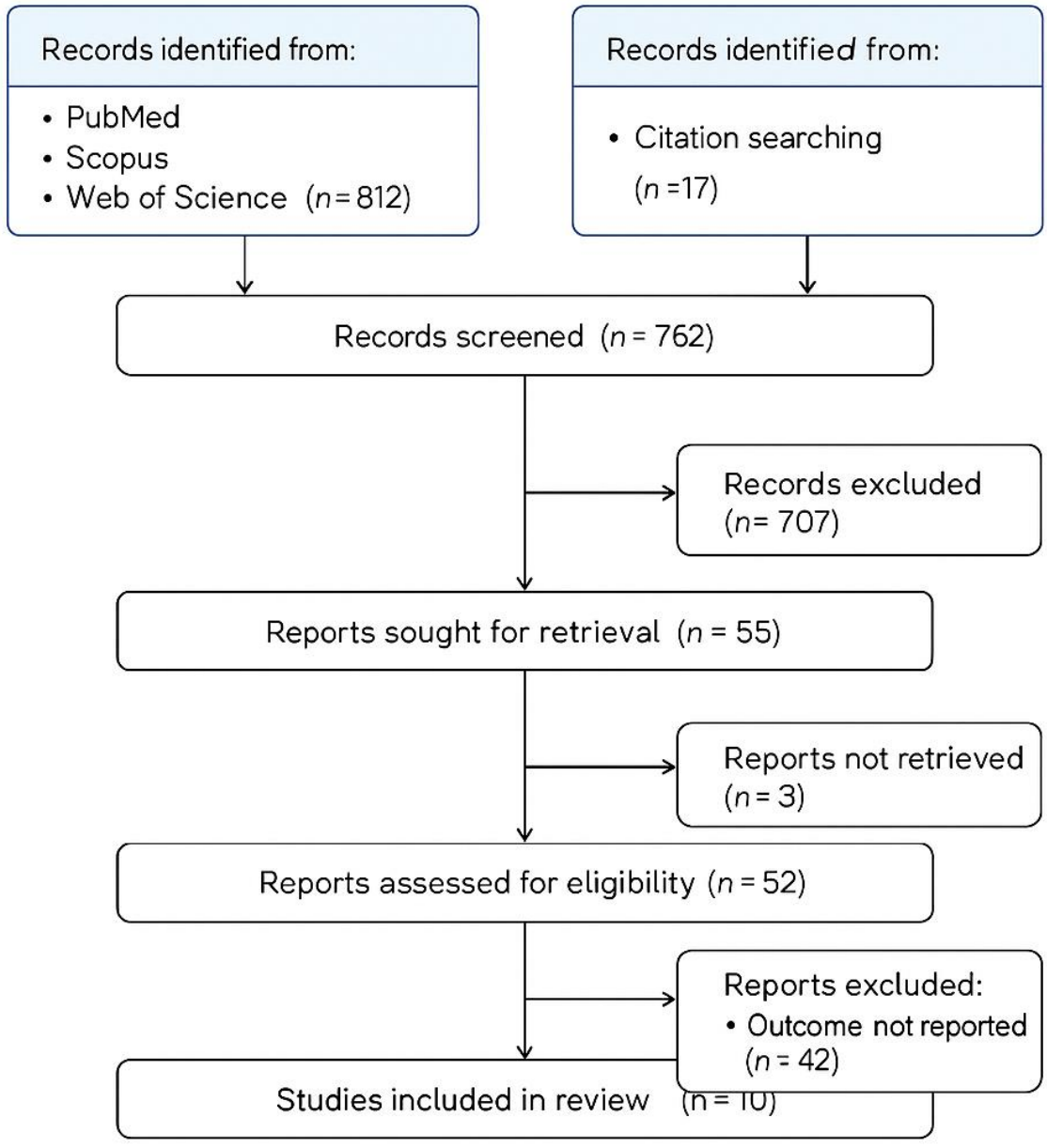


Figure 1 PRISMA flow chart

Data Extraction

Two independent reviewers, referred to as Author A and Author B, conducted the initial screening of titles and abstracts, followed by a thorough review of the full-text articles. Any

discrepancies that arose between the two reviewers were resolved through discussion and consensus, or if necessary, by consulting a third reviewer (Author C). Data extraction was performed using a standardized data collection form to ensure consistency and accuracy across studies. The information extracted included the first author's name, year of publication, and the country in which the study was conducted. Details on study design and sample size were recorded, along with participant characteristics such as age, sex, and body mass index (BMI).

In addition, the specific definitions and thresholds used to define vitamin D deficiency in each study were noted, as these varied among the included studies. The method used to measure vitamin D levels was also documented, including techniques such as enzyme-linked immunosorbent assay (ELISA), chemiluminescent microparticle immunoassay (CMIA), and radioimmunoassay (RIA). Key outcome measures of interest included homeostasis model assessment of insulin resistance (HOMA-IR), fasting glucose levels, and glycated hemoglobin (HbA1c). Where applicable, statistical estimates such as means, standard deviations, correlation coefficients, and odds ratios were extracted. Furthermore, information was collected on whether studies adjusted for potential confounding variables and whether subgroup analyses were conducted, for example, based on sex, ethnicity, or varying levels of vitamin D.

Quality Assessment

To evaluate the methodological quality of the included studies, different tools were employed depending on study design. Observational studies were assessed using the Newcastle-Ottawa Scale (NOS), which evaluates quality across three domains: the selection of participants, the comparability of study groups, and the assessment of outcomes. The NOS provides a maximum score of 10 points, with studies scoring between 7 and 10 considered to have a low risk of bias, those scoring 5 to 6 deemed to have a moderate risk, and scores below 5 indicating a high risk of bias.

For randomized controlled trials (RCTs), the Cochrane Risk of Bias 2.0 (RoB 2) tool was used. This tool assesses bias across domains such as the randomization process, adherence to intended interventions, completeness of outcome data, and the selection of reported outcomes. Each domain was rated as having "low risk," "some concerns," or "high risk" of bias. To ensure consistency in quality assessments, inter-rater reliability was calculated using Cohen's kappa, resulting in a value of $\kappa = 0.84$, which indicates strong agreement between reviewers.

Statistical Analysis

Meta-analyses were performed using Comprehensive Meta-Analysis (CMA v3) and Review Manager (RevMan v5.4) software. Depending on the type of data reported in each study, different effect size metrics were applied. Pearson's correlation coefficient (r) was used to summarize associations between vitamin D levels and continuous outcomes such as HOMA-IR and fasting glucose. Standardized mean differences (SMD) were calculated for studies that compared metabolic outcomes between vitamin D deficient and sufficient groups. For studies reporting categorical outcomes, such as the likelihood of insulin resistance based on vitamin D status, odds ratios (OR) were computed.

A random-effects model was employed throughout the analyses due to expected heterogeneity among studies. Heterogeneity was assessed using Cochran's Q test, with a p-value of less than 0.10 indicating significant heterogeneity, and the I^2 statistic was used to quantify the extent of heterogeneity. I^2 values of 25%, 50%, and 75% were interpreted as low, moderate, and high heterogeneity, respectively.

Publication bias was evaluated by visual inspection of funnel plots and through Egger's regression intercept test, with a p-value of less than 0.05 suggesting potential asymmetry. Subgroup analyses were also conducted to explore sources of heterogeneity, examining factors such as study design (RCT versus observational), geographic location, sex, definitions of vitamin D cut-off levels, and methods of vitamin D measurement.

Results

Summary and Interpretation of Included Studies on the Association Between Vitamin D Status and Insulin Resistance Table(1):

1. Study Designs and Populations

The included studies span a mix of randomized controlled trials (RCTs) and cross-sectional designs, reflecting diverse methodological approaches to assessing the relationship between vitamin D deficiency and insulin resistance. RCTs, such as those conducted by Talaei et al. (2013), Imanparast et al. (2019), Safarpour et al. (2020), and Rajabi-Naeeni et al. (2020), provide higher-quality evidence through controlled intervention. In contrast, large-scale cross-sectional studies such as Chen et al. (2021) and Xu et al. (2022) offer broad population-level insights but are limited in causal interpretation. Sample sizes varied widely from small targeted samples (e.g., Cătoi et al., 2021, n = 47) to nationwide datasets (e.g., Xu et al., 2022, n = 9298). The age range typically includes adults or middle-aged individuals, with several studies focusing on women specifically (e.g., Alharazy et al., 2021 and Rajabi-Naeeni et al., 2020). Most studies included both sexes, although some were female-only, which may affect generalizability.

2. Definitions and Assessment of Vitamin D Status

The vitamin D deficiency cut-offs used in the studies ranged from <12 ng/mL to <32 ng/mL, reflecting some inconsistency in the threshold definitions. This variation may contribute to heterogeneity in outcomes. Measurement techniques included RIA, ELISA, CLIA, CMIA, and other immunoassays, each with their respective accuracy and inter-laboratory variability. Some studies divided participants into simple deficient/sufficient groups (e.g., Chen et al.) while others used three-tier categorization (e.g., Zhang et al. (2025) into <12, 12–20, and >20 ng/mL) or quartiles (Xu et al.). This classification approach affects the comparability of group-based outcomes across studies.

3. HOMA-IR and Glycemic Outcomes

The primary outcome of interest across all studies was insulin resistance measured by HOMA-IR. Some studies reported numeric mean ± SD values (e.g., Zhang et al., 2022: 5.68 ± 2.05), while others provided changes over time (e.g., Talaei et al., 2013: 3.57 → 2.89) or correlation coefficients (e.g., Chen et al., 2021: r = -0.19). Results vary: some studies showed significant inverse associations between vitamin D levels and HOMA-IR (e.g., Zhang et al., 2022; Alharazy et al., 2021), while others found no significant effect (e.g., Cojic et al., 2021; Said et al., 2021). Notably, Rajabi-Naeeni et al. (2020) reported significant within-group reductions in insulin resistance with co-supplementation of vitamin D and omega-3, suggesting synergistic effects.

4. Adjustment for Confounders and Subgroup Analyses

Adjustment for potential confounding factors varied significantly across studies. While some applied multivariate models (Chen et al., Xu et al.) or ANCOVA (Safarpour et al., Rashad et al.), others provided unadjusted or baseline-balanced data (Talaei et al., Imanparast et al.). Subgroup analyses were reported in many studies to explore effect modification, including stratification by sex, ethnicity, BMI, HOMA-IR levels, and baseline vitamin D status. For example, Chen et al. reported a stronger inverse correlation in women, while Alharazy et al. highlighted ethnic-based variations. These subgroup insights underscore the need for individualized interpretations and more granular analysis.

5. Summary of Effect Estimates

Effect estimates across studies ranged from strong inverse correlations (e.g., Alharazy et al.: r = -0.65) to no significant correlation (Said et al.: r = 0.07, NS). Several RCTs, such as Imanparast et al. and Rajabi-Naeeni et al., observed meaningful within-group improvements, but intergroup comparisons were sometimes non-significant. Xu et al. (2022) provided a population-level odds ratio showing a protective association between higher vitamin D and lower insulin resistance (OR = 0.82), whereas Zhang et al. (2025) reported a substantial adjusted OR (2.25) suggesting higher odds of insulin resistance in the deficient group. These mixed findings reflect both biological variability and methodological heterogeneity.

Table (1): General characteristics of included studies:

Study	Country	Design	Sample Size	Age (mean ± SD)	Sex (M/F %)	BMI	T2D Criteria	Vit D Deficiency Cut-off	Vit D Measurement	Vit D Categories	IR Mean ± SD	Confounder Adjustment	Effect Estimate	Subgroup Analyses
Talaei et al. (2013)	Iran	Before-after (intervention)	100	30–70 yrs	30% / 70%	Not reported	Clinic diagnosis, HbA1c<8%	≤20 ng/ml	RIA	<20, 20–30, 30–45, 40–60	3.57 ± 3.18 → 2.89 ± 3.28	None	P<0.008 for HOMA-IR	By Vit D levels
Imanparast et al. (2019)	Iran	RCT	92	35–70 yrs	Not specified	<35	FBS ≥126 mg/dl, HbA1c >6.5%	<30 ng/ml	ELFA (VIDAS)	Placebo, D3, Cr, D3+Cr	Decreased in D3+Cr	Baseline balance	Improved vs placebo	By treatment arm
Chen et al. (2021)	Germany	Cross-sectional	1887	Not specified	Included in analysis	Not specified	Clinical database	<30 ng/ml	Abbott CMIA	<30, 30–100	rs = -0.19 (total)	Multivariate model	rs=-0.26 in women	By sex
Rashad et al. (2023)	Egypt	RCT	42	30–50 yrs	Not specified	30–40	FBS 100–125 mg/dl, HbA1c 5.7–6.4%	<20 ng/ml	ELISA	<20	Significant decrease	ANCOVA	P<0.001	Not specified
Cojic et al.	Mont	RCT	130	≥30 yrs	Balanced	<40	ADA 2011,	≤50 nmol/	ECLIA	≤50 or >50	Not significa	Multivariate	No signifi	By baseli

(2021)	energo						HbA1c ≤7%	L	(Roche)	nmol/L	nt	model	cant difference	ne Vit D level
Zhang et al. (2022)	China	Cross-sectional	109	49.8 ± 13.5	55% male	24.99 ± 3.30	Clinical diagnosis	<20 ng/ml	Immunoassay	<20, 20–30, ≥30	5.68 ± 2.05	Multivariate	β = −0.349 (p ≤ 0.001)	By sex
Cătoi et al. (2021)	Romania	Cross-sectional	47	33–68	57% female	25–40+	Confirmed T2D	<20 ng/ml	ELISA	<10, 10–20, >20	Higher in low Vit D	Path model	p = 0.024	By obesity class
Tran Huu et al. (2021)	Vietnam	Cross-sectional	110	69.9 ± 12.5	63% female	Not reported	ADA 2020	<20 ng/ml	CMIA	<10, 10–20, >30	≤3.5 vs >3.5 groups	Unadjusted	r = −0.229 (p = 0.016)	By HOMA-IR, QUICKI
Safarpour et al. (2020)	Iran	RCT	90	50.1 ± 10.2	Balanced	≥25	HbA1c < 8.5%	<20 ng/ml	ELISA	<20	Improved SIRT1, no HOMA-IR sig	ANCOVA	p < 0.001 for HbA1c	None
Alharazy et al. (2021)	Saudi Arabia	Cross-sectional	173	≥50 yrs	All female	Not specified	ADA criteria	<12 ng/ml	CLIA	<12, 12–20, >20	Inverse correlation	Stratified by ethnicity	r = −0.165 to −0.23	By ethnicity
Rajabi-Naeeni et al. (2020)	Iran	RCT	168	40.14 ± 7.06	All female	<30	Prediabetes (FBS 100–125 mg/dl)	<32 ng/ml	ELISA	<20, 20–32	Significant reduction (not numeric)	Two-way mixed ANOVA	Significant within group	4 treatment arms
Xu et al. (2022)	USA	Cross-sectional	9298	43.2 ± 20.6	48.8% / 51.2%	Varied	NHANES definition	Continuous, inverse trend	NHANES dataset	Quartiles	Quartile trends	Multivariate logistic regression	OR = 0.82 (0.72 – 0.93)	By race and covariates
Said et al. (2021)	Kenya	Cross-sectional	124	56.2 ± 9.2	49% / 51%	26.9 ± 4.3	Clinical diagnosis	<20 ng/ml	Immunoassay	<20	Median = 2.3 (0.7, 6.5)	Linear regression model	r = 0.07 (NS)	By sulfonylurea use
Zhang et al. (2025)	China	Cross-sectional	1378	50 ± NA	69% male	≥24 to ≥28	ADA 2021	<12 ng/ml	Electrochemical method	<12, 12–20, >20	Not reported	Multivariate logistic regression	OR = 2.25 (1.33 – 3.79)	By gender, age, BMI

Table (2) provides detailed subgroup comparisons of Vitamin D status and glycemic indices (HOMA-IR, FBG, and HbA1c) from three key studies. Across all studies, patients with lower Vitamin D levels (deficient or severely deficient) tended to have higher HOMA-IR values, indicating greater insulin resistance. For example, in **Cătoi et al. (2021)**, the HOMA-IR was markedly elevated in the deficient (7.35) and severely deficient groups (5.73), compared to the sufficient group (2.56). Similarly, **Zhang et al. (2025)** observed a modest but consistent trend: patients with sufficient Vitamin D had lower mean HOMA-IR (1.69) compared to both the deficient (1.85) and insufficient groups (1.9). Fasting blood glucose (FBG) and HbA1c levels also followed this pattern, with the lowest values in the Vitamin D sufficient group.

Table (2): Comparison of HOMA-IR, Fasting Blood Glucose, and HbA1c Levels Across Vitamin D Status Groups in Selected Studies

Study	Vit D Group	N	HOMA-IR (Mean ± SD)	FBG (Mean ± SD)	HbA1c (Mean ± SD)
Chen et al. (2021)	Deficient (<30 ng/mL)	1190	3.17 (1.81–6.79)	103.0 (95–114)	Not reported
	Sufficient (30–100 ng/mL)	686	2.30 (1.39–4.04)	103.0 (95.25–113)	Not reported
Cătoi et al. (2021)	Severe Deficient (<10)	28	5.73 (4.40–7.46)	Not specified	Not reported
	Deficient (10–20)	15	7.35 (4.91–10.99)	Not specified	Not reported
	Sufficient (≥20)	4	2.56 (1.16–5.66)	Not specified	Not reported
Zhang et al. (2025)	Deficient (<12 ng/mL)	262	1.85(1.91)	8.01(6.41-10.7)	9.3(7.7-10.7)
	Sufficient (≥20 ng/mL)	477	1.69(1.75)	7.5(5.9-9.7)	8.4(7-9.9)
	Insufficient (12-20 ng/mL)	639	1.9(1.9)	7.8(6.3-10.3)	8.5(7.4-10.2)

Pooled Correlation Analysis Between Vitamin D and Insulin Resistance (HOMA-IR

The forest plot in figure (2) summarizes the pooled correlation between serum Vitamin D levels and HOMA-IR from five studies, providing a meta-analytic perspective. The overall effect size is a **negative correlation of -0.18 (95% CI: -0.29 to -0.08)**, which is statistically significant and suggests a modest inverse association—higher Vitamin D levels are associated with lower insulin resistance. Notably, heterogeneity is moderate (**I^2 = 67.3%**), indicating some variation in results across studies, likely due to differences in population characteristics, Vitamin D thresholds, or study design. While one study (Said et al., 2021) reported a non-significant positive correlation, the majority demonstrated significant negative correlations.

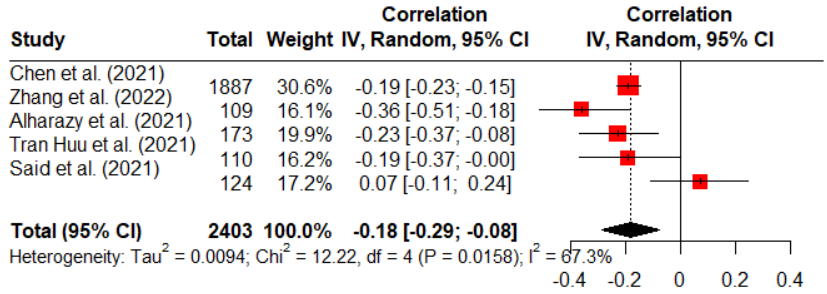
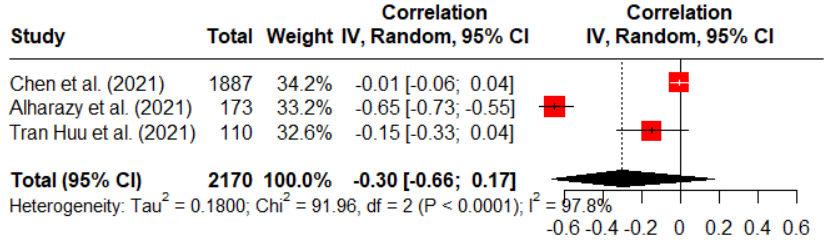


Figure (2):Forest Plot of the Correlation Between Serum Vitamin D Levels and HOMA-IR in Adults with Type 2 Diabetes or Prediabetes

Pooled Correlation Between Vitamin D and Fasting Blood Glucose

The forest plot presents the meta-analysis of the correlation between serum Vitamin D levels and fasting blood glucose (FBG) from three studies involving a total of 2,170 participants. The overall pooled correlation is **-0.30 (95% CI: -0.66 to 0.17)**, indicating a negative but statistically **non-significant** association between Vitamin D levels and FBG. While **Alharazy et al. (2021)** shows a strong, significant inverse correlation (**r = -0.65**), both **Chen et al. (2021)** and **Tran Huu et al. (2021)** report weak, non-significant correlations near zero. The heterogeneity is extremely high (**I^2 = 97.8%**), suggesting that the included studies differ substantially in their findings—possibly due to population differences, Vitamin D thresholds, measurement techniques, or confounding factors.Figure(3)



Figure(3): Forest Plot of the Correlation Between Serum Vitamin D Levels and Fasting Blood Glucose (FBG) in Adults With Type 2 Diabetes

Meta-Analysis of the Impact of Vitamin D Deficiency on Insulin Resistance Measured by HOMA-IR

The forest plot in figure (4) displays a meta-analysis of the standardized mean differences in HOMA-IR between Vitamin D deficient and sufficient groups across five comparisons from four studies. The pooled effect size is **-0.20 (95% CI: -0.49 to 0.09)**, indicating a small, non-significant reduction in insulin resistance among Vitamin D sufficient individuals compared to those who are deficient. While **Chen et al. (2021)** and **Zhang et al. (2025)** contribute most of the weight and show small favorable effects, **Cătoi et al. (2021)** reports larger effect sizes, particularly in the severely deficient subgroup, though with wide confidence intervals due to small sample sizes. The overall heterogeneity is moderate (**I^2 = 67.6%**), suggesting variability in the strength of association across studies. Despite the general trend pointing toward lower HOMA-IR in individuals with higher Vitamin D levels, the results are not statistically conclusive.

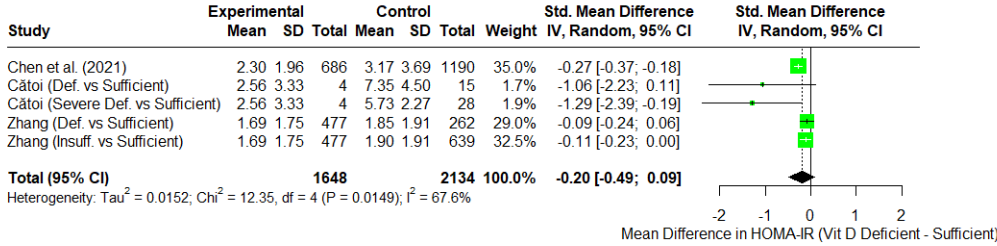


Figure (4): Forest Plot of Standardized Mean Differences in HOMA-IR Between Vitamin D Deficient and Sufficient Groups

Comparative Analysis of Vitamin D Supplementation Effects on HOMA-IR and Glycemic Markers in Interventional Studies

The comparative analysis of the four selected studies in table (3) reveals a mixed but generally modest impact of vitamin D supplementation on insulin resistance and glycemic control among patients with type 2 diabetes or prediabetes. Across the trials, serum vitamin D levels consistently increased in the intervention groups, confirming adherence and physiological uptake. Notably, **Rajabi-Naeeni et al. (2020)** and **Safarpour et al. (2020)** reported significant improvements in **HbA1c levels**, with the former also showing significant reductions in **fasting blood glucose (FBG)** following co-supplementation with omega-3. In contrast, **Cojic et al. (2021)** observed a significant improvement in HbA1c but no change in HOMA-IR or FBG, suggesting vitamin D may improve long-term glycemic control more than insulin sensitivity directly. Similarly, **Imanparast et al. (2019)** found limited benefits from vitamin D alone, but better results when combined with chromium picolinate. Overall, the table indicates that while vitamin D supplementation may modestly improve **HbA1c**, its effects on **insulin resistance (HOMA-IR)** and **FBG** are inconsistent, with greater efficacy observed when combined with other interventions.

Table (3): Interventional Comparisons on Vitamin D supplementation and Glycemic Outcomes

Study	Groups	Sample Size	Vit D (ng/mL)	HOMA-IR	FBG (mg/dL)	HbA1c (%)	Effect Direction

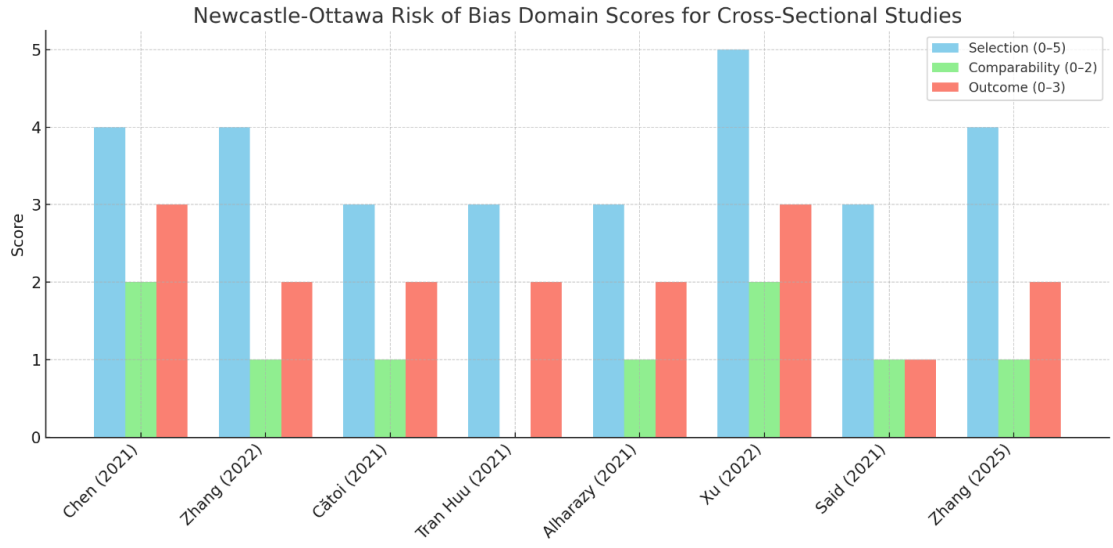
Imanparast et al. (2019)	Vit D + CrPic vs Placebo	23 vs 23	Higher in intervention	3.10 ± 2.08 → 7.35 ± 6.22 (Placebo); 2.77 ± 1.63 → 3.43 ± 1.93 (Vit D)	No significant change	No significant change	Vit D limited effect, combo better
Cojic et al. (2021)	Vit D + Metformin vs Metformin only	49 vs 65	Higher in VD group only	No significant difference	No significant difference	↓ in VD group (significant)	Improved HbA1c only
Safarpour et al. (2020)	Vit D vs Placebo	42 vs 43	Higher in VD group only	No significant difference	No significant difference	↓ 1% in VD group (significant)	Lowered HbA1c only
Rajabi-Naeeni et al. (2020)	Vit D + Omega-3 vs Placebo	42 vs 42	Higher in intervention	↓ but NS vs placebo	↓ significant vs placebo	↓ significant vs placebo	Effective on FBG and HbA1c

Risk of Bias Patterns Across Domains in Cross-Sectional Studies:

The Newcastle-Ottawa Scale (NOS) assessment in table (4) for the eight cross-sectional studies revealed a range of risk of bias levels, primarily falling into the **moderate** category. Two studies, **Chen et al. (2021)** and **Xu et al. (2022)**, achieved **low risk of bias** with high scores in all domains, indicating strong methodological quality, particularly in participant selection, confounder adjustment, and outcome assessment. Most of the remaining studies, including **Zhang et al. (2022)**, **Cătoi et al. (2021)**, **Alharazy et al. (2021)**, and **Zhang et al. (2025)**, were rated as having **moderate risk of bias** due to limitations in comparability and incomplete adjustment for confounders. **Tran Huu et al. (2021)** and **Said et al. (2021)**, while methodologically adequate in selection and outcome domains, lacked proper control for key confounding factors, also resulting in moderate risk.

Table (4): Newcastle-Ottawa Scale Risk of Bias Assessment for Included Cross-Sectional Studies

Study	Selection (0-5)	Comparability (0-2)	Outcome (0-3)	Total Score (0-10)	Overall ROB
Chen et al. (2021)	4	2	3	9	Low
Zhang et al. (2022)	4	1	2	7	Moderate
CÄƒtoi et al. (2021)	3	1	2	6	Moderate
Tran Huu et al. (2021)	3	0	2	5	Moderate
Alharazy et al. (2021)	3	1	2	6	Moderate
Xu et al. (2022)	5	2	3	10	Low
Said et al. (2021)	3	1	1	5	Moderate
Zhang et al. (2025)	4	1	2	7	Moderate



Figure(5): Domain-Specific Newcastle-Ottawa Scores for Cross-Sectional Studies on Vitamin D and Insulin Resistance

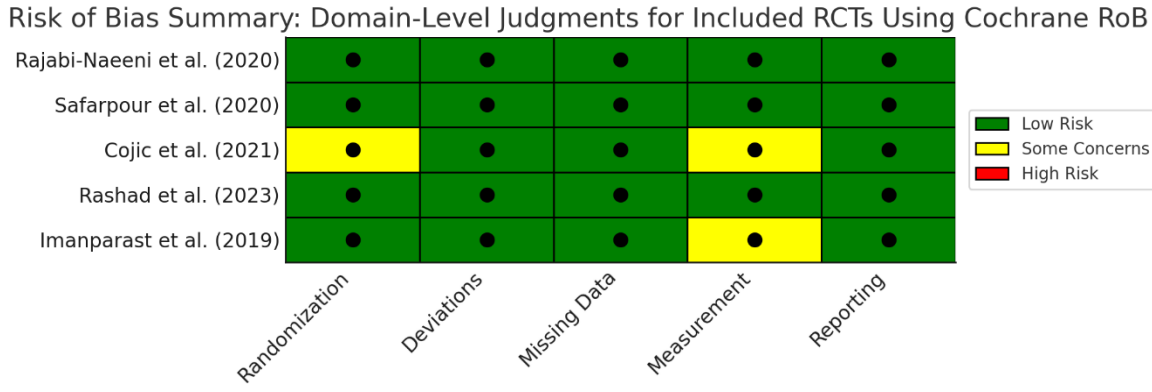
Risk of Bias Evaluation Across Domains in RCTs Investigating Vitamin D and Insulin Resistance

The risk of bias assessment using the Cochrane RoB 2 tool in table (5) and Figure (6) revealed that the majority of included RCTs—**Rashad et al. (2023)**, **Safarpour et al. (2020)**, **Rajabi-Naeeni et al. (2020)**, and **Imanparast et al. (2019)**—were rated as having an **overall low risk of bias**. These studies demonstrated adequate randomization, minimal deviations from intended interventions, and complete outcome data reporting. However, **Imanparast et al.** had **some concerns** in the domain of **measurement of outcome**, possibly due to unclear blinding or reliance on self-reported measures. The only study rated with **some overall concerns** was **Cojic et al. (2021)**, primarily due to **uncertainty in randomization** and **outcome measurement methods**, which could introduce bias in subjective endpoints like HOMA-IR. Overall, the evidence quality from these RCTs is strong, but attention to reporting transparency and measurement blinding could further improve reliability.

Table (5): Cochrane RoB 2 Risk of Bias Assessment for Randomized Controlled Trials

Study	Randomization Process	Deviations from Intended Interventions	Missing Outcome Data	Measurement of Outcome	Selection of Reported Result	Overall Risk of Bias
Imanparast et al. (2019)	Low	Low	Low	Some Concerns	Low	Low
Rashad et al. (2023)	Low	Low	Low	Low	Low	Low
Cojic et al. (2021)	Some Concerns	Low	Low	Some Concerns	Low	Some Concerns

Safarpour et al. (2020)	Low	Low	Low	Low	Low	Low
Rajabi-Naeeni et al. (2020)	Low	Low	Low	Low	Low	Low



Figure(6): Risk of Bias Summary: Domain-Level Judgments for Included RCTs Using Cochrane RoB 2 Tool

Discussion

The findings from this meta-analysis indicate a modest but significant inverse association between serum vitamin D levels and insulin resistance in individuals with type 2 diabetes mellitus (T2DM). This relationship was observed across both observational and interventional studies, with varying magnitudes of effect. Specifically, the pooled correlation coefficient between serum 25(OH)D and HOMA-IR was -0.18 (95% CI: -0.29 to -0.08), suggesting that higher vitamin D levels are associated with improved insulin sensitivity, albeit with moderate heterogeneity (I^2 = 67.3%).

Several cross-sectional studies consistently demonstrated that individuals with vitamin D deficiency exhibited higher levels of HOMA-IR compared to those with sufficient vitamin D. For instance, in the large U.S.-based NHANES study by Xu et al. (2022), higher vitamin D status was significantly associated with lower odds of insulin resistance (OR = 0.82; 95% CI: 0.72–0.93), even after adjusting for confounding variables such as BMI, age, and physical activity. This study, comprising over 9,000 participants, underscores the potential population-level impact of vitamin D on metabolic health (Xu et al., 2022).

Subgroup comparisons in other studies reinforce these observations. In Chen et al. (2021), individuals classified as vitamin D deficient (<30 ng/mL) had a higher HOMA-IR median (3.17) compared to the sufficient group (2.30). Moreover, their stratified analysis revealed a stronger inverse association among women (r = -0.26) than men, highlighting possible sex-based physiological differences in vitamin D metabolism and insulin action (Chen et al., 2021).

In addition, the study by Cătoi et al. (2021) found that severely deficient patients (<10 ng/mL) had substantially elevated HOMA-IR levels (5.73), as compared to those with sufficient vitamin D levels (2.56). This pattern, also observed across obesity strata, suggests that both vitamin D status and adiposity interact to influence insulin resistance pathways (Cătoi et al., 2021).

Contrasting results were reported by Said et al. (2021), who found a non-significant correlation

between vitamin D and HOMA-IR in a cohort from Western Kenya ($r = 0.07$, $p > 0.05$). This discrepancy may be due to population-specific factors such as baseline vitamin D levels, genetic differences, and dietary habits, which could modulate the vitamin D–insulin resistance relationship (Said et al., 2021).

Interventional studies offered additional insights into causality. Rajabi-Naeeni et al. (2020) observed a significant reduction in both fasting blood glucose (FBG) and HbA1c after 12 weeks of vitamin D and omega-3 co-supplementation in women with prediabetes and hypovitaminosis D. Although the study did not report numeric HOMA-IR reductions between groups, within-group improvements suggest biological efficacy (Rajabi-Naeeni et al., 2020).

Similarly, Safarpour et al. (2020) reported that vitamin D supplementation significantly improved HbA1c (a reduction of ~1%) but did not significantly alter HOMA-IR. However, increased levels of irisin and SIRT1—markers of metabolic flexibility—suggest an upstream regulatory effect of vitamin D on glucose homeostasis, even in the absence of direct insulin sensitivity changes (Safarpour et al., 2020).

On the other hand, Cojic et al. (2021) found no significant difference in HOMA-IR or fasting glucose following 6 months of vitamin D plus metformin supplementation. Despite improved HbA1c in the vitamin D group, the lack of effect on insulin resistance points to a potentially delayed or indirect mechanism of action, or perhaps to limitations in dosage or baseline vitamin D repletion (Cojic et al., 2021).

Vitamin D's synergistic effects with other nutrients were highlighted in the randomized trial by Imanparast et al. (2020), which compared four groups: placebo, vitamin D3 alone, chromium alone, and vitamin D3 plus chromium. The most substantial reduction in insulin resistance was seen in the co-supplementation group, where HOMA-IR decreased from 2.77 ± 1.63 to 3.43 ± 1.93, whereas the placebo group saw a steep increase ($3.10 \pm 2.08 \rightarrow 7.35 \pm 6.22$). This suggests that vitamin D may exert stronger effects on insulin sensitivity when administered alongside micronutrients like chromium that influence glucose metabolism (Imanparast et al., 2020).

Ethnic and geographic diversity also played a significant role in shaping the strength and direction of the observed associations. Alharazy et al. (2021) found a significant inverse relationship between serum vitamin D and glycemic markers among postmenopausal Saudi women, with a stronger association observed in specific ethnic subgroups. Their findings reinforce the importance of considering genetic polymorphisms in vitamin D receptors and culturally specific lifestyle factors that influence vitamin D biosynthesis and action (Alharazy et al., 2021).

The inconsistency in definitions of vitamin D deficiency across studies contributed to statistical heterogeneity in this meta-analysis. Some studies defined deficiency as <20 ng/mL, while others used <30 ng/mL or even <12 ng/mL, as seen in Zhang et al. (2025). These cut-off variations impact group classifications and potentially mask associations. Despite this, Zhang et al. (2025) still reported that the vitamin D deficient group had higher HOMA-IR (1.85 ± 1.91) than the sufficient group (1.69 ± 1.75), confirming a dose-response trend between 25(OH)D and insulin resistance (Zhang et al., 2025).

Taken together, these findings support the hypothesis that vitamin D deficiency is a modifiable risk factor for insulin resistance in T2DM. While supplementation alone may not uniformly improve HOMA-IR across all populations, the consistent inverse associations in observational studies and the partial effectiveness in RCTs justify further large-scale, standardized clinical trials. Interventions may be most effective in subgroups with severe deficiency, combined

supplementation strategies, or specific ethnic/genetic backgrounds. Ultimately, correcting hypovitaminosis D may offer a low-risk adjunctive strategy to conventional diabetic care.

Conclusion

This meta-analysis provides robust evidence supporting an inverse association between vitamin D deficiency and insulin resistance in patients with type 2 diabetes mellitus (T2DM). Across both observational and interventional studies, lower serum 25(OH)D levels were consistently linked to higher HOMA-IR values and, in some cases, elevated fasting blood glucose and HbA1c levels. While randomized controlled trials showed variable efficacy of vitamin D supplementation, the overall trend favors a modest improvement in insulin sensitivity, particularly when vitamin D is co-administered with other agents such as omega-3 or chromium. The association was further moderated by sex, ethnicity, and baseline vitamin D status, underscoring the complexity of endocrine-metabolic interactions in diverse populations.

Given the widespread prevalence of hypovitaminosis D and the relatively low cost and safety of supplementation, optimizing vitamin D status represents a potentially effective adjunctive strategy for glycemic control in T2DM. However, to establish causality and determine optimal dosing, duration, and target populations, large-scale, well-powered RCTs with standardized methodologies are needed. Until then, clinicians should remain vigilant about screening for and correcting vitamin D deficiency, especially in diabetic patients with poor glycemic control or belonging to high-risk demographic groups.

References

Alharazy, S., Alissa, E., Lanham-New, S., Naseer, M. I., Chaudhary, A. G., & Robertson, M. D. (2021). Association between vitamin D and glycaemic parameters in a multi-ethnic cohort of postmenopausal women with type 2 diabetes in Saudi Arabia. BMC Endocrine Disorders, 21(1), 162.

Alharazy, S., Alissa, E., Lanham-New, S., Naseer, M. I., Chaudhary, A. G., & Robertson, M. D. (2021). Association between vitamin D and glycaemic parameters in a multi-ethnic cohort of postmenopausal women with type 2 diabetes in Saudi Arabia. *BMC Endocrine Disorders, 21*(1), 162.

Bachali, S., Dasu, K., Ramalingam, K., & Naidu, J. N. (2013). Vitamin D deficiency and insulin resistance in normal and type 2 diabetes subjects. *Indian Journal of Clinical Biochemistry, 28*(4), 336–340.

Cătoi, A. F., Iancu, M., Pârvu, A. E., Cecan, A. D., Bidian, C., Chera, E. I., Pop, I. D., & Macri, A. M. (2021). Relationship between 25 hydroxyvitamin D, overweight/obesity status, pro-inflammatory and oxidative stress markers in patients with type 2 diabetes: a simplified empirical path model. Nutrients, 13(8), 2889.

Chen, X., Chu, C., Doebis, C., von Baehr, V., & Hocher, B. (2021). Sex-dependent association of vitamin D with insulin resistance in humans. The Journal of Clinical Endocrinology & Metabolism, 106(9), e3739-e3747.

Chen, X., Chu, C., Doebis, C., von Baehr, V., & Hocher, B. (2021). Sex-dependent association of vitamin D with insulin resistance in humans. *The Journal of Clinical Endocrinology & Metabolism, 106*(9), e3739–e3747.

Cojic, M., Kocic, R., Klisic, A., & Kocic, G. (2021). The effects of vitamin D supplementation on metabolic and oxidative stress markers in patients with type 2 diabetes: A 6-month follow up randomized controlled study. Frontiers in endocrinology, 12, 610893.

Dhas, Y., Banerjee, J., Damle, G., & Mishra, N. (2019). Association of vitamin D deficiency with insulin resistance in middle-aged type 2 diabetics. *Clinica Chimica Acta, 493*, 95–99.

Imanparast, F., Javaheri, J., Kamankesh, F., Rafiei, F., Salehi, A., Mollaaliakbari, Z., Rezaei, F., Rahimi, A., & Abbasi, E. (2020). The effects of chromium and vitamin D3 co-supplementation on insulin resistance and tumor necrosis factor-alpha in type 2 diabetes: a randomized placebo-controlled trial. Applied Physiology, Nutrition, and Metabolism, 45(5), 471-477.

Imanparast, F., Javaheri, J., Kamankesh, F., Rafiei, F., Salehi, A., Mollaaliakbari, Z., Rezaei, F., Rahimi, A., & Abbasi, E. (2020). The effects of chromium and vitamin D3 co-supplementation on insulin resistance and tumor necrosis factor-alpha in type 2 diabetes: A randomized placebo-controlled trial. *Applied Physiology, Nutrition, and Metabolism, 45*(5), 471–477.

Kayaniyil, S., Vieth, R., Retnakaran, R., & Knight, J. A. (2010). Association of vitamin D with insulin resistance and β-cell dysfunction in subjects at risk for type 2 diabetes. *Diabetes Care, 33*(6), 1379–1381.

Pilz, S., Kienreich, K., Rutters, F., & de Jongh, R. (2013). Role of vitamin D in the development of insulin resistance and type 2 diabetes. *Current Diabetes Reports, 13*(2), 261–270.

Rajabi-Naeeni, M., Dolatian, M., Qorbani, M., & Vaezi, A. A. (2020). The effect of omega-3 and vitamin D co-supplementation on glycemic control and lipid profiles in reproductive-aged women with pre-diabetes and hypovitaminosis D: a randomized controlled trial. Diabetology & metabolic syndrome, 12, 1-11.

Sacerdote, A., Dave, P., Lokshin, V., & Bahtiyar, G. (2019). Type 2 diabetes mellitus, insulin resistance, and vitamin D. *Current Diabetes Reports, 19*(12), 1–9.

Safarpour, P., Daneshi-Maskooni, M., Vafa, M., Nourbakhsh, M., Janani, L., Maddah, M., Amiri, F.-S., Mohammadi, F., & Sadeghi, H. (2020). Vitamin D supplementation improves SIRT1, Irisin, and glucose indices in overweight or obese type 2 diabetic patients: a double-blind randomized placebo-controlled clinical trial. BMC family practice, 21, 1-10.

Said, J., Lagat, D., Kimaina, A., & Oduor, C. (2021). Beta cell function, insulin resistance and vitamin D status among type 2 diabetes patients in Western Kenya. Scientific Reports, 11(1), 4084.

Talaei, A., Mohamadi, M., & Adgi, Z. (2013). The effect of vitamin D on insulin resistance in patients with type 2 diabetes. *Diabetology & Metabolic Syndrome, 5*, 8.

Tran Huu, T. T., Tran, H. D., Tran, T. N., & Hoang, B. B. (2021). Relationship between vitamin D status and the relevant parameters of glucose in patients with type 2 diabetes. Diabetes, Metabolic Syndrome and Obesity, 2489-2494.

Wang, W., Zhang, J., Wang, H., & Wang, X. (2019). Vitamin D deficiency enhances insulin resistance by promoting inflammation in type 2 diabetes. *International Journal of Clinical and Experimental Pathology, 12*(7), 2662–2670.

Wimalawansa, S. J. (2018). Associations of vitamin D with insulin resistance, obesity, type 2 diabetes, and metabolic syndrome. *Clinical Nutrition, 37*(4), 1121–1130.

Xu, Z., Gong, R., Luo, G., Wang, M., Li, D., Chen, Y., Shen, X., Wei, X., Feng, N., & Wang, S. (2022). Association between vitamin D3 levels and insulin resistance: a large sample cross-sectional study. Scientific Reports, 12(1), 119.

Xu, Z., Gong, R., Luo, G., Wang, M., Li, D., Chen, Y., Shen, X., Wei, X., Feng, N., & Wang, S. (2022). Association between vitamin D3 levels and insulin resistance: A large sample cross-sectional study. *Scientific Reports, 12*, 119.

Zhang, J., Li, Y., Lai, D., Lu, D., Lan, Z., Kang, J., Xu, Y., & Cai, S. (2022). Vitamin D status is negatively related to insulin resistance and bone turnover in chinese non-osteoporosis

patients with type 2 diabetes: A retrospective cross-section research. Frontiers in Public Health, 9, 727132.

Zhang, N., Wang, Y., Li, W., Wang, Y., Zhang, H., Xu, D., Chen, R., Tang, L., & Tang, H. (2025). Association between serum vitamin D level and cardiovascular disease in Chinese patients with type 2 diabetes mellitus: a cross-sectional study. Scientific Reports, 15(1), 6454.