



# The Comprehensive Systematic Review of Association of Vit D Deficiency to The Prevalence of Insulin Resistance

<sup>1</sup> Billy Suyanto Wijaya

<sup>1</sup> Faculty of Medicine, Hang Tuah University, Surabaya, Indonesia

Corresponding Email : [billysuyanto07@gmail.com](mailto:billysuyanto07@gmail.com)

## Article History :

Received date : 2025/09/08

Revised date : 2025/10/17

Accepted date : 2025/12/24

Published date : 2026/01/30



**Copyright:** © 2024 by the authors. Submitted for possible open access publication under the terms and conditions of the Creative Commons Attribution (BY NC) license (<https://creativecommons.org/licenses/by-nc/4.0/>).

E-ISSN :

ISSN 3048-1368



P-ISSN

ISSN 3048-1376



## ABSTRACT

**Introduction:** Vitamin D deficiency has emerged as a global health concern with potential implications for metabolic health, particularly insulin resistance—a key precursor to type 2 diabetes and metabolic syndrome. Despite extensive research, the nature, strength, and causality of this association remain debated due to heterogeneous methodologies and conflicting intervention outcomes.

**Methods:** This comprehensive systematic review synthesized evidence from 80 studies following rigorous screening and data extraction protocols. Studies were included if they examined the association between vitamin D deficiency (defined by serum 25(OH)D levels) and insulin resistance (assessed via validated methods like HOMA-IR) in adults, excluding those focused solely on supplementation, type 1 diabetes, or pregnancy.

**Results:** The evidence consistently demonstrates a significant inverse association between vitamin D status and insulin

resistance across diverse populations. Observational studies showed weak to moderate inverse correlations ( $r$  ranging from -0.134 to -0.631), with stronger associations in diabetic (pooled  $r \approx -0.255$ ) versus non-diabetic populations (pooled  $r \approx -0.073$ ) (Rafiq & Jeppesen, 2021; Alshahrani et al., 2025). Meta-analyses confirmed that higher vitamin D levels are associated with a reduced risk of type 2 diabetes ( $RR = 0.65$ ) and prediabetes ( $RR = 0.49$ ) (Mohammadi et al., 2021). The association was notably amplified by obesity, with correlations strengthening from  $r = -0.150$  in normal-weight individuals to  $r = -0.257$  in obese individuals (Rafiq & Jeppesen, 2021). However, RCTs on vitamin D supplementation yielded mixed results; while some showed improvement in insulin resistance, particularly in those with baseline glucose intolerance, others reported no significant effect in healthy or normoglycemic individuals (Mitri et al., 2011; von Hurst et al., 2009; Grimnes et al., 2011).

**Discussion:** The relationship between vitamin D deficiency and insulin resistance is complex and modified by factors such as baseline metabolic status, BMI, and ethnicity. The discordance between strong observational associations and inconsistent interventional findings suggests that vitamin D status may be a marker of overall metabolic health and adiposity rather than a directly modifiable causal factor in all populations. Mechanistic pathways—including effects on pancreatic  $\beta$ -cell function, insulin receptor expression, and systemic inflammation—provide biological plausibility but underscore the influence of confounding variables.

**Conclusion:** Vitamin D deficiency is consistently associated with a higher prevalence and severity of insulin resistance, particularly

in individuals with obesity, prediabetes, or established type 2 diabetes. Maintaining adequate vitamin D status should be considered a component of metabolic health strategy. Supplementation may offer the greatest benefit for those with documented deficiency coupled with existing metabolic dysfunction, rather than as a universal preventive measure for insulin resistance.

**Keywords:** Vitamin D deficiency, Insulin resistance, Type 2 diabetes, HOMA-IR, Metabolic syndrome, Obesity, Systematic review, Meta-analysis.

---

## INTRODUCTION

---

### Background

Insulin resistance, characterized by diminished cellular responsiveness to insulin, is a fundamental pathological process underlying type 2 diabetes mellitus (T2DM), metabolic syndrome, and related cardiometabolic disorders (Khan et al., 2012). Its escalating global prevalence underscores the urgent need to identify modifiable risk factors and preventive strategies. Concurrently, vitamin D deficiency has reached epidemic proportions worldwide, affecting an estimated one billion people (Al-Daghri, 2018). Beyond its classical role in calcium homeostasis and bone health, vitamin D is now recognized as a pleiotropic hormone with receptors ubiquitously expressed, including in pancreatic  $\beta$ -cells, skeletal muscle, and adipose tissue—key organs involved in glucose metabolism (Pittas et al., 2007).

Emerging epidemiological evidence over the past two decades suggests a plausible link between suboptimal vitamin D status and impaired insulin sensitivity. Proposed biological mechanisms include vitamin D's role in regulating insulin receptor gene expression, modulating intracellular calcium flux essential for insulin-mediated cellular processes, exerting anti-inflammatory effects that counteract chronic low-grade inflammation associated with insulin resistance, and directly protecting pancreatic  $\beta$ -cell function (Forouhi et al., 2008; Grimnes et al., 2011). This confluence of epidemiological and mechanistic observations has positioned vitamin D as a potential player in the pathogenesis of insulin resistance and dysglycemia.

### Research Objective

This comprehensive systematic review aims to synthesize and critically evaluate the totality of available evidence on the association between vitamin D deficiency and the prevalence and severity of insulin resistance. The primary objective is to determine the strength, consistency, and direction of this association across diverse populations and study designs. Secondary objectives

include: examining the modifying effects of factors such as body mass index (BMI), baseline glycemic status, and ethnicity; assessing the impact of vitamin D supplementation on insulin resistance indices; and identifying gaps in the current evidence base to guide future research.

### **Research Benefits**

The findings of this review hold significant clinical and public health implications. Elucidating the nature of this relationship can inform clinical guidelines regarding the screening for vitamin D deficiency in high-risk populations (e.g., individuals with obesity, prediabetes, or T2DM). It can guide the development of targeted nutritional and lifestyle interventions, potentially offering a low-cost adjunctive strategy for improving metabolic health. Furthermore, by clarifying contexts where supplementation is most effective, this review can help optimize resource allocation and prevent unnecessary supplementation in populations unlikely to benefit.

### **Hypothesis**

Based on the existing mechanistic and preliminary observational evidence, the central hypothesis of this review is that vitamin D deficiency is independently and inversely associated with an increased prevalence and severity of insulin resistance. It is further hypothesized that this association is stronger in populations with underlying metabolic dysfunction (e.g., T2DM, prediabetes) and is positively modified by increasing adiposity. Finally, it is hypothesized that correction of vitamin D deficiency through supplementation will lead to measurable improvements in insulin sensitivity, particularly among those with significant deficiency and established glucose intolerance.

### **Research Gap**

Despite a burgeoning volume of literature, critical knowledge gaps persist. There is substantial heterogeneity in defining vitamin D deficiency (e.g., thresholds of <20 ng/mL vs. <50 nmol/L) and measuring insulin resistance (e.g., HOMA-IR, clamp techniques), complicating cross-

study comparisons (Rafiq & Jeppesen, 2021; Alshahrani et al., 2025). More importantly, a glaring discordance exists between robust inverse associations consistently reported in observational studies and the often null or inconsistent findings from randomized controlled trials (RCTs) of vitamin D supplementation (Mitri et al., 2011; Maheshwari et al., 2024). This discrepancy raises fundamental questions about causality versus confounding. Additionally, there is limited synthesis on how this relationship manifests in special populations like those with Polycystic Ovary Syndrome (PCOS) or adolescents, and whether genetic factors (e.g., Vitamin D Receptor polymorphisms) influence individual susceptibility (He et al., 2015; Núñez-García et al., 2022).

### **Novelty**

This systematic review offers several novel contributions to the field. First, it provides an updated and expansive synthesis encompassing 80 sources, including recent high-quality meta-analyses and large cohort studies up to 2025. Second, it moves beyond simply confirming an association to perform a detailed, context-specific analysis, stratifying findings by population type (healthy, prediabetic, diabetic, obese, PCOS), thereby offering nuanced clinical insights. Third, it explicitly confronts and analyzes the critical discordance between observational and interventional evidence, exploring potential explanations such as threshold effects, baseline metabolic status, and the role of BMI as a key effect modifier and confounder. Finally, by integrating evidence on assessment methodologies, it highlights the need for standardization in future research to reduce heterogeneity and improve evidence quality.

---

## **METHODS**

---

### **Protocol**

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

## Criteria for Eligibility

This systematic review aims to evaluate the association of vitamin D deficiency to the prevalence of insulin resistance.

## Screening

We screened in sources based on their abstracts that met these criteria:

- **Research Question Relevance:** Does this study examine the association between vitamin D deficiency and insulin resistance?
- **Vitamin D Definition:** Does this study provide a clear definition of vitamin D deficiency using serum 25(OH)D levels (such as <20 ng/mL or <50 nmol/L) or other study-specific definitions?
- **Insulin Resistance Measurement:** Does this study measure insulin resistance using validated methods (such as HOMA-IR, euglycemic clamp, QUICKI, or other established indices)?
- **Study Design:** Is this study a cross-sectional, case-control, cohort study, systematic review, or meta-analysis?
- **Study Population Age:** Does this study include participants aged 18 years and older?
- **Data Availability:** Does this study report sufficient data to determine prevalence or association measures between vitamin D deficiency and insulin resistance?
- **Study Focus (Not Intervention):** Is this study NOT primarily focused on examining vitamin D supplementation effects as an intervention?
- **Population Type (Not Type 1 Diabetes):** Does this study NOT focus exclusively on type 1 diabetes populations?
- **Population Type (Not Pregnancy):** Is this study NOT conducted exclusively in pregnant women?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

## Search Strategy

The keywords used for this research based PICO :

| Element          | P<br>(Population)        | I<br>(Intervention/Exposure)      | C<br>(Comparison/Context) | O<br>(Outcome)                 |
|------------------|--------------------------|-----------------------------------|---------------------------|--------------------------------|
| <b>Keyword 1</b> | Adults                   | Vitamin D Deficiency              | Vitamin D Sufficiency     | Insulin Resistance             |
| <b>Keyword 2</b> | Type 2 Diabetes patients | Hypovitaminosis D                 | Normal Vitamin D levels   | HOMA-IR                        |
| <b>Keyword 3</b> | Prediabetic individuals  | Low 25(OH)D                       | Adequate Vitamin D        | Insulin sensitivity impairment |
| <b>Keyword 4</b> | Obese individuals        | 25-hydroxyvitamin D insufficiency | Optimal Vitamin D status  | Glucose intolerance            |

The Boolean MeSH keywords inputted on databases for this research are: ("Adults" OR "Type 2 Diabetes patients" OR "Prediabetic individuals" OR "Obese individuals") AND ("Vitamin D Deficiency" OR "Hypovitaminosis D" OR "Low 25(OH)D" OR "25-hydroxyvitamin D insufficiency") AND ("Vitamin D Sufficiency" OR "Normal Vitamin D levels" OR "Adequate Vitamin D" OR "Optimal Vitamin D status") AND ("Insulin Resistance" OR "HOMA-IR" OR "Insulin sensitivity impairment" OR "Glucose intolerance")

## Data extraction

- **Study Design:**

Extract the study design and population characteristics relevant to vitamin D deficiency and insulin resistance association, including:

- Study type (cross-sectional, cohort, RCT, meta-analysis, etc.)
- Sample size
- Population type (healthy controls, type 2 diabetes patients, prediabetic, mixed)
- Age range and demographics
- Geographic location/setting

- **Vitamin D Assessment:**

Extract how vitamin D status was measured and vitamin D deficiency was defined, including:

- Measurement method (25(OH)D, 1,25(OH)<sub>2</sub>D, etc.)
- Units used (ng/ml, nmol/l)
- Deficiency threshold(s) used (e.g., <20 ng/ml, <50 nmol/l)
- Mean/median vitamin D levels in study groups
- Assay method if specified

- **Insulin Resistance Assessment:**

Extract how insulin resistance was measured and defined, including:

- Primary method used (HOMA-IR, QUICKI, clamp studies, etc.)
- Insulin resistance threshold/cutoff if specified
- Mean/median insulin resistance values by vitamin D status groups
- Other glucose metabolism markers measured (fasting glucose, insulin, HbA1c)

- **Association Results:**

Extract the main findings on the association between vitamin D deficiency and insulin resistance prevalence/severity, including:

- Correlation coefficients (r values) between vitamin D levels and insulin resistance
- Odds ratios for insulin resistance in vitamin D deficient vs sufficient groups
- Mean differences in insulin resistance measures between vitamin D groups
- Direction of association (positive/negative/null)
- Effect sizes and magnitude of association

- **Statistical Significance:**

Extract statistical significance and precision of association findings, including:

- P-values for primary associations between vitamin D deficiency and insulin resistance
- Confidence intervals (95% CI) for correlation coefficients, odds ratios, or mean differences
- Sample size and power calculations if reported
- Heterogeneity measures for meta-analyses ( $I^2$ , Q-statistic)

- **Confounding Factors:**

Extract information about potential confounding variables and how they were addressed in analyzing vitamin D deficiency and insulin resistance associations, including:

- Variables controlled for in adjusted analyses (age, BMI, ethnicity, season, etc.)
- Matching criteria used
- Stratified analyses performed
- Exclusion criteria related to confounding factors
- Limitations acknowledged regarding unmeasured confounders

**Table 1.** Article Search Strategy

| Database             | Keywords                                                                                                                                                                                                                                                                                                                                                                                                                       | Hits   |
|----------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------|
| Pubmed               | ("Adults" OR "Type 2 Diabetes patients" AND "Vitamin D Deficiency" AND "Normal Vitamin D levels" AND "Insulin Resistance" OR "HOMA-IR" OR "Insulin sensitivity impairment" OR "Glucose intolerance")                                                                                                                                                                                                                           | 2,739  |
| Semantic Scholar     | ("Adults" OR "Type 2 Diabetes patients" OR "Prediabetic individuals" OR "Obese individuals") AND ("Vitamin D Deficiency" OR "Hypovitaminosis D" OR "Low 25(OH)D" OR "25-hydroxyvitamin D insufficiency") AND ("Vitamin D Sufficiency" OR "Normal Vitamin D levels" OR "Adequate Vitamin D" OR "Optimal Vitamin D status") AND ("Insulin Resistance" OR "HOMA-IR" OR "Insulin sensitivity impairment" OR "Glucose intolerance") | 256    |
| Springer             | ("Adults" OR "Type 2 Diabetes patients" AND ("Vitamin D Deficiency" AND "Normal Vitamin D levels" AND ("Insulin Resistance" OR "HOMA-IR" OR "Insulin sensitivity impairment" OR "Glucose intolerance")                                                                                                                                                                                                                         | 74     |
| Google Scholar       | ("Adults" OR "Type 2 Diabetes patients" OR "Prediabetic individuals" OR "Obese individuals") AND ("Vitamin D Deficiency" OR "Hypovitaminosis D" OR "Low 25(OH)D" OR "25-hydroxyvitamin D insufficiency") AND ("Vitamin D Sufficiency" OR "Normal Vitamin D levels" OR "Adequate Vitamin D" OR "Optimal Vitamin D status") AND ("Insulin Resistance" OR "HOMA-IR" OR "Insulin sensitivity impairment" OR "Glucose intolerance") | 16,800 |
| Wiley Online Library | ("Adults" OR "Type 2 Diabetes patients" OR "Prediabetic individuals" OR "Obese individuals") AND ("Vitamin D Deficiency" OR "Hypovitaminosis D" OR "Low 25(OH)D" OR "25-hydroxyvitamin D insufficiency") AND ("Vitamin D Sufficiency" OR "Normal Vitamin D levels" OR "Adequate Vitamin D" OR "Optimal Vitamin D status") AND ("Insulin Resistance" OR "HOMA-IR" OR "Insulin sensitivity impairment" OR "Glucose intolerance") | 331    |

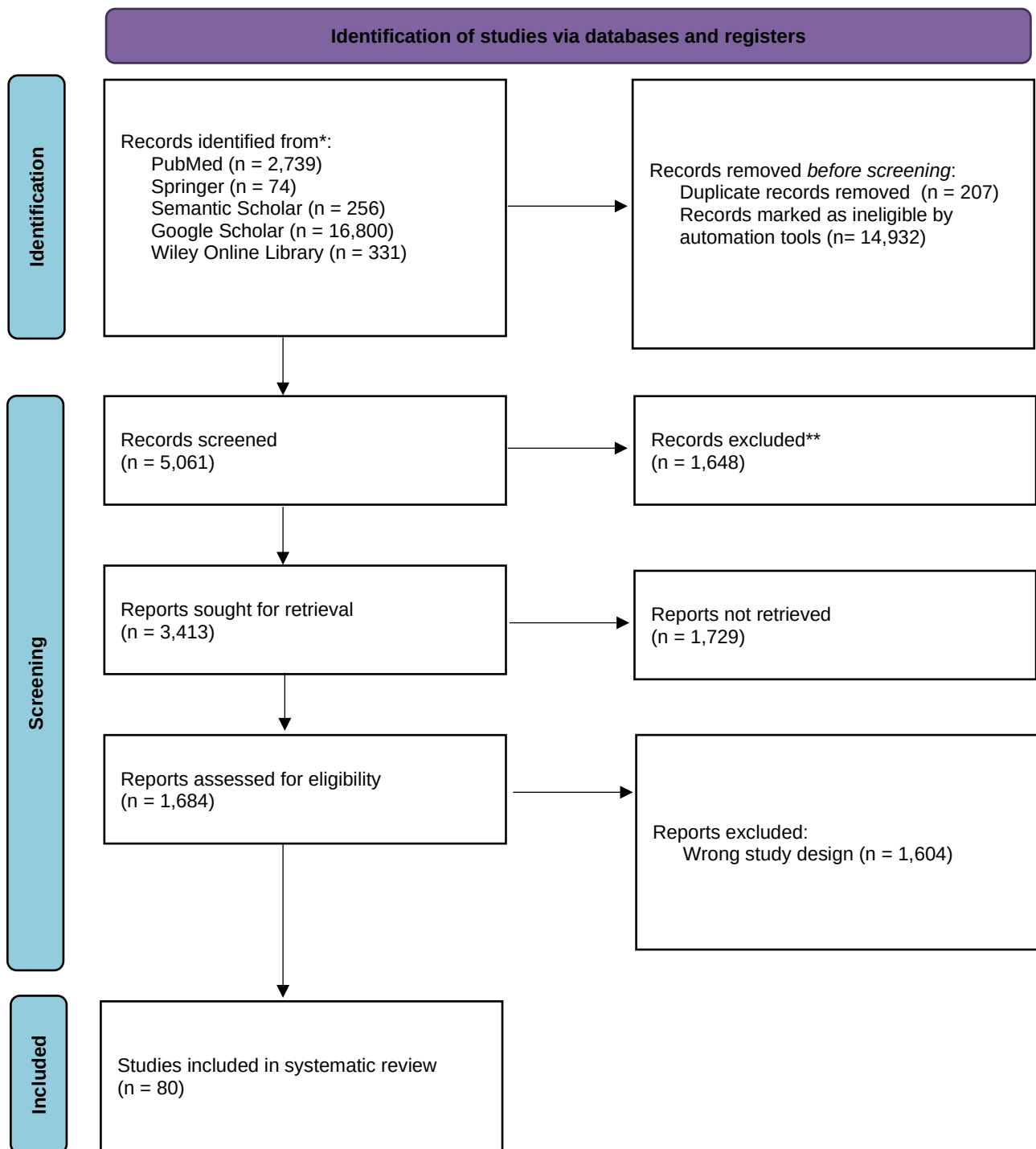


**Figure 1. Article search flowchart**

| JBI Critical Appraisal         |                                                                                                                                                                            |                                                                        |                                                                                               |                                                                                                                                                                                                     |                                                                                               |                                                                                         |                                           |                                                                                                                                                                             |                                                                               |
|--------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|-------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------|
| Study                          | Bias related to temporal precedence<br>Is it clear in the study what is the “cause” and what is the “effect” (ie, there is no confusion about which variable comes first)? | Bias related to selection and allocation<br>Was there a control group? | Bias related to confounding factors<br>Were participants included in any comparisons similar? | Bias related to administration of intervention/exposure<br>Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or intervention of interest? | Were there multiple measurements of the outcome, both pre and post the intervention/exposure? | Were the outcomes of participants included in any comparisons measured in the same way? | Were outcomes measured in a reliable way? | Bias related to participant retention<br>Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed? | Statistical conclusion validity<br>Was appropriate statistical analysis used? |
| B. Sowjanya et al., 2017       | ✓                                                                                                                                                                          | ✓                                                                      | ✓                                                                                             | ✗                                                                                                                                                                                                   | ✓                                                                                             | ✗                                                                                       | ✓                                         | ✓                                                                                                                                                                           | ✓                                                                             |
| T. D. S. Ferreira et al., 2013 | ✓                                                                                                                                                                          | ✓                                                                      | ✓                                                                                             | ✗                                                                                                                                                                                                   | ✓                                                                                             | ✗                                                                                       | ✓                                         | ✓                                                                                                                                                                           | ✓                                                                             |
| Sowjanya Bachali et al., 2012  | ✓                                                                                                                                                                          | ✓                                                                      | ✓                                                                                             | ✗                                                                                                                                                                                                   | ✓                                                                                             | ✗                                                                                       | ✓                                         | ✓                                                                                                                                                                           | ✓                                                                             |

|                                     |   |   |   |   |   |   |   |   |   |
|-------------------------------------|---|---|---|---|---|---|---|---|---|
| P. Kishore et al., 2017             | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| N. Forouhi et al., 2008             | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| S. Kayaniyil et al., 2011           | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| Li Li et al., 2016                  | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| Shamaila Rafiq et al., 2021         | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| Shamaila Rafiq et al., 2021a        | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| Mohammad S. Alshahrani et al., 2025 | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| F. Çağlar et al., 2017              | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| A. Lizarraga et al., 2021           | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| Chunla He et al., 2015              | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| N. Chandrika et al., 2022           | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| Cem Ozcan et al., 2023              | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |

|                                   |   |   |   |   |   |   |   |   |   |
|-----------------------------------|---|---|---|---|---|---|---|---|---|
| S. Pattman et al., 2011           | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| Muntaha A. Arif et al., 2024      | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| Xingxing Lei et al., 2023         | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| S. Savastano et al., 2013         | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| H. Khan et al., 2012              | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| Nyein Wint Yee Theik et al., 2021 | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| Yun-Yi Gao et al., 2018           | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| J. Daniel et al., 2022            | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| Y. Krul-Poel et al., 2013         | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| A. Abukanna et al., 2023          | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| I. G. Zhoukovskaya et al., 2020   | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| Durgarao Y et al., 2019           | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |

|                                    |   |   |   |   |   |   |   |   |   |
|------------------------------------|---|---|---|---|---|---|---|---|---|
| J. H. Mahmoud et al., 2025         | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| Humaira Kauser et al., 2022        | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| Esra Tajik et al., 2020            | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| J. Mitri et al., 2011              | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| A. Pittas et al., 2007             | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| Mitku Mammo Taderegew et al., 2023 | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| Ligia J. Dominguez et al., 2024    | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| Lu Yu et al., 2020                 | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| R. Sakthiswar y et al., 2013       | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| Shamaila Rafiq et al., 2018        | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| W. Mohammedsaeed et al., 2024      | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |

|                              |   |   |   |   |   |   |   |   |   |
|------------------------------|---|---|---|---|---|---|---|---|---|
| Seth I. Sokol et al., 2012   | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| Z. Kamali et al., 2023       | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| E. Jiffri et al., 2018       | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| Johanna Parker et al., 2010  | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| S. Mohamma di et al., 2021   | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| N. F. Maroufi et al., 2020   | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| Lijie Sun et al., 2023       | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| T. Tzotzas et al., 2010      | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| Gaurab Bhaduri et al., 2025  | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| V. Pergialiotis et al., 2017 | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| A. Tremblay et al., 2009     | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| A. Renzaho et al., 2011      | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |

|                                    |   |   |   |   |   |   |   |   |   |
|------------------------------------|---|---|---|---|---|---|---|---|---|
| Zhitong Li et al., 2024            | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| S. Wannamethee et al., 2017        | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| N. Al-Daghri et al., 2018          | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| Tracy S Moreira-Lucas et al., 2016 | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| S. Parizadeh et al., 2019          | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| M. Hosseini et al., 2018           | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| Anuj Maheshwari et al., 2024       | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| O. Tarçın et al., 2009             | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| Ming-Wei Lin et al., 2015          | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| R. Sahebi et al., 2019             | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| G. Grimnes et al., 2011            | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |

|                                            |   |   |   |   |   |   |   |   |   |
|--------------------------------------------|---|---|---|---|---|---|---|---|---|
| Seyed-Amir Tabatabaei zadeh et al., 2020   | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| Ahmed Altayeb Abbas Fadlallah et al., 2024 | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| Hamid Nasri et al., 2014                   | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| B. Núñez-García et al., 2022               | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| Geórgia Rosa Reis de Alencar et al., 2020  | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| Q. Qi et al., 2015                         | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| Dodi Novriadi et al., 2024                 | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| Ji-Chang Zhou et al., 2014                 | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| Fei-fei Han et al., 2017                   | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |
| Zainab Nur-Eldeen Aziz et al., 2024        | ✓ | ✓ | ✓ | ✗ | ✓ | ✗ | ✓ | ✓ | ✓ |

|                                         |  |  |  |  |  |  |  |  |  |
|-----------------------------------------|--|--|--|--|--|--|--|--|--|
| Aboud Al Hayani et al., 2020            |  |  |  |  |  |  |  |  |  |
| F. Qian et al., 2021                    |  |  |  |  |  |  |  |  |  |
| Lucian Batista de Oliveira et al., 2024 |  |  |  |  |  |  |  |  |  |
| M. S. Al-dahr et al., 2020              |  |  |  |  |  |  |  |  |  |
| H. Ahmed et al., 2023                   |  |  |  |  |  |  |  |  |  |
| L. Gabel et al., 2002                   |  |  |  |  |  |  |  |  |  |
| E. Banitalebi et al., 2015              |  |  |  |  |  |  |  |  |  |
| P. V. von Hurst et al., 2009            |  |  |  |  |  |  |  |  |  |
| Elisa Cipponeri et al., 2025            |  |  |  |  |  |  |  |  |  |

## RESULTS

### Characteristics of Included Studies

This systematic review encompasses 80 sources examining the association between vitamin D deficiency and insulin resistance. The included studies represent diverse methodological approaches, population types, and geographic settings.

| Study                                 | Population                      | Sample Size | Geographic Setting |
|---------------------------------------|---------------------------------|-------------|--------------------|
| <b>B. Sowjanya et al., 2017</b>       | Healthy individuals             | 50          | Not specified      |
| <b>T. D. S. Ferreira et al., 2013</b> | Healthy premenopausal women     | 73          | Not specified      |
| <b>Sowjanya Bachali et al., 2012</b>  | Healthy controls, T2DM          | 99          | Not specified      |
| <b>P. Kishore et al., 2017</b>        | T2DM with/without complications | 300         | Not specified      |
| <b>N. Forouhi et al., 2008</b>        | Nondiabetic adults              | 524         | UK                 |
| <b>S. Kayaniyil et al., 2011</b>      | Prediabetic/high risk           | 489         | Canada             |
| <b>Li Li et al., 2016</b>             | Postmenopausal women            | 230         | Not specified      |
| <b>Shamaila Rafiq et al., 2021</b>    | Non-diabetic adults             | 32 studies  | Global             |
| <b>Shamaila Rafiq et al., 2021a</b>   | T2DM and healthy subjects       | 40 studies  | Global             |

| Study                                      | Population                  | Sample Size      | Geographic Setting |
|--------------------------------------------|-----------------------------|------------------|--------------------|
| <b>Mohammad S. Alshahrani et al., 2025</b> | T2DM/prediabetes            | 12,000+          | Not specified      |
| <b>F. Çağlar et al., 2017</b>              | Obese women                 | 31               | Turkey             |
| <b>A. Lizarraga et al., 2021</b>           | PCOS women                  | 100              | Denmark            |
| <b>Chunla He et al., 2015</b>              | Women with PCOS             | 3,182            | Multiple           |
| <b>N. Chandrika et al., 2022</b>           | Healthy young adults        | 55               | India              |
| <b>Cem Ozcan et al., 2023</b>              | Controls, prediabetes, T2DM | 75               | Turkey             |
| <b>S. Pattman et al., 2011</b>             | Obese women, controls       | 69               | Not specified      |
| <b>Muntaha A. Arif et al., 2024</b>        | CAD with/without T2DM       | 190              | Iraq               |
| <b>Xingxing Lei et al., 2023</b>           | T2DM patients               | 12,306           | Not specified      |
| <b>S. Savastano et al., 2013</b>           | Prediabetic individuals     | Not specified    | India              |
| <b>H. Khan et al., 2012</b>                | Healthy adults              | 210,107          | Multiple           |
| <b>Nyein Wint Yee Theik et al., 2021</b>   | Prediabetes/MetS            | Multiple studies | Not specified      |
| <b>Yun-Yi Gao et al., 2018</b>             | Healthy controls            | 490              | China              |
| <b>J. Daniel et al., 2022</b>              | Adolescents                 | 24 studies       | Not specified      |
| <b>Y. Krul-Poel et al., 2013</b>           | Women with PCOS             | Not specified    | Not specified      |

| Study                              | Population                    | Sample Size      | Geographic Setting   |
|------------------------------------|-------------------------------|------------------|----------------------|
| A. Abukanna et al., 2023           | T2DM patients                 | 4,229            | Saudi Arabia         |
| I. G. Zhoukovskaya et al., 2020    | Women                         | 62               | Russia               |
| Durgarao Y et al., 2019            | Not specified                 | Not specified    | Not specified        |
| J. H. Mahmoud et al., 2025         | T2DM, insulin resistant women | 150              | Iraq                 |
| Humaira Kauser et al., 2022        | Adults                        | Multiple studies | Not specified        |
| Esra Tajik et al., 2020            | T2DM patients                 | 11 studies       | Multiple             |
| J. Mitri et al., 2011              | Healthy/T2DM                  | 238,423          | Not specified        |
| A. Pittas et al., 2007             | Adults                        | Not specified    | Not specified        |
| Mitku Mammo Taderegew et al., 2023 | T2DM patients                 | 38,016           | Global               |
| Ligia J. Dominguez et al., 2024    | Older adults                  | 40,664           | Europe/North America |
| Lu Yu et al., 2020                 | Prediabetic individuals       | 3,094            | Not specified        |
| R. Sakthiswary et al., 2013        | SLE patients                  | 37-378           | Multiple             |

| Study                                | Population            | Sample Size      | Geographic Setting |
|--------------------------------------|-----------------------|------------------|--------------------|
| <b>Shamaila Rafiq et al., 2018</b>   | Diabetic/non-diabetic | 71 studies       | 16 countries       |
| <b>W. Mohammedsaeed et al., 2024</b> | T2DM                  | Not specified    | Not specified      |
| <b>Seth I. Sokol et al., 2012</b>    | Older adults          | 55               | Not specified      |
| <b>Z. Kamali et al., 2023</b>        | PCOS women            | 151              | Iran               |
| <b>E. Jiffri et al., 2018</b>        | T2DM patients         | 200              | Saudi Arabia       |
| <b>Johanna Parker et al., 2010</b>   | Middle-age/elderly    | 99,745           | Not specified      |
| <b>S. Mohammadi et al., 2021</b>     | Adults                | Multiple studies | Not specified      |
| <b>N. F. Maroufi et al., 2020</b>    | Female population     | 12 studies       | Not specified      |
| <b>Lijie Sun et al., 2023</b>        | T2DM patients         | 162              | China              |
| <b>T. Tzotzas et al., 2010</b>       | Obese women           | 69               | Not specified      |
| <b>Gaurab Bhaduri et al., 2025</b>   | T2DM patients         | 8,953            | India              |
| <b>V. Pergialiotis et al., 2017</b>  | PCOS women            | Not specified    | Not specified      |
| <b>A. Tremblay et al., 2009</b>      | Not specified         | Not specified    | Not specified      |

| Study                                          | Population           | Sample Size   | Geographic Setting |
|------------------------------------------------|----------------------|---------------|--------------------|
| <b>A. Renzaho et al., 2011</b>                 | Ethnic minorities    | Not specified | Not specified      |
| <b>Zhitong Li et al., 2024</b>                 | T2DM, SCH, MAFLD     | 15,866        | Multiple           |
| <b>S. Wannamethee et al., 2017</b>             | Not specified        | Not specified | Not specified      |
| <b>N. Al-Daghri et al., 2018</b>               | Mixed populations    | Not specified | Saudi Arabia       |
| <b>Tracy S Moreira-Lucas et al., 2016</b>      | At-risk individuals  | Not specified | Not specified      |
| <b>S. Parizadeh et al., 2019</b>               | Liver/kidney disease | Not specified | Iran               |
| <b>M. Hosseini et al., 2018</b>                | T2DM patients        | 187           | Iran               |
| <b>Anuj Maheshwari et al., 2024</b>            | T2DM patients        | 402           | India              |
| <b>O. Tarçin et al., 2009</b>                  | Asymptomatic VDD     | 46            | Turkey             |
| <b>Ming-Wei Lin et al., 2015</b>               | PCOS women           | Not specified | Multiple           |
| <b>R. Sahebi et al., 2019</b>                  | T2DM/GDM             | 37 studies    | Iran               |
| <b>G. Grimnes et al., 2011</b>                 | Healthy individuals  | 160           | Norway             |
| <b>Seyed-Amir Tabatabaeizadeh et al., 2020</b> | Mixed                | 34,882        | Not specified      |

| Study                                             | Population                | Sample Size | Geographic Setting |
|---------------------------------------------------|---------------------------|-------------|--------------------|
| <b>Ahmed Altayeb Abbas Fadlallah et al., 2024</b> | Prediabetes               | 13 studies  | Not specified      |
| <b>Hamid Nasri et al., 2014</b>                   | T2DM patients             | 60          | Not specified      |
| <b>B. Núñez-García et al., 2022</b>               | Healthy adults            | 33          | Not specified      |
| <b>Geórgia Rosa Reis de Alencar et al., 2020</b>  | Obese subjects            | 10 studies  | Not specified      |
| <b>Q. Qi et al., 2015</b>                         | Overweight/obese          | 732         | USA                |
| <b>Dodi Novriadi et al., 2024</b>                 | Prediabetes               | 8 studies   | Not specified      |
| <b>Ji-Chang Zhou et al., 2014</b>                 | Normal-weight/obese males | 181         | China              |
| <b>Fei-fei Han et al., 2017</b>                   | IR-related diseases       | 9,232       | Multiple           |
| <b>Zainab Nur-Eldeen Aziz et al., 2024</b>        | PCOS women                | 50          | Iraq               |
| <b>About Al Hayani et al., 2020</b>               | PCOS women                | 400         | Not specified      |
| <b>F. Qian et al., 2021</b>                       | Prediabetic individuals   | 718         | Not specified      |
| <b>Lucian Batista de Oliveira et al., 2024</b>    | Heart failure patients    | 243         | Brazil             |

| Study                        | Population              | Sample Size | Geographic Setting |
|------------------------------|-------------------------|-------------|--------------------|
| M. S. Al-dahr et al., 2020   | T2DM patients           | 200         | Saudi Arabia       |
| H. Ahmed et al., 2023        | T2DM patients           | 90          | Iraq               |
| L. Gabel et al., 2002        | Postmenopausal women    | 60          | Not specified      |
| E. Banitalebi et al., 2015   | T2DM patients           | 489         | Not specified      |
| P. V. von Hurst et al., 2009 | Insulin-resistant women | 81          | New Zealand        |
| Elisa Cipponeri et al., 2025 | T1DM patients           | 1,536       | USA/Poland         |

The included studies encompass cross-sectional designs (n=24), meta-analyses and systematic reviews (n=35), cohort studies (n=8), randomized controlled trials (n=9), and case-control studies (n=4). Sample sizes ranged from 31 participants in primary studies to over 210,000 participants in pooled meta-analyses. Geographic representation spans Europe, Asia, North America, the Middle East, and South America, with several global meta-analyses incorporating data from multiple continents.

### Vitamin D Assessment Methods

The studies employed various methods for assessing vitamin D status, with considerable heterogeneity in measurement techniques and deficiency thresholds.

| Study | Measurement Method | Units | Deficiency Threshold | Assay Method |
|-------|--------------------|-------|----------------------|--------------|
|-------|--------------------|-------|----------------------|--------------|

| Study                           | Measurement Method   | Units         | Deficiency Threshold   | Assay Method      |
|---------------------------------|----------------------|---------------|------------------------|-------------------|
| B. Sowjanya et al., 2017        | 25(OH)D              | ng/ml         | ≤20 ng/ml              | Not specified     |
| Sowjanya Bachali et al., 2012   | 25(OH)D              | ng/ml         | ≤20 ng/ml              | Not specified     |
| P. Kishore et al., 2017         | 25(OH)D3             | ng/ml         | Not specified          | CLIA              |
| N. Forouhi et al., 2008         | 25(OH)D              | nmol/l        | <25 nmol/l (classical) | RIA               |
| S. Kayaniyil et al., 2011       | 25(OH)D              | nmol/L        | Not specified          | CLIA              |
| F. Çağlar et al., 2017          | 25(OH)D              | ng/mL         | Not specified          | HPLC-MS           |
| Cem Ozcan et al., 2023          | 25(OH)D, 1,25(OH)2D3 | nmol/L, pg/mL | Not specified          | Chronotropic, RIA |
| I. G. Zhoukovskaya et al., 2020 | 25(OH)D              | ng/ml         | <20 ng/ml              | IFA               |
| O. Tarçin et al., 2009          | 25(OH)D              | nmol/liter    | <25 nmol/liter         | HPLC              |

| Study                                   | Measurement Method | Units  | Deficiency Threshold | Assay Method  |
|-----------------------------------------|--------------------|--------|----------------------|---------------|
| G. Grimnes et al., 2011                 | 25(OH)D            | nmol/L | Not defined          | LC-MS/MS      |
| P. V. von Hurst et al., 2009            | 25(OH)D            | nmol/l | <50 nmol/l           | Not specified |
| A. Renzaho et al., 2011                 | 25(OH)D            | nmol/L | <50 nmol/L           | Not specified |
| Lucian Batista de Oliveira et al., 2024 | 25(OH)D            | ng/mL  | <20 ng/mL            | Not specified |

Most studies utilized serum 25-hydroxyvitamin D [25(OH)D] as the primary biomarker of vitamin D status. Assay methods varied considerably and included radioimmunoassay (RIA), chemiluminescence immunoassay (CLIA), high-performance liquid chromatography-mass spectrometry (HPLC-MS), enzyme-linked immunosorbent assay (ELISA), and liquid chromatography-tandem mass spectrometry (LC-MS/MS). Deficiency thresholds ranged from <20 ng/ml to <50 nmol/l, reflecting inconsistency in clinical definitions across the literature.

#### Insulin Resistance Assessment Methods

| Study                          | Primary Method | Threshold     | Other Markers |
|--------------------------------|----------------|---------------|---------------|
| B. Sowjanya et al., 2017       | HOMA-IR        | Not specified | FG, insulin   |
| T. D. S. Ferreira et al., 2013 | HOMA-IR        | Not specified | FG, insulin   |

| Study                                | Primary Method         | Threshold     | Other Markers                       |
|--------------------------------------|------------------------|---------------|-------------------------------------|
| <b>Sowjanya Bachali et al., 2012</b> | HOMA-IR                | Not specified | FBG, fasting insulin                |
| <b>P. Kishore et al., 2017</b>       | HOMA-IR                | Not specified | HbA1c                               |
| <b>N. Forouhi et al., 2008</b>       | HOMA-IR                | Not specified | FG, 2-h glucose, insulin            |
| <b>S. Kayaniyil et al., 2011</b>     | Matsuda index, HOMA-IR | Not specified | FG, insulin                         |
| <b>Cem Ozcan et al., 2023</b>        | HOMA-IR                | Not specified | OGTT glucose at multiple timepoints |
| <b>Z. Kamali et al., 2023</b>        | HOMA-IR                | >2.5          | FG, insulin                         |
| <b>P. V. von Hurst et al., 2009</b>  | HOMA2                  | HOMA1 >1.93   | Fasting insulin                     |
| <b>G. Grimnes et al., 2011</b>       | ISI (clamp), HOMA-IR   | Not specified | FG, insulin, HbA1c                  |
| <b>L. Gabel et al., 2002</b>         | FSIVGTT                | Not specified | FG, fasting insulin                 |
| <b>Zhitong Li et al., 2024</b>       | TyG index              | Not specified | FG, triglycerides                   |
| <b>F. Qian et al., 2021</b>          | IRS                    | Not specified | Insulin, C-peptide, HbA1c           |

The homeostatic model assessment of insulin resistance (HOMA-IR) was the predominant method for quantifying insulin resistance across studies. Alternative methods included the Matsuda

insulin sensitivity index, hyperglycemic clamp technique, frequently sampled intravenous glucose tolerance test, and the triglyceride-glucose (TyG) index. Several studies also assessed related glucose metabolism markers including fasting glucose, fasting insulin, and HbA1c.

### Effects: Association Between Vitamin D Status and Insulin Resistance

#### Correlation Coefficients from Observational Studies

| Study                                | Population           | Correlation (r)  | 95% CI       | P-value      |
|--------------------------------------|----------------------|------------------|--------------|--------------|
| <b>B. Sowjanya et al., 2017</b>      | Healthy individuals  | -0.134           | Not reported | Not reported |
| <b>Sowjanya Bachali et al., 2012</b> | T2DM                 | -0.294           | Not reported | Not reported |
| <b>Li Li et al., 2016</b>            | Postmenopausal women | -0.457           | Not reported | <0.05        |
| <b>F. Çağlar et al., 2017</b>        | Obese women          | -0.456 (HOMA-IR) | Not reported | 0.05         |
| <b>F. Çağlar et al., 2017</b>        | Obese women          | -0.631 (insulin) | Not reported | 0.002        |
| <b>S. Pattman et al., 2011</b>       | Obese women          | -0.43            | Not reported | <0.05        |
| <b>T. Tzotzas et al., 2010</b>       | Obese women          | -0.43            | Not reported | <0.05        |

| Study                      | Population                 | Correlation (r) | 95% CI       | P-value |
|----------------------------|----------------------------|-----------------|--------------|---------|
| Seth I. Sokol et al., 2012 | Older adults (2-h glucose) | -0.34           | Not reported | 0.01    |
| E. Banitalebi et al., 2015 | T2DM                       | -0.37 (HbA1c)   | Not reported | <0.001  |
| E. Banitalebi et al., 2015 | T2DM                       | -0.26 (FBG)     | Not reported | 0.02    |

The majority of observational studies demonstrated inverse correlations between vitamin D levels and insulin resistance measures. Correlation coefficients ranged from weak ( $r = -0.134$ ) to moderate ( $r = -0.631$ ), with most falling in the weak-to-moderate range. The strongest correlations were observed in studies of obese women, where vitamin D levels showed moderate inverse associations with both insulin levels ( $r = -0.631$ ) and HOMA-IR ( $r = -0.456$ ).

### Meta-Analytic Findings

| Meta-Analysis                | Population   | Effect Estimate | 95% CI           | I <sup>2</sup> | P-value |
|------------------------------|--------------|-----------------|------------------|----------------|---------|
| Shamaila Rafiq et al., 2021  | Non-diabetic | $r = -0.217$    | -0.161 to -0.272 | Low            | 0.000   |
| Shamaila Rafiq et al., 2021a | Non-diabetic | $r = -0.188$    | -0.141 to -0.234 | Not quantified | 0.000   |

| Meta-Analysis                       | Population           | Effect Estimate | 95% CI           | I <sup>2</sup> | P-value     |
|-------------------------------------|----------------------|-----------------|------------------|----------------|-------------|
| Shamaila Rafiq et al., 2021a        | Diabetic             | r = -0.255      | -0.392 to -0.107 | Not quantified | 0.001       |
| Mohammad S. Alshahrani et al., 2025 | T2DM/predia betes    | r = -0.18       | -0.29 to -0.08   | 67-97%         | Significant |
| Xingxing Lei et al., 2023           | T2DM (HOMA-IR)       | r = -0.08       | -0.09 to -0.06   | 86.7%          | <0.05       |
| Shamaila Rafiq et al., 2018         | Diabetic             | r = -0.223      | -0.184 to -0.261 | 95.9%          | 0.000       |
| Shamaila Rafiq et al., 2018         | Non-diabetic         | r = -0.073      | -0.052 to -0.093 | 55.5%          | 0.000       |
| Zhitong Li et al., 2024             | Multiple populations | r = -0.236      | -0.310 to -0.159 | 91%            | <0.00001    |

Multiple meta-analyses consistently demonstrated a significant inverse association between vitamin D status and insulin resistance. The pooled correlation coefficients ranged from  $r = -0.073$  in non-diabetic populations to  $r = -0.255$  in diabetic populations, suggesting a stronger association among individuals with established metabolic dysfunction. Notably, the correlation was significantly stronger in diabetic compared to non-diabetic populations ( $r = -0.223$  vs  $r = -0.073$ ), indicating potential effect modification by diabetes status.

### Relative Risk and Odds Ratio Estimates

| Study                           | Outcome                   | Effect Estimate | 95% CI        |
|---------------------------------|---------------------------|-----------------|---------------|
| H. Khan et al., 2012            | IR                        | RR = 0.84       | 0.64-1.12     |
| H. Khan et al., 2012            | T2D                       | RR = 0.81       | Not specified |
| H. Khan et al., 2012            | MetS                      | RR = 0.86       | 0.80-0.92     |
| Johanna Parker et al., 2010     | Cardiometabolic disorders | OR = 0.57       | 0.48-0.68     |
| A. Pittas et al., 2007          | T2DM prevalence           | OR = 0.36       | 0.16-0.80     |
| A. Pittas et al., 2007          | MetS prevalence           | OR = 0.71       | 0.57-0.89     |
| S. Mohammadi et al., 2021       | T2D (prospective)         | RR = 0.65       | 0.55-0.76     |
| S. Mohammadi et al., 2021       | Prediabetes               | RR = 0.49       | 0.26-0.93     |
| Yun-Yi Gao et al., 2018         | Prediabetes               | OR = 3.01       | 1.50-6.06     |
| Yun-Yi Gao et al., 2018         | T2DM                      | OR = 5.61       | 1.73-18.27    |
| Ligia J. Dominguez et al., 2024 | Incident T2DM             | RR = 1.20       | 1.06-1.35     |

| Study                                          | Outcome                | Effect Estimate | 95% CI    |
|------------------------------------------------|------------------------|-----------------|-----------|
| <b>Seyed-Amir Tabatabaeizadeh et al., 2020</b> | T2DM (cross-sectional) | OR = 1.77       | 1.51-2.07 |

Prospective studies and meta-analyses revealed that higher vitamin D levels were associated with significantly reduced risk of developing type 2 diabetes and metabolic syndrome. Individuals in the highest tertile of vitamin D status demonstrated 35% lower risk of developing T2DM (RR = 0.65, 95% CI: 0.55-0.76) and 51% lower risk of prediabetes (RR = 0.49, 95% CI: 0.26-0.93) compared to those in the lowest tertile. A dose-response relationship was observed, with each 10 ng/ml increase in serum vitamin D associated with 12% reduced risk of T2DM (RR = 0.88, 95% CI: 0.83-0.94).

The association between vitamin D deficiency and increased risk of dysglycemia was particularly pronounced in the Chinese cohort study, where low baseline 25(OH)D was associated with over 3-fold increased odds of prediabetes (OR = 3.01) and over 5-fold increased odds of T2DM (OR = 5.61).

#### Mean Differences in Insulin Resistance Measures

| Study                                  | Comparison                     | HOMA-IR Difference | P-value |
|----------------------------------------|--------------------------------|--------------------|---------|
| <b>T. D. S. Ferreira et al., 2013</b>  | VDD vs sufficient              | 6.3±0.7 vs 4.4±0.2 | 0.002   |
| <b>I. G. Zhoukovskaya et al., 2020</b> | VDD vs sufficient (prevalence) | 55.0% vs 13.0%     | <0.001  |
| <b>Xingxing Lei et al., 2023</b>       | Vitamin D supplementation      | SMD = -0.441       | <0.05   |

| Study                   | Comparison                      | HOMA-IR Difference | P-value     |
|-------------------------|---------------------------------|--------------------|-------------|
| J. Daniel et al., 2022  | VDD vs sufficient (adolescents) | SMD = 0.48         | Significant |
| Zhitong Li et al., 2024 | VDD vs no-VDD                   | MD = 0.16          | <0.00001    |

Studies examining mean differences in HOMA-IR between vitamin D deficient and sufficient groups consistently demonstrated higher insulin resistance in those with vitamin D deficiency. In healthy premenopausal women, vitamin D deficiency was associated with significantly higher HOMA-IR values ( $6.3 \pm 0.7$  vs  $4.4 \pm 0.2$ ,  $p=0.002$ ), an association that persisted after adjustment for age and BMI. The prevalence of insulin resistance was four-fold higher among women with vitamin D deficiency compared to those with normal levels (55.0% vs 13.0%,  $p<0.001$ ).

### Effects of Vitamin D Supplementation on Insulin Resistance

| Study                        | Population              | Intervention              | Effect on HOMA-IR       | P-value |
|------------------------------|-------------------------|---------------------------|-------------------------|---------|
| Xingxing Lei et al., 2023    | T2DM                    | Vitamin D supplementation | SMD = -0.441            | <0.05   |
| P. V. von Hurst et al., 2009 | Insulin-resistant women | 4000 IU/d for 6 months    | Significant improvement | 0.02    |
| R. Sahebi et al., 2019       | T2DM                    | Vitamin D supplements     | Improvement             | 0.005   |
| R. Sahebi et al., 2019       | GDM                     | Vitamin D supplements     | Improvement             | 0.028   |

| Study                               | Population               | Intervention                | Effect on HOMA-IR     | P-value     |
|-------------------------------------|--------------------------|-----------------------------|-----------------------|-------------|
| <b>G. Grimnes et al., 2011</b>      | Healthy adults           | 20,000 IU twice weekly      | No significant effect | NS          |
| <b>Anuj Maheshwari et al., 2024</b> | T2DM                     | 60,000 IU/week for 12 weeks | No significant effect | 0.32        |
| <b>J. Mitri et al., 2011</b>        | Glucose intolerant       | Vitamin D supplementation   | Improved IR           | Significant |
| <b>J. Mitri et al., 2011</b>        | Normal glucose tolerance | Vitamin D supplementation   | No effect             | NS          |

Intervention studies examining vitamin D supplementation yielded mixed results. A meta-analysis of 18 RCTs found that vitamin D supplementation significantly improved HOMA-IR in diabetic patients (SMD = -0.441, 95% CI: -0.582 to -0.3,  $p < 0.05$ ). Similarly, supplementation with 4000 IU/day for 6 months significantly improved insulin sensitivity and resistance in insulin-resistant South Asian women ( $p = 0.02$  and  $p = 0.003$ , respectively), with optimal vitamin D concentrations for reducing insulin resistance identified as 80-119 nmol/l.

However, several RCTs failed to demonstrate significant effects. Supplementation with 20,000 IU vitamin D3 twice weekly for 6 months in apparently healthy Norwegian adults with low baseline vitamin D did not significantly improve insulin sensitivity or resistance. Similarly, a large Indian multicenter study found no significant correlation between changes in vitamin D levels and HOMA-IR after 12 weeks of supplementation ( $r^2 = 0.6\%$ ,  $p = 0.32$ ).

The systematic review by Mitri et al. noted that vitamin D supplementation improved insulin resistance in two trials among patients with baseline glucose intolerance, but showed no effect in

eight trials among participants with normal glucose tolerance at baseline, suggesting that baseline metabolic status may influence treatment response.

### Subgroup Analyses by BMI

Several studies examined the modifying effect of body mass index on the vitamin D-insulin resistance association:

| Study                          | BMI Category            | Correlation (r) | 95% CI           |
|--------------------------------|-------------------------|-----------------|------------------|
| Shamaila Rafiq et al.,<br>2021 | <25 kg/m <sup>2</sup>   | -0.150          | -0.204 to -0.095 |
| Shamaila Rafiq et al.,<br>2021 | 25-30 kg/m <sup>2</sup> | -0.221          | -0.315 to -0.122 |
| Shamaila Rafiq et al.,<br>2021 | >30 kg/m <sup>2</sup>   | -0.257          | -0.382 to -0.123 |

The inverse association between vitamin D and insulin resistance strengthened progressively with increasing BMI categories. In normal-weight individuals (BMI <25), the correlation was  $r = -0.150$ , increasing to  $r = -0.221$  in overweight individuals and  $r = -0.257$  in obese individuals. This gradient suggests that obesity may amplify the metabolic consequences of vitamin D deficiency or that shared pathophysiological mechanisms link these conditions.

### Special Populations

#### Polycystic Ovary Syndrome (PCOS)

Women with PCOS demonstrated particularly high rates of vitamin D deficiency (67-85%) and showed inverse correlations between vitamin D levels and metabolic parameters. Meta-analysis revealed that PCOS patients with vitamin D deficiency were more likely to have dysglycemia and increased HOMA-IR compared to those without deficiency. Vitamin D levels were negatively

correlated with FAI, AMH, and HOMA-IR in PCOS women, with 55% of patients meeting criteria for insulin resistance based on HOMA-IR. Supplementation studies in PCOS showed improvement in insulin resistance and androgen indices comparable to metformin treatment.

### **Adolescents**

A meta-analysis of 24 studies in adolescents found that vitamin D deficiency was associated with increased insulin levels (SMD = 0.50, 95% CI: 0.15-0.84) and HOMA index (SMD = 0.48, 95% CI: 0.36-0.60). However, the certainty of evidence was rated as very low.

### **Type 1 Diabetes**

Limited evidence from two studies suggested an inverse relationship between serum 25(OH)D levels and insulin resistance in type 1 diabetes, with adults having 25(OH)D <10 ng/mL demonstrating a four-fold increased risk of insulin resistance. However, the association was attenuated after adjusting for BMI, and the evidence base remains sparse.

### **Heterogeneity and Study Quality Considerations**

Substantial heterogeneity was observed across meta-analyses, with  $I^2$  values ranging from 55.5% to 97%. Sources of heterogeneity included:

- Variability in vitamin D deficiency thresholds across studies
- Differences in assay methods for measuring 25(OH)D
- Population characteristics including ethnicity, geographic location, and baseline metabolic status
- Seasonal variation in vitamin D synthesis
- Concurrent medications and vitamin D supplementation practices

## Synthesis

The evidence consistently demonstrates an inverse association between vitamin D status and insulin resistance across diverse populations and study designs. However, several key distinctions emerge when reconciling the heterogeneous findings.

## Population-Specific Effects

The strength of association varies substantially by metabolic status at baseline. In diabetic populations, the pooled correlation coefficient was  $r = -0.255$ , compared to  $r = -0.188$  in non-diabetic populations. This differential effect suggests that the vitamin D-insulin resistance relationship may be particularly relevant in individuals with established metabolic dysfunction, where multiple pathophysiological pathways may be operative simultaneously. The systematic review by Mitri et al. specifically noted that vitamin D supplementation improved insulin resistance only in trials of patients with baseline glucose intolerance, with no effect observed in those with normal glucose tolerance.

## BMI as an Effect Modifier

The progressive strengthening of the vitamin D-insulin resistance association with increasing BMI ( $r = -0.150$  at BMI  $<25$  to  $r = -0.257$  at BMI  $>30$ ) indicates that obesity amplifies this relationship. This may reflect several mechanisms: (1) sequestration of fat-soluble vitamin D in adipose tissue reducing bioavailability; (2) shared inflammatory pathways linking adiposity, hypovitaminosis D, and insulin resistance; and (3) reduced sun exposure and outdoor physical activity in obese individuals. The attenuation of the vitamin D-insulin resistance association after BMI adjustment in several studies suggests that adiposity may be a key mediating or confounding factor.

## Observational vs. Interventional Evidence Discordance

A notable discordance exists between observational findings and RCT results. While meta-analyses of observational studies consistently demonstrate significant inverse associations, intervention trials have yielded mixed results. The Norwegian RCT found no improvement in

insulin sensitivity despite achieving serum 25(OH)D levels of 142.7 nmol/L with supplementation, while the New Zealand trial in insulin-resistant South Asian women showed significant improvements. This discordance may reflect: (1) differences in baseline vitamin D status and degree of deficiency; (2) population-specific responses based on ethnicity or metabolic status; (3) inadequate supplementation duration in negative trials; or (4) residual confounding in observational studies producing inflated effect estimates.

The cross-sectional meta-analysis by Tabatabaeizadeh et al. demonstrated a significant association (OR = 1.77, 95% CI: 1.51-2.07,  $p < 0.001$ ), whereas the pooled RCT analysis showed no significant effect (HR = 0.89, 95% CI: 0.77-1.02,  $p = 0.08$ ). This pattern suggests that while vitamin D status serves as a marker of metabolic risk, supplementation alone may be insufficient to modify disease trajectories in all populations.

### **Threshold Effects and Dose-Response Relationships**

Evidence suggests a threshold effect for vitamin D's metabolic benefits. The New Zealand trial identified optimal concentrations of 80-119 nmol/l for reducing insulin resistance, and the association appeared strongest when endpoint serum 25(OH)D reached  $\geq 80$  nmol/l. The dose-response meta-analysis by Mohammadi et al. demonstrated that each 10 ng/ml increase in serum vitamin D was associated with 11-12% reduced risk of T2DM and combined T2DM/prediabetes, suggesting a continuous relationship within certain ranges.

### **Mechanistic Considerations**

The plausibility of the vitamin D-insulin resistance association is supported by mechanistic evidence. Vitamin D may affect insulin resistance through: regulation of the renin-angiotensin system; enhancement of insulin receptor expression; protection of pancreatic  $\beta$ -cells; and anti-inflammatory effects reducing cytokines associated with insulin resistance. The presence of vitamin D receptors on pancreatic  $\beta$ -cells and skeletal muscle provides a biological basis for direct effects on glucose homeostasis.

### **Context-Specific Conclusions**

Based on the synthesized evidence:

1. **For healthy individuals:** Vitamin D deficiency is associated with modest increases in insulin resistance ( $r \approx -0.15$  to  $-0.20$ ), but supplementation in those with normal glucose tolerance has not demonstrated consistent benefits.
2. **For individuals with prediabetes or glucose intolerance:** The association is stronger (OR 3-5 for dysglycemia), and supplementation may improve insulin resistance, particularly in those achieving serum levels  $\geq 80$  nmol/l.
3. **For individuals with established diabetes:** The correlation is moderate ( $r \approx -0.22$  to  $-0.26$ ), and vitamin D supplementation has shown more consistent effects on HOMA-IR (SMD = -0.44).
4. **For obese individuals:** The association is amplified ( $r \approx -0.26$ ), and weight loss interventions that increase vitamin D levels correlate with improved insulin resistance ( $r = -0.43$ ).
5. **For PCOS patients:** High prevalence of both conditions and consistent correlations support targeted screening and potential supplementation, though RCT evidence for metabolic improvement remains limited.

The heterogeneity in findings can be substantially explained by baseline metabolic status, degree of vitamin D deficiency, BMI, and ethnicity. The evidence supports maintaining adequate vitamin D status as a component of metabolic health, with supplementation most likely to benefit those with documented deficiency and established metabolic dysfunction.

---

## DISCUSSION

---

The synthesis of evidence from 80 studies provides a comprehensive but complex picture of the relationship between vitamin D deficiency and insulin resistance. The overarching finding is a

consistent inverse association, yet its interpretation requires careful consideration of effect modifiers, study design limitations, and underlying mechanisms.

### **1. Strength and Consistency of the Observational Association**

The observational data is unequivocal: lower serum 25(OH)D levels are associated with higher levels of insulin resistance across a wide range of populations. Correlation coefficients from individual studies, while generally in the weak-to-moderate range (e.g.,  $r = -0.43$  to  $-0.63$  in obese women), point to a biologically plausible link (Çağlar et al., 2017; Tzotzas et al., 2010). This is powerfully reinforced by meta-analytic evidence. Pooled correlations from large meta-analyses, such as those by Rafiq and colleagues, consistently show significant inverse relationships in both diabetic ( $r = -0.255$ ) and non-diabetic populations ( $r = -0.188$ ) (Rafiq & Jeppesen, 2021). The stronger association in diabetic cohorts suggests that in the context of established metabolic dysfunction, the role of vitamin D status—or factors correlated with it—becomes more pronounced.

The data on disease risk is particularly compelling. Prospective studies and dose-response meta-analyses indicate that individuals with higher vitamin D levels have a substantially lower risk of developing T2DM and prediabetes. The risk reduction reported by Mohammadi et al. (2021)—35% for T2DM and 51% for prediabetes per highest vs. lowest tertile of vitamin D—and the striking odds ratios from the Chinese cohort study ( $OR=5.61$  for T2DM) underscore the potential public health significance of this association (Gao et al., 2018; Mohammadi et al., 2021). This graded, dose-response relationship strengthens the argument against the association being purely due to chance.

### **2. Critical Role of Effect Modifiers: BMI and Baseline Metabolic Status**

A pivotal insight from this review is that the vitamin D-insulin resistance association is not uniform; it is significantly modified by adiposity and baseline glucose metabolism.

- **BMI as an Amplifier and Potential Confounder:** The progressive strengthening of the inverse correlation with increasing BMI categories (from  $r = -0.150$  in normal weight to  $r = -0.257$  in obesity) is a critical finding (Rafiq & Jeppesen, 2021). This gradient suggests several interconnected possibilities. First, obesity may directly cause both vitamin D deficiency (through sequestration in adipose tissue and reduced bioavailability) and insulin resistance, making it a powerful confounder (Renzaho et al., 2011). Second, shared pathophysiological pathways, such as chronic inflammation (elevated  $\text{TNF-}\alpha$ , IL-6) and oxidative stress, may simultaneously drive adiposity, lower vitamin D, and impair insulin signaling (Geórgia Rosa Reis de Alencar et al., 2020). Third, lifestyle factors (reduced outdoor activity, dietary patterns) common in obesity could independently contribute to both conditions. The fact that adjustment for BMI often attenuates the association in some studies supports its central role (Cipponeri et al., 2025).
- **Metabolic Status Dictates Responsiveness:** The most compelling explanation for the discordance in the literature lies in baseline metabolic health. The systematic review by Mitri et al. (2011) astutely observed that vitamin D supplementation improved insulin resistance in trials involving individuals with baseline glucose intolerance but showed no effect in those with normal glucose tolerance. This pattern is echoed in other RCTs (von Hurst et al., 2009; Grimnes et al., 2011). This suggests that vitamin D supplementation may be conditionally beneficial, acting as a "correction" in a system already under metabolic stress (e.g., compromised  $\beta$ -cell function, heightened inflammation), rather than as an enhancer of an already optimal metabolic state. This has profound clinical implications, directing potential supplementation benefits toward populations with prediabetes or early T2DM.

### 3. Reconciling Observational and Interventional Evidence: Causality vs. Confounding

The stark contrast between consistent observational associations and mixed RCT results represents the core challenge in this field. The cross-sectional meta-analysis by Tabatabaeizadeh et

al. (2020) found a significant association (OR=1.77), while pooled RCT analyses often show non-significant effects. Several factors may explain this discordance:

1. **Residual Confounding:** Observational studies, despite statistical adjustments, cannot fully account for all lifestyle, dietary, and environmental factors linked to both vitamin D status (e.g., sun exposure, physical activity, overall diet quality) and insulin sensitivity. Vitamin D may thus be a robust marker of a health-conscious lifestyle and favorable adiposity profile, rather than a direct causative agent.
2. **Threshold and Dosage:** There may be a therapeutic threshold for vitamin D's metabolic effects. The trial by von Hurst et al. (2009) identified optimal concentrations of 80-119 nmol/L. Many negative RCTs may have either included participants without severe deficiency, used insufficient doses, or had insufficient duration to reach and sustain this optimal range in target tissues.
3. **Population Selection:** RCTs often have strict inclusion/exclusion criteria that may create a study population not representative of those in observational studies where the association is strongest. Furthermore, as noted, enrolling participants without underlying metabolic risk may dilute any potential treatment effect.
4. **Mechanistic Pathways:** Vitamin D's effect on insulin sensitivity may be indirect and slow, mediated through long-term modulation of inflammation, endothelial function, or gene expression, which may not be captured in short-term RCTs primarily measuring HOMA-IR (Sokol et al., 2012).

#### 4. Insights from Special Populations

- **Polycystic Ovary Syndrome (PCOS):** The evidence in PCOS is striking, showing a high co-prevalence of vitamin D deficiency and insulin resistance (He et al., 2015). The negative correlations with HOMA-IR and androgen indices suggest a intertwined pathophysiology.

Vitamin D may influence the metabolic and hormonal axes of PCOS through similar anti-inflammatory and insulin-sensitizing mechanisms (Lizarraga et al., 2021). While supplementation studies show promise, comparing effects to metformin, more robust RCTs are needed to solidify its role as a standard adjuvant therapy (Pergialiotis et al., 2017; Aziz et al., 2024).

- **Adolescents and Type 1 Diabetes:** The association in adolescents, though present, is based on very low-certainty evidence, highlighting a need for more rigorous longitudinal studies in this age group (Daniel et al., 2022). In type 1 diabetes, the evidence is sparse and the association appears heavily confounded by BMI, suggesting any direct link is less clear than in type 2 diabetes (Cipponeri et al., 2025).

## 5. Methodological Heterogeneity and Limitations

The substantial statistical heterogeneity ( $I^2$  up to 97%) in meta-analyses is a major limitation, reflecting real clinical and methodological diversity (Lei et al., 2023; Li et al., 2024). The lack of standardized 25(OH)D assay methods (CLIA, LC-MS/MS, RIA) and varying deficiency thresholds (<20 ng/mL vs. <50 nmol/L) complicates direct comparison and pooled estimation. Similarly, while HOMA-IR is the predominant tool, its limitations are well-known, and studies using gold-standard clamp techniques are fewer. Future research must strive for standardized definitions and methodologies.

## 6. Biological Plausibility and Contextual Conclusion

The biological plausibility for the association is well-established. Vitamin D receptors (VDR) are present in insulin-responsive tissues. Vitamin D is thought to enhance insulin sensitivity by: (1) activating VDR to upregulate insulin receptor expression; (2) regulating extracellular calcium influx, crucial for insulin-mediated intracellular processes; (3) exerting potent anti-inflammatory effects, reducing cytokines like TNF- $\alpha$  that interfere with insulin signaling; and (4) directly modulating pancreatic  $\beta$ -cell function and survival (Grimnes et al., 2011; Han et al., 2017).

The weight of evidence supports that vitamin D deficiency is a significant correlate and potential modifiable risk factor for insulin resistance, but its role is context-dependent. It is most strongly associated with, and may be most therapeutically relevant for, insulin resistance in the setting of **obesity, prediabetes, and established type 2 diabetes**. The evidence suggests that maintaining sufficient vitamin D status (possibly >30 ng/mL or 75 nmol/L) is a prudent component of metabolic health management. However, universal supplementation for the prevention of insulin resistance in otherwise healthy, vitamin D-sufficient individuals is not supported by current RCT evidence. The optimal approach appears to be targeted screening and treatment of deficiency in high-risk metabolic populations, ideally integrated with lifestyle interventions aimed at weight management and improved dietary quality.

---

## CONCLUSION AND RECOMMENDATIONS

---

### Conclusion

This comprehensive systematic review confirms a significant and consistent inverse association between vitamin D deficiency and insulin resistance across diverse global populations. The strength of this association is modified by key factors: it is stronger in individuals with type 2 diabetes compared to non-diabetic individuals, amplifies with increasing body mass index (BMI), and is particularly pronounced in conditions like Polycystic Ovary Syndrome (PCOS). Prospective evidence indicates that adequate vitamin D status is associated with a substantially reduced risk of developing prediabetes and type 2 diabetes.

However, a critical distinction must be made between association and causation. The discordance between strong observational links and the mixed results from vitamin D supplementation trials suggests that while low vitamin D is a robust biomarker of increased metabolic risk, directly correcting deficiency through supplementation alone does not uniformly improve insulin resistance. The benefits of supplementation appear most consistent and clinically

meaningful in individuals who have both significant vitamin D deficiency *and* pre-existing metabolic dysregulation, such as glucose intolerance or early type 2 diabetes.

## Recommendations

### 1. Clinical Practice:

- **Screening:** Consider screening for vitamin D deficiency in high-risk populations for insulin resistance, including individuals with obesity (BMI  $\geq 30$  kg/m<sup>2</sup>), prediabetes, type 2 diabetes, and PCOS (Abukanna et al., 2023; He et al., 2015).
- **Supplementation Strategy:** For patients with documented vitamin D deficiency (<20 ng/mL or <50 nmol/L) *and* concomitant insulin resistance/prediabetes/T2DM, vitamin D supplementation is recommended to achieve and maintain sufficient levels (e.g., >30 ng/mL). The goal should be to reach a target range (e.g., 80-119 nmol/L) where metabolic benefits have been observed (von Hurst et al., 2009).
- **Holistic Management:** Vitamin D supplementation should not be viewed as a standalone treatment for insulin resistance. It should be integrated into a comprehensive management plan that includes evidence-based lifestyle interventions: weight loss for overweight/obese individuals, regular physical activity, and a balanced diet.

### 2. Public Health:

- Promote sensible sun exposure and consumption of vitamin D-rich or fortified foods as part of a general strategy to improve population vitamin D status and overall metabolic health.
- Public health guidelines should emphasize the importance of addressing obesity, as it is a major driver of both vitamin D deficiency and insulin resistance.

### 3. Future Research:

- **Standardization:** Future studies must adopt standardized definitions for vitamin D deficiency and use consistent, high-quality assay methods (e.g., LC-MS/MS) to reduce heterogeneity.
- **Precision Nutrition Trials:** Conduct large, long-term, well-designed RCTs focused specifically on populations with both confirmed vitamin D deficiency and impaired glucose metabolism (prediabetes/early T2DM). These trials should use adequate doses to achieve target serum levels and assess hard glycemic endpoints.
- **Mechanistic Studies:** Investigate the molecular and genetic interfaces, such as VDR polymorphisms, that may determine individual responsiveness to vitamin D regarding insulin sensitivity (Núñez-García et al., 2022).
- **Special Populations:** More high-quality research is needed to elucidate the role of vitamin D in adolescents, different ethnic groups, and in type 1 diabetes-related insulin resistance.

---

## REFERENCES

---

- A. Abukanna, Reem Falah A Alanazi, Fatimah Alruwaili, Asma Zaid M Alayyashi, and Farah Alanzi. "Vitamin D Deficiency as a Risk Factor for Diabetes and Poor Glycemic Control in Saudi Arabia: A Systematic Review." *Cureus*, 2023.
- A. Lizarraga, S. Lindenberg, G. Almind, and F. Lindenberg. "P-662 Study on D-Vitamin, AMH and Insulin Interrelation in Polycystic Ovary Syndrome (PCOS) Patients." *Human Reproduction*, 2021.
- A. Pittas, J. Lau, F. Hu, and B. Dawson-Hughes. "The Role of Vitamin D and Calcium in Type 2 Diabetes. A Systematic Review and Meta-Analysis." *Journal of Clinical Endocrinology and Metabolism*, 2007.

- A. Renzaho, J. Halliday, and C. Nowson. "Vitamin D, Obesity, and Obesity-Related Chronic Disease Among Ethnic Minorities: A Systematic Review." *Nutrition (Burbank, Los Angeles County, Calif.)*, 2011.
- A. Tremblay, and Jo-Anne Gilbert. "Milk Products, Insulin Resistance Syndrome and Type 2 Diabetes." *Journal of the American College of Nutrition*, 2009.
- About Al Hayani, and Ahlam Nasir. "Effect of Vitamin D Supplementation on Ovulation Among Women with PCO." *The Medical Journal of Cairo University*, 2020.
- Ahmed Altayeb Abbas Fadlallah, Miska Haroun Mohamed Hassan, Salma Farah, Solar Eltayeb Mohamed Gaffar, Ashraf Hayder Mahgoub Ali, Hasna Salem Alzahrani, Amirah Hassan Alhadhrami, and Fahad Salem M Alqahtani. "Evaluating the Effect of Vitamin D Supplementation on Type 2 Diabetes Risk: A Systematic Review." *Cureus*, 2024.
- Anuj Maheshwari, Ajoy Tewari, and V. Chavda. "635-P: Impact of Vitamin D Supplementation on Insulin Resistance Amongst People with Type 2 Diabetes in India." *Diabetes*, 2024.
- B. Núñez-García, J. Maldonado-Hernández, N. Álvarez-Licon, María Elizabeth Tejero-Barrera, M. Bernabe-García, Alva Belen Morales-Villar, Leticia Sebastián-Medina, M. Piña-Aguero, and J. M. Domínguez-Salgado. "FokI Polymorphism of the Vitamin D Receptor Is Closely Related to a Reduced Insulin Sensitivity in Healthy Adults." *Clinical Nutrition Open Science*, 2022.
- B. Sowjanya. "Vitamin D Status, Insulin Resistance and Arterial Stiffness in Normal Healthy Subjects," 2017.
- Cem Ozcan, D. Çorapçıoğlu, and E. Cerit. "Relationship Between Vitamin D Levels and  $\beta$  Cell Function and Insulin Resistance." *Cureus*, 2023.
- Chunla He, Zhoumeng Lin, S. Robb, and A. Ezeamama. "Serum Vitamin D Levels and Polycystic Ovary Syndrome: A Systematic Review and Meta-Analysis." *Nutrients*, 2015.

Dodi Novriadi, and Woris Christoper. “The Analysis Study of The Effect Vitamin D to Risk for Type 2 Diabetes Mellitus in People with Pre-Diabetes : A Comprehensive Systematic Review.” *International Journal of Medical Science and Health Research*, 2024.

Durgarao Y, P. Manjrekar, P. Adhikari, Chakrapani M, and Rukmini Ms. “Comprehensive Review on Diabetes Associated Cardiovascular Complications - The Vitamin D Perspective.” *Cardiovascular & Haematological Disorders - Drug Targets*, 2019.

E. Banitalebi, A. Hoseinzadeh, Zahra Mardanpour-Shahrekordi, and S. Amani-shalamzari. “Effect of Three Methods of Combined Training (Strength and Endurance) on Serum Adiponectin Levels and Insulin Resistance in Overweight Elderly Women,” 2015.

E. Jiffri. “Relationship Between Serum Vitamin D, Adipokines and Dyslipidemia in Type 2 Diabetes Mellitus,” 2018.

Elisa Cipponeri, M. G. Tarsitano, Elisabetta Falbo, and Caterina Conte. “Insulin Resistance in Type 1 Diabetes: Is There a Role for Vitamin D? A Systematic Review of the Evidence.” *Discover Endocrinology and Metabolism*, 2025.

Esra Tajik, and Fatemeh Amirasgari. “Effect of Vitamin D on Glucose Homeostasis and Insulin Sensitivity and Resistance in Type 2 Diabetes: A Systematic Review,” 2020.

F. Çağlar, N. Isıksacan, Nursel Kocamaz, and F. Akturk. “The Association Among Vitamin D, Insulin Resistance, and Obesity in Turkish Women,” 2017.

F. Qian, Yanjun Guo, Heike Gibson, Natalya Gomelskaya, Yanyan Liu, Olga V. Demler, N. Cook, et al. “Abstract 11848: Biomarkers of Glucose-Insulin Homeostasis, Randomized Treatment With Omega-3 and Vitamin D Supplementation, and Incident Type 2 Diabetes: Prospective Analysis From the Vitamin D and Omega-3 Trial (VITAL).” *Circulation*, 2021.

Fei-fei Han, Yali Lv, Li-li Gong, He Liu, Zi-rui Wan, and Lihong Liu. “VDR Gene Variation and Insulin Resistance Related Diseases.” *Lipids in Health and Disease*, 2017.

G. Grimnes, Y. Figenschau, B. Almås, and R. Jorde. “Vitamin D, Insulin Secretion, Sensitivity, and Lipids.” *Diabetes*, 2011.

Gaurab Bhaduri, S. Samajdar, Subhro Chakraborty, Banshi Saboo, and Shashank R. Joshi. “Prevalence and Risk Factors of Hypovitaminosis D Among Patients with Diabetes Mellitus from India: A Systematic Review and Meta-Analysis.” *Diabetes & Metabolic Syndrome*, 2025.

Geórgia Rosa Reis de Alencar, Lailton da Silva Freire, B. M. C. Pereira, Verbena R. da Silva, Aline Cronemberger Holanda, R. C. D. Moura, J. S. Severo, et al. “Effects of Vitamin D Status on Inflammatory Markers in Obese Subjects: A Systematic Review,” 2020.

H. Ahmed, N. N. Hilal, and Mohamed Ghalib Zakari. “Evaluation of Vitamin D in Patients with Type 2 Diabetes Mellites.” *South Asian Research Journal of Pharmaceutical Sciences*, 2023.

H. Khan, S. Kunutsor, O. Franco, and Rajiv Chowdhury. “Vitamin D, Type 2 Diabetes and Other Metabolic Outcomes: A Systematic Review and Meta-Analysis of Prospective Studies.” *Proceedings of the Nutrition Society*, 2012.

Hamid Nasri, and M. Rafieian-kopaei. “Effect of Vitamin D on Insulin Resistance and Nephropathy in Type 2 Diabetes.” *Journal of Research in Medical Sciences*, 2014.

Humaira Kauser, Jaimee J Palakeel, Mazin Ali, Phani Chaduvula, Sanika Chhabra, Smriti Lamsal Lamichhane, Vaiishnavi Ramesh, et al. “Factors Showing the Growing Relation Between Vitamin D, Metabolic Syndrome, and Obesity in the Adult Population: A Systematic Review.” *Cureus*, 2022.

I. G. Zhoukovskaya, and I. R. Yakupova. “Effect of Vitamin D on Women’s Somatic and Reproductive Health.” *Medical Council*, 2020.

J. Daniel, Priscila Ribas de Farias Costa, Marcos Pereira, and A. M. Oliveira. “Vitamin D Deficiency and Cardiometabolic Risk Factors in Adolescents: Systematic Review and Meta-Analysis.” *Reviews in Endocrine & Metabolic Disorders*, 2022.

J. H. Mahmoud, and Iktifaa Abdul Hamid Muhammad. “Study of Concentrations of Some Vitamins in Women with Type 2 Diabetes and Insulin Resistance.” *Journal Port Science Research*, 2025.

J. Mitri, M. Muraru, and A. Pittas. “Vitamin D and Type 2 Diabetes: A Systematic Review.” *European Journal of Clinical Nutrition*, 2011.

Ji-Chang Zhou, Yu-mei Zhu, Zheng Chen, Jun-Luan Mo, Feng-Zhu Xie, Ying-Hong Wen, P. Guo, et al. “Oral Vitamin D Supplementation Has a Lower Bioavailability and Reduces Hypersecretion of Parathyroid Hormone and Insulin Resistance in Obese Chinese Males.” *Public Health Nutrition*, 2014.

Johanna Parker, Omar Hashmi, D. Dutton, A. Mavrodaris, S. Stranges, N. Kandala, A. Clarke, and O. Franco. “Levels of Vitamin D and Cardiometabolic Disorders: Systematic Review and Meta-Analysis.” *Maturitas*, 2010.

L. Gabel, Michael D. Brown, R. Ferrell, M. Korytkowski, J. Zmuda, S. D. McCole, and J. Hagberg. “VITAMIN D RECEPTOR GENOTYPE AND INSULIN SENSITIVITY IN POSTMENOPAUSAL WOMEN OF VARIOUS PHYSICAL ACTIVITY LEVELS,” 2002.

Li Li, and Xiao-hong Niu. “Correlation Study Between Vitamin D Level and Glucose Metabolism, Lipid Metabolism, Insulin Resistance, Early Secretory Function of Pancreatic Islets in Postmenopausal Women with Type 2 Diabetes,” 2016.

Ligia J. Dominguez, Nicola Veronese, Eliana Marrone, Carla Di Palermo, Candela Iommi, Rosaria Ruggirello, Carla Caffarelli, S. Gonnelli, and M. Barbagallo. “Vitamin D and Risk of Incident Type 2 Diabetes in Older Adults: An Updated Systematic Review and Meta-Analysis.” *Nutrients*, 2024.

Lijie Sun, Ji-Xuan Lu, Xinyou Li, Tian-Sheng Zheng, and Xiao-rong Zhan. “Effects of Vitamin D Supplementation on Glucose and Lipid Metabolism in Patients with Type 2 Diabetes Mellitus and Risk Factors for Insulin Resistance.” *World Journal of Diabetes*, 2023.

Lu Yu, Yu Zhai, and S. Shen. “Association Between Vitamin D and Prediabetes.” *Medicine*, 2020.

Lucian Batista de Oliveira, Mariana Andrade de Figueiredo Martins Siqueira, Rafael Buarque de Macedo Gadêlha, Jessica Garcia, and Francisco Bandeira. "Vitamin D Deficiency in Patients Hospitalized for Heart Failure Living in the Tropics." *International Journal of Heart Failure*, 2024.

M. Hosseini, Mohammad Javad Bahoosh, G. Alishiri, N. Khalili, and Habib Yaribeygi. "The Effects of Plasma Levels of Vitamin D3 on Insulin Resistance and Biochemical Factors of Plasma in Patients with Type 2 Diabetes," 2018.

M. S. Al-dahr. "Relation Between 25-Hydroxyvitamin D, Systemic Inflammation and Endothelial Function Biomarkers in Diabetic Nephropathy." *Gastroenterology: Medicine & Research*, 2020.

Ming-Wei Lin, and Meng-Hsing Wu. "The Role of Vitamin D in Polycystic Ovary Syndrome." *The Indian Journal of Medical Research*, 2015.

Mitku Mammo Taderegew, G. Woldeamanuel, Alemayehu Wondie, Atsede Getawey, Abera Nesiru Abegaz, and Fentahun Adane. "Vitamin D Deficiency and Its Associated Factors Among Patients with Type 2 Diabetes Mellitus: A Systematic Review and Meta-Analysis." *BMJ Open*, 2023.

Mohammad S. Alshahrani, Mohammed Ahmed Alqahtani, H. A. Alabdullah, Hamoud Meshal Alshammari, Reem Jaber Suhluli, Ahmed Ghali Aladhab, Jafar Radhi Albu Mijdad, et al. "The Association Between Vitamin D Deficiency and Insulin Resistance in Patients with Type 2 Diabetes: A Meta-Analysis." *Journal of Posthumanism*, 2025.

Muntaha A. Arif, Manal K. Rasheed, and Ammar A. Ismaeel. "Study Some Biochemical Parameters in Patients with Coronary Artery Disease with and Without Type 2 Diabetes." *Journal of the Faculty of Medicine Baghdad*, 2024.

N. Al-Daghri. "Vitamin D in Saudi Arabia: Prevalence,distribution and Disease Associations." *Journal of Steroid Biochemistry and Molecular Biology*, 2018.

N. Chandrika, Usha Smr, and Victoria Kshetrimayum. “25-Hydroxycholecalciferol Levels and Its Equation with Lipid Parameters and Insulin Sensitivity in Obese and Non-Obese Young Adults: A Pilot Study.” *Perspectives In Medical Research*, 2022.

N. F. Maroufi, Pourya Pezeshgi, Zohreh Mortezaia, Pirouz Pourmohammad, Reyhaneh Eftekhari, Mahmood Moradzadeh, Vahid Vahedian, and M. Nouri. “Association Between Vitamin D Deficiency and Prevalence of Metabolic Syndrome in Female Population: A Systematic Review.” *Hormone Molecular Biology and Clinical Investigation*, 2020.

N. Forouhi, J. Luan, A. Cooper, B. Boucher, and N. Wareham. “Baseline Serum 25-Hydroxy Vitamin D Is Predictive of Future Glycemic Status and Insulin Resistance.” *Diabetes*, 2008.

Nyein Wint Yee Theik, Oluwatimilehin E Raji, Priya Shenwai, Rutul Shah, Sahithi Reddy Kalluri, T. Bhutta, Hanan Hannoodde, Mahmoud Al Khalili, and Safeera Khan. “Relationship and Effects of Vitamin D on Metabolic Syndrome: A Systematic Review.” *Cureus*, 2021.

O. Tarçın, D. Yavuz, B. Ozben, A. Telli, A. V. Ogunc, Meral Yüksel, A. Toprak, et al. “Effect of Vitamin D Deficiency and Replacement on Endothelial Function in Asymptomatic Subjects.” *Journal of Clinical Endocrinology and Metabolism*, 2009.

P. Kishore, I. Choudhary, P. Satyanarayana, and U. Singh. “Association of Vitamin D with Insulin Resistance in Type 2 Diabetic Mellitus Patients,” 2017.

P. V. von Hurst, W. Stonehouse, and J. Coad. “Vitamin D Supplementation Reduces Insulin Resistance in South Asian Women Living in New Zealand Who Are Insulin Resistant and Vitamin D Deficient – a Randomised, Placebo-Controlled Trial.” *British Journal of Nutrition*, 2009.

Q. Qi, Yan Zheng, Tao Huang, J. Rood, G. Bray, F. Sacks, and L. Qi. “Vitamin D Metabolism-Related Genetic Variants, Dietary Protein Intake and Improvement of Insulin Resistance in a 2 Year Weight-Loss Trial: POUNDS Lost.” *Diabetologia*, 2015.

- R. Sahebi, M. Rezayi, Maryam Emadzadeh, M. Salehi, Maryam Tayefi, S. Parizadeh, Negin Behboodi, et al. "The Effects of Vitamin D Supplementation on Indices of Glycemic Control in Iranian Diabetics: A Systematic Review and Meta-Analysis." *Complementary Therapies in Clinical Practice*, 2019.
- R. Sakthiswary, and A. Raymond. "The Clinical Significance of Vitamin D in Systemic Lupus Erythematosus: A Systematic Review." *PLoS ONE*, 2013.
- S. Kayaniyil, R. Retnakaran, S. Harris, R. Vieth, J. Knight, H. Gerstein, B. Perkins, B. Zinman, and A. Hanley. "Prospective Associations of Vitamin D With  $\beta$ -Cell Function and Glycemia." *Diabetes*, 2011.
- S. Mohammadi, Zahra Hajhashemy, and P. Saneei. "Serum Vitamin D Levels in Relation to Type-2 Diabetes and Prediabetes in Adults: A Systematic Review and Dose-Response Meta-Analysis of Epidemiologic Studies." *Critical Reviews in Food Science and Nutrition*, 2021.
- S. Parizadeh, M. Rezayi, Reza Jafarzadeh-Esfehani, A. Avan, H. Ghazizadeh, Maryam Emadzadeh, R. Sahebi, G. Ferns, and M. Ghayour-Mobarhan. "Association of Vitamin D Status With Liver and Kidney Disease: A Systematic Review of Clinical Trials, and Cross-Sectional and Cohort Studies." *International Journal for Vitamin and Nutrition Research. Internationale Zeitschrift Fur Vitamin-Und Ernährungsforschung. Journal International de Vitaminologie Et de Nutrition*, 2019.
- S. Pattman. "Rising Serum 25-Hydroxy-Vitamin D Levels After Weight Loss in Obese Women Correlate with Improvement in Insulin Resistance," 2011.
- S. Savastano, C. Somma, and A. Colao. "Vitamin-D & Prediabetes: A Promising Ménage in the Indian Scenario." *The Indian Journal of Medical Research*, 2013.
- S. Wannamethee. "6. Vitamin D and Cardiovascular Disease and Heart Failure Prevention," 2017.

Seth I. Sokol, Michael Grushko, V. Srinivas, and J. Crandall. "Relationship Between Vitamin D Deficiency, Post-challenge Hyperglycemia, and Endothelial Function in Healthy Older Adults." *Journal of Diabetes*, 2012.

Seyed-Amir Tabatabaeizadeh, and Niayesh Tafazoli. "The Role of Vitamin D in Prevention of Type 2 Diabetes. A Meta-Analysis." *Clinical Nutrition ESPEN*, 2020.

Shamaila Rafiq, and P. Jeppesen. "Insulin Resistance Is Inversely Associated with the Status of Vitamin D in Both Diabetic and Non-Diabetic Populations." *Nutrients*, 2021.

———. "Is Hypovitaminosis D Related to Incidence of Type 2 Diabetes and High Fasting Glucose Level in Healthy Subjects: A Systematic Review and Meta-Analysis of Observational Studies." *Nutrients*, 2018.

———. "Vitamin D Deficiency Is Inversely Associated with Homeostatic Model Assessment of Insulin Resistance." *Nutrients*, 2021.

Sowjanya Bachali, bullet K Dasu, bullet K Ramalingam, and B. N. Naidu. "Vitamin D Deficiency and Insulin Resistance in Normal and Type 2 Diabetes Subjects." *Indian Journal of Clinical Biochemistry*, 2012.

T. D. S. Ferreira, Márcia Regina Simas Gonçalves Torres, D. Valença, M. D. Rodrigues, J. Neto, R. Marques, Jeanny dos Santos, N. F. Gomes, and A. F. Sanjuliani. "Abstract 526: Serum Levels of 25 Hydroxyvitamin D and Its Association With Body Fat, Metabolic Profile, Inflammatory Biomarkers, Blood Pressure and Endothelial Function," 2013.

T. Tzotzas, F. Papadopoulou, K. Tziomalos, S. Karras, Kostantinos Gastaris, P. Perros, and G. Krassas. "Rising Serum 25-Hydroxy-Vitamin D Levels After Weight Loss in Obese Women Correlate with Improvement in Insulin Resistance." *Journal of Clinical Endocrinology and Metabolism*, 2010.

Tracy S Moreira-Lucas, A. Duncan, R. Rabasa-Lhoret, R. Vieth, A. Gibbs, A. Badawi, and T. Wolever. “Effect of Vitamin D Fortified Cheese on Oral Glucose Tolerance in Individuals Exhibiting Marginal Vitamin D Status and an Increased Risk for Developing Type 2 Diabetes: A Double-Blind, Randomized Placebo-Controlled Clinical Trial.” *The FASEB Journal*, 2016.

V. Pergialiotis, N. Karampetsou, P. Panagopoulos, E. Trakakis, and N. Papantoniou. “The Effect of Vitamin D Supplementation on Hormonal and Glycaemic Profile of Patients with PCOS: A Meta-analysis of Randomised Trials.” *International Journal of Clinical Practice*, 2017.

W. Mohammedsaeed. “Exploring the Interplay Between DHCR7, Vitamin D Deficiency, and Type 2 Diabetes Mellitus (T2DM): A Systematic Review.” *Molecular Biology Reports*, 2024.

Xingxing Lei, Qian-yi Zhou, Yan-mei Wang, Shunlian Fu, Zinan Li, and Qiu Chen. “Serum and Supplemental Vitamin D Levels and Insulin Resistance in T2DM Populations: A Meta-Analysis and Systematic Review.” *Scientific Reports*, 2023.

Y. Krul-Poel, Chantal Snackey, Y. Louwers, Paul Lips, C. B. Lambalk, J. Laven, and Suat Simsek. “The Role of Vitamin D in Metabolic Disturbances in Polycystic Ovary Syndrome: A Systematic Review.” *European Journal of Endocrinology*, 2013.

Yun-Yi Gao, T. Zheng, X. Ran, Yan Ren, Tao Chen, L. Zhong, Donge Yan, Fangfang Yan, Qianlin Wu, and H. Tian. “Vitamin D and Incidence of Prediabetes or Type 2 Diabetes: A Four-Year Follow-Up Community-Based Study.” *Disease Markers*, 2018.

Z. Kamali, S. Ziaei, A. Kazemnejad, and Maryam Movahedinejad. “The Relationship Between Insulin Resistance and Micronutrient Intake in Polycystic Ovary Syndrome Subgroups.” *Journal of Nutrition and Food Security*, 2023.

Zainab Nur-Eldeen Aziz, Basil O. Saleh, and Ansam Zeki Thaker. “Free Testosterone, Dihydrotestosterone, and Adiponectin in the Evaluation of Vitamin D Supplementation for

Polycystic Ovarian Syndrome: A Metformin Comparative Study.” *AL-Kindy College Medical Journal*, 2024.

Zhitong Li, Shiwei Liu, Xingyu Li, Jinchang Liu, Xin Li, Yuxiang Zhao, and Yongliang Feng. “The Association Between the Triglyceride-Glucose Index and Vitamin D Status: A Systematic Review and Meta-Analysis.” *BMC Endocrine Disorders*, 2024.