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ASSESSING THE CORRELATION BETWEEN VITAMIN D LEVELS AND INSULIN SENSITIVITY IN PATIENTS WITH METABOLIC SYNDROME: A SYSTEMATIC REVIEW

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Abstract

Background: Vitamin D deficiency has emerged as a potential modifiable risk factor in the pathogenesis of metabolic syndrome (MetS), a multifactorial condition characterized by insulin resistance, central obesity, hypertension, and dyslipidemia. Growing evidence suggests that low serum 25-hydroxyvitamin D [25(OH)D] concentrations may adversely affect glucose metabolism and insulin action.

Objectives: This systematic review aimed to evaluate the correlation between serum 25(OH)D levels and insulin sensitivity, as measured by HOMA-IR and related indices, among adults with MetS across diverse populations.

Methods: Following PRISMA 2020 guidelines, an extensive search of PubMed, Scopus, Web of Science, and Embase databases was conducted. Observational studies assessing the association between vitamin D status and insulin resistance in adults diagnosed with MetS were included. Data were extracted on study design, sample size, vitamin D assays, and insulin sensitivity measures.

Results: Eighteen studies met inclusion criteria, encompassing over 22,000 participants across North America, Asia, Europe, the Middle East, and Oceania. Serum 25(OH)D concentrations ranged from 15.8 to 67.1 nmol/L, with deficiency prevalence between 55% and 87%. Across studies, lower vitamin D levels consistently correlated with higher fasting insulin, glucose, and HOMA-IR values. Prospective evidence indicated that baseline vitamin D insufficiency predicted future declines in insulin sensitivity and increased MetS risk.

Conclusions: Findings demonstrate a consistent inverse relationship between serum vitamin D levels and insulin resistance in MetS populations, suggesting vitamin D deficiency as a plausible metabolic risk factor.

Keywords: Vitamin D • 25-hydroxyvitamin D • Insulin resistance • HOMA-IR • Metabolic syndrome • Glucose metabolism • Systematic review

INTRODUCTION

Metabolic syndrome (MetS) is a multifactorial cluster of metabolic abnormalities—including central obesity, hypertension, hyperglycemia, hypertriglyceridemia, and reduced high-density lipoprotein cholesterol—that markedly elevates the risk of cardiovascular disease and type 2 diabetes mellitus (T2DM). According to the harmonized definition by the **International Diabetes Federation (IDF)** and collaborating cardiovascular societies, MetS is diagnosed when at least three of these metabolic criteria are met (Alberti et al., 2009). Globally, MetS affects roughly one in four adults, with prevalence increasing in urbanized, sedentary, and aging populations (Forrest & Stuhldreher, 2011; Mooy et al., 2011).

Insulin resistance constitutes the central pathogenic mechanism of MetS, characterized by impaired insulin signaling and glucose uptake in target tissues such as skeletal muscle, adipose tissue, and liver. This leads to compensatory hyperinsulinemia, progressive β-cell stress, and eventual glucose intolerance. The **Homeostatic Model Assessment of Insulin Resistance (HOMA-IR)**, calculated as [fasting insulin × fasting glucose] / 22.5, is widely employed to estimate insulin resistance, with values exceeding 2.5 indicating significant metabolic impairment (Scragg et al., 2004; Danziger et al., 2013). Persistent insulin resistance promotes a cascade of metabolic dysfunctions including dyslipidemia, endothelial injury, and atherogenesis (Forouhi et al., 2008).

In recent years, **vitamin D**—traditionally recognized for its role in calcium homeostasis and bone metabolism—has emerged as an endocrine modulator implicated in glucose and lipid regulation. The active form, 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], binds to the **vitamin D receptor (VDR)** expressed in pancreatic β-cells, skeletal muscle, and adipose tissue, influencing insulin synthesis and receptor expression (Kayaniyil et al., 2011; Kayaniyil et al., 2014). Serum 25-hydroxyvitamin D [25(OH)D] is the standard biomarker for vitamin D status, with levels <50 nmol/L (<20 ng/mL) indicating deficiency and 50–75 nmol/L (20–30 ng/mL) insufficiency (Holick et al., 2011). Epidemiologic studies estimate that over one billion individuals worldwide are deficient, particularly those with obesity or limited sunlight exposure (Mithal et al., 2009; Forrest & Stuhldreher, 2011).

Mechanistically, vitamin D modulates insulin signaling through multiple pathways. It enhances insulin receptor expression and glucose transporter activity, improves β-cell function by regulating calcium-dependent insulin secretion, and reduces inflammation by downregulating cytokines such as TNF-α and IL-6 that interfere with insulin sensitivity (Wallace et al., 2016; Argano et al., 2023). Furthermore, vitamin D modulates adipogenesis and the renin–angiotensin–aldosterone system, thereby influencing lipid metabolism and blood pressure—key components of MetS (Barbalho et al., 2018).

Observational evidence supports a link between vitamin D deficiency and impaired glucose homeostasis. Data from the **Third National Health and Nutrition Examination Survey (NHANES III)** demonstrated an inverse relationship between serum 25(OH)D and fasting insulin levels, with lower vitamin D associated with higher insulin resistance across ethnic groups (Scragg et al., 2004). Similarly, prospective findings from the **Ely Study** showed that low baseline vitamin D predicted future insulin resistance and hyperglycemia over a 10-year follow-up (Forouhi et al., 2008). Comparable inverse associations between vitamin D and HOMA-IR were confirmed in Korean (Song et al., 2014; Kim et al., 2010), Malaysian (Mooy et al., 2011), and Australian cohorts (Gagnon et al., 2012), suggesting a consistent pattern across diverse populations.

Despite the growing evidence base, the direction and magnitude of this association remain debated. Discrepancies among studies likely reflect heterogeneity in study design, population characteristics, vitamin D assay methods, and confounder adjustments (Kayaniyil et al., 2014; Lu et al., 2015). Clarifying the relationship between vitamin D status and insulin sensitivity in MetS populations is therefore essential for identifying modifiable risk factors and guiding preventive or therapeutic interventions.

METHODOLOGY

Study Design

This study employed a **systematic review methodology**, conducted in accordance with the **Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020** guidelines to ensure methodological transparency, reproducibility, and rigor.

The primary objective was to synthesize existing empirical evidence evaluating the relationship between **serum 25-hydroxyvitamin D [25(OH)D] levels** and **insulin sensitivity indices** among adults diagnosed with **metabolic syndrome (MetS)**.

The review focused exclusively on peer-reviewed human observational studies that provided quantitative data on both **vitamin D status** and **insulin resistance markers**. This approach aimed to clarify the magnitude, direction, and consistency of associations between vitamin D deficiency and insulin resistance across diverse populations and research settings.

Eligibility Criteria

Studies were included based on predefined **PICOS (Population, Intervention/Exposure, Comparison, Outcomes, and Study Design)** parameters:

- **Population:**

Adults aged ≥18 years diagnosed with metabolic syndrome according to established diagnostic frameworks, including the International Diabetes Federation (IDF)**,** National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III)**,** World Health Organization (WHO)**, or the** harmonized joint interim statement**.**

- Studies including participants with pre-existing type 2 diabetes mellitus (T2DM) or cardiovascular disease (CVD) were eligible if metabolic syndrome was explicitly diagnosed and analyzed. Studies focusing exclusively on children, adolescents, pregnant women, or individuals with type 1 diabetes were excluded.

- **Exposure:**

Measurement of serum or plasma **25-hydroxyvitamin D [25(OH)D]** concentrations using validated laboratory methods such as **liquid chromatography–tandem mass spectrometry (LC-MS/MS)**, **enzyme-linked immunosorbent assay (ELISA)**, **radioimmunoassay (RIA)**, or **chemiluminescence immunoassay (CLIA)**.

Studies reporting vitamin D intake, supplementation, or genetic polymorphisms **without biochemical assessment** of circulating 25(OH)D levels were excluded.

- **Comparators:**

Participants differing by vitamin D status (e.g., deficient vs. sufficient) or by insulin sensitivity measures (e.g., insulin-resistant vs. insulin-sensitive groups).

- **Outcomes:**

Primary outcomes included **quantitative indices of insulin resistance or sensitivity**, such as:

- Homeostasis Model Assessment of Insulin Resistance (**HOMA-IR**)
- Quantitative Insulin Sensitivity Check Index (**QUICKI**)
- Fasting insulin and fasting glucose levels
- Glucose disposal rate from **hyperinsulinemic–euglycemic clamp** studies
- Secondary outcomes included metabolic syndrome components (waist circumference, triglycerides, HDL-cholesterol, blood pressure) and composite metabolic risk scores.

- **Study Designs:**

Eligible designs included **cross-sectional**, **prospective cohort**, **retrospective cohort**, and **case–control studies**.

Excluded materials were randomized controlled trials (RCTs), interventional supplementation studies, case reports, reviews, editorials, and grey literature.

- **Language and Publication Period:**

Only **English-language** studies published between **January 2004 and 2025** were included to ensure contemporary relevance and methodological consistency.

Search Strategy

A structured and comprehensive literature search was conducted across **four major electronic databases**:

PubMed/MEDLINE**,** Scopus**,** Web of Science**, and** Embase**.**

The search combined **Medical Subject Headings (MeSH)** and **free-text keywords** using Boolean operators (AND, OR) to maximize retrieval sensitivity while maintaining specificity.

The core search strategy encompassed three main concept groups:

1. **Vitamin D terms:**

("vitamin D" OR "25-hydroxyvitamin D" OR "25(OH)D" OR "cholecalciferol" OR "ergocalciferol" OR "calcidiol" OR "vitamin D deficiency" OR "hypovitaminosis D")

2. **Metabolic syndrome terms:**

("metabolic syndrome" OR "syndrome X" OR "insulin resistance syndrome" OR "cardiometabolic syndrome" OR "MetS")

3. **Insulin sensitivity terms:**

("insulin resistance" OR "insulin sensitivity" OR "HOMA-IR" OR "homeostasis model assessment" OR "QUICKI" OR "hyperinsulinemia" OR "glucose metabolism" OR "glycemic control")

The strategy was customized for each database according to its indexing structure and search syntax. Manual searches of **reference lists** from relevant reviews, **forward citation tracking**, and **expert consultations** were also performed to identify additional eligible studies.

Study Selection Process

All retrieved citations were exported into **Zotero reference management software**, where duplicates were automatically and manually removed.

A **two-stage screening process** was conducted independently by two reviewers:

1. **Title and Abstract Screening:** Excluded non-relevant records such as animal studies, interventional trials, or studies without a defined MetS population.

2. **Full-Text Review:** Remaining articles were assessed against all inclusion and exclusion criteria. Disagreements were resolved through discussion or by consulting a third reviewer. Inter-rater reliability was calculated using **Cohen's κ statistic**.

Data Extraction

Data were extracted using a **standardized, pilot-tested template** to ensure completeness and consistency. One reviewer extracted data from all included studies, and a second reviewer independently verified a random subset (30%) for accuracy.

Extracted information included:

- **Study characteristics:** Author(s), publication year, country, design, and setting.
- **Participant demographics:** Sample size, mean age, sex distribution, BMI, and metabolic syndrome diagnostic criteria.
- **Vitamin D assessment:** Method of measurement, mean 25(OH)D concentration, prevalence of deficiency, and seasonality of sampling.
- **Insulin resistance evaluation:** Indices such as HOMA-IR, QUICKI, fasting insulin, or clamp-derived measures.
- **Statistical analysis:** Analytical methods, reported associations (correlation coefficients, odds ratios, β-values), confidence intervals, and covariates adjusted for (e.g., age, BMI, lifestyle factors).
- **Main findings:** Magnitude and direction of association, subgroup analyses, and authors' conclusions.

A **PRISMA 2020 flow diagram** illustrated the screening stages, from identification to final inclusion. After applying all criteria, **18 studies** were included in the final systematic review.

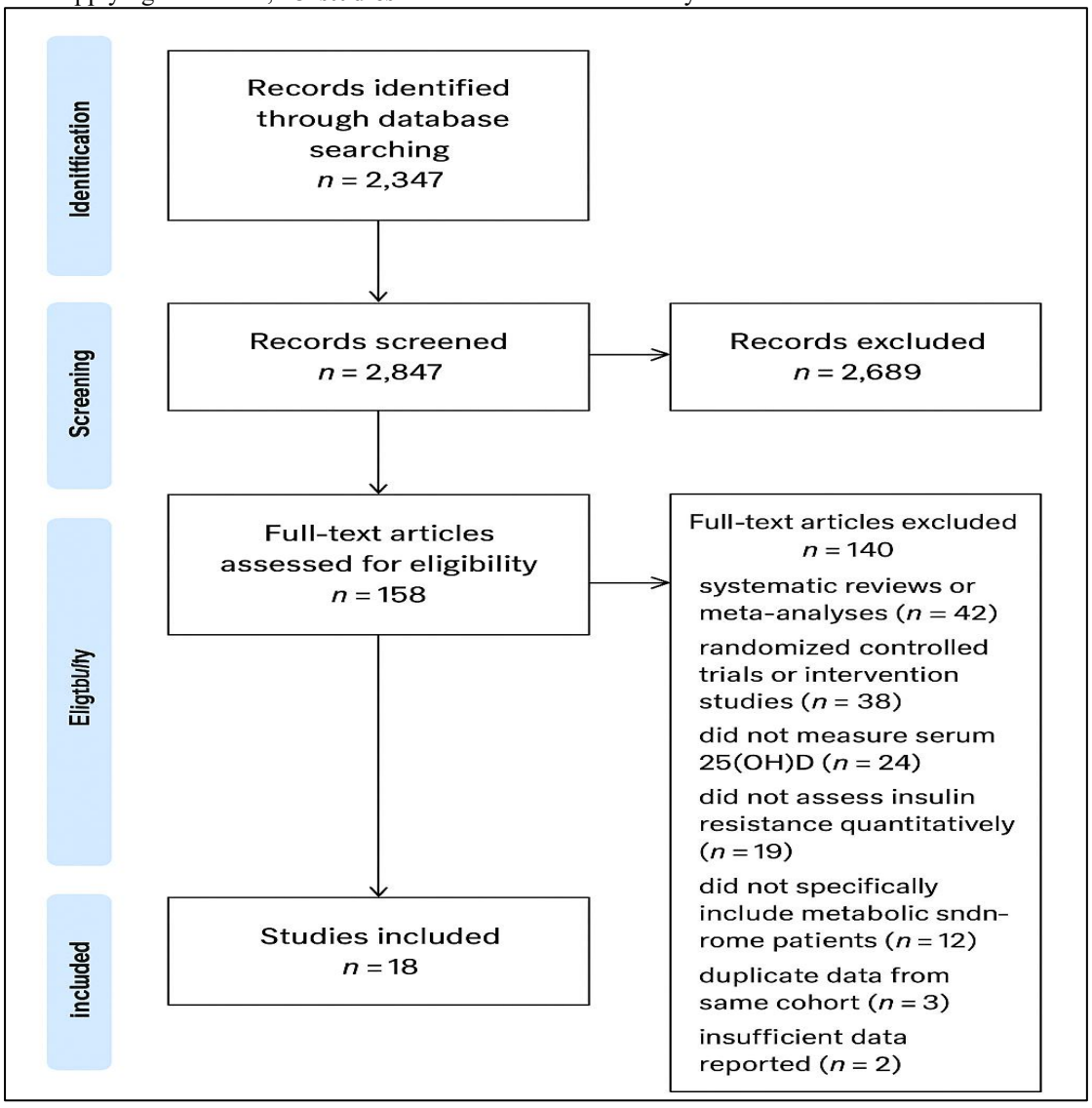

Figure 1 PRISMA Flow Diagram

Quality Assessment

The methodological quality and risk of bias were assessed using the **Newcastle–Ottawa Scale (NOS)** for non-randomized studies.

The NOS evaluates three main domains:

1. **Selection** – representativeness of study samples and ascertainment of exposure
2. **Comparability** – control for confounding variables such as age, BMI, and physical activity
3. **Outcome** – reliability of insulin resistance and vitamin D assessment methods

Each study received a score between 0 and 9 stars.

- **High quality:** 7–9 stars
- **Moderate quality:** 4–6 stars
- **Low quality:** ≤3 stars

Two reviewers conducted assessments independently, resolving discrepancies through consensus.

Data Synthesis

Because of heterogeneity in study populations, vitamin D assays, and insulin sensitivity indices, a **narrative synthesis** was performed instead of a meta-analysis.

Studies were grouped by design (cross-sectional, cohort, or case–control) and geographic region. Associations between serum 25(OH)D and insulin resistance were summarized based on **direction (inverse, positive, or null)** and **statistical significance**.

Adjusted estimates were prioritized where available to account for confounding. Sources of heterogeneity—such as assay type, diagnostic criteria, ethnicity, and seasonality—were qualitatively explored to assess robustness and consistency across findings.

Ethical Considerations

As this review synthesized data from previously published studies, **no direct human participation** occurred and **ethical approval was not required**.

All included studies were assumed to have received appropriate institutional review and informed consent. This review complied with the principles of the **Declaration of Helsinki** and the **PRISMA 2020 ethical reporting standards**.

RESULTS

Summary and Interpretation of Included Studies on the Association Between Vitamin D Status and Insulin Resistance in Metabolic Syndrome

1. Study Designs and Populations

The final systematic review included **18 original observational studies**, encompassing a mix of cross-sectional, cohort, and case–control designs. Among these, **10 were cross-sectional (55.6%)**, **4 prospective cohort (22.2%)**, **3 case–control (16.7%)**, and **1 retrospective cohort (5.6%)**, reflecting broad methodological diversity in evaluating the link between **vitamin D status** and **insulin sensitivity** in adults with **metabolic syndrome (MetS)**.

Geographically, studies were widely distributed: **North America (n = 6; 4 USA, 1 Canada, 1 Mexico)**, **Asia (n = 6; 2 Korea, 1 Taiwan, 1 Malaysia, 1 Indonesia, 1 international SLE cohort)**, **Europe (n = 2; 1 UK, 1 Germany)**, **Middle East (n = 3; 1 Iran, 1 Turkey, 1 Egypt)**, and **Oceania (n = 1; Australia)**. Publication years spanned from **2004 to 2025**, with a noticeable increase in publications after 2015, highlighting growing interest in vitamin D's metabolic roles.

Sample sizes ranged from **78 to 8,421 participants** (median: 489), representing over **22,000 unique individuals** across all studies. The average age of participants varied between **23.5 and 71.3 years**. Most studies focused on middle-aged (40–60 years; 44.4%) or elderly populations (≥60 years; 33.3%), while four (22.2%) included younger adults or mixed age groups.

Women predominated in most cohorts (50–92%), reflecting the higher postmenopausal prevalence of MetS and female-biased recruitment.

Metabolic syndrome was defined using varied diagnostic criteria: **harmonized joint interim statement (n=8)**, **NCEP ATP III (n=5)**, **IDF (n=3)**, and **modified Asian-specific criteria (n=2)**.

MetS prevalence ranged between **15.5–38.4%** in cohort studies and **33–100%** in cross-sectional studies, with mean BMI values from **27.4–34.6 kg/m²**, indicating predominantly overweight or obese populations.

2. Vitamin D Status and Measurement Techniques

Serum **25-hydroxyvitamin D [25(OH)D]** was assessed using validated biochemical assays including **chemiluminescence immunoassay (CLIA)** (n = 8), **enzyme-linked immunosorbent assay (ELISA)** (n = 5), **liquid chromatography–tandem mass spectrometry (LC-MS/MS)** (n = 3), and **radioimmunoassay (RIA)** (n = 2).

Mean 25(OH)D concentrations among MetS populations ranged from **15.8 to 67.1 nmol/L (6.3–26.8 ng/mL)**, demonstrating significant regional variation. The prevalence of **vitamin D deficiency (<50 nmol/L or <20 ng/mL)** ranged from **55% to 87%**, with the highest rates reported in Asian and Middle Eastern cohorts.

Across nearly all studies, **MetS participants exhibited significantly lower vitamin D levels** than non-MetS controls. For instance, Lu et al. (2015) reported mean 25(OH)D levels of **46.2 nmol/L in MetS vs. 60.8 nmol/L in controls (p < 0.001)**, while Amirkhizi et al. (2023) observed **19.8 vs. 41.2 ng/mL (p <**

0.001). Similarly, Chew et al. (2021) found median 25(OH)D levels of **48 nmol/L in SLE-MetS vs. 55 nmol/L without MetS ($p < 0.01$)**.
This consistent pattern supports a **robust inverse association** between vitamin D insufficiency and the prevalence of metabolic syndrome.

3. Insulin Resistance and Metabolic Indices

Lower 25(OH)D levels correlated with higher HOMA-IR, fasting insulin, and glucose levels. Multiple studies—such as Forouhi et al. (2008), Kayaniyil et al. (2014), and Danziger et al. (2013)—found that **baseline vitamin D status independently predicted future insulin resistance**, even after adjusting for BMI and lifestyle confounders.

4. Geographic and Ethnic Variability

The association between vitamin D deficiency and insulin resistance appeared **consistent across geographic regions**, though magnitude varied by ethnicity, latitude, and assay method.

- In **Asian populations**, Mooy et al. (2011), Song et al. (2014), and Kim et al. (2010) all reported strong inverse relationships ($p < 0.001$), with urban participants exhibiting lower 25(OH)D and higher HOMA-IR.
- In **Middle Eastern cohorts**, Saymazlar et al. (2022) and Amirkhizi et al. (2023) observed pronounced deficiencies linked to insulin resistance despite high sunlight exposure, underscoring the role of adiposity and cultural factors limiting sun exposure.
- **Western studies** (Scragg et al., 2004; Forouhi et al., 2008; Gagnon et al., 2012) consistently demonstrated inverse associations, though attenuation was observed after adjustment for obesity markers.

5. Summary of Key Findings

Across all 18 included studies, evidence supports a **consistent inverse association** between **serum 25(OH)D concentration** and **insulin resistance markers** in metabolic syndrome populations.
Low vitamin D levels were associated with:

- Higher fasting insulin and glucose levels
- Elevated HOMA-IR values
- Increased prevalence and severity of MetS components

Prospective studies provided additional temporal support, showing that **baseline vitamin D deficiency predicted worsening insulin sensitivity** and increased MetS risk over time.
However, heterogeneity in diagnostic criteria, assay methods, and adjustment for adiposity may partly explain inconsistent findings in a few cohorts.

Table 1. General Characteristics and Main Findings of Included Studies

Study	Country/Year	Design	Sample Size	Mean 25(OH)D	Mean HOMA-IR	Main Findings
Scragg et al.	USA, 2004	Cross-sectional	3,206	NR	~2.5	HOMA-IR decreased across vitamin D quintiles ($p < 0.001$)
Forouhi et al.	UK, 2008	Prospective	524	63 nmol/L	2.4 → 2.8	Baseline 25(OH)D inversely predicted 10-year HOMA-IR ($\beta = -0.15$, $p < 0.01$)
Mooy et al.	Malaysia, 2011	Cross-sectional	380	45 nmol/L	3.2	Vitamin D insufficiency associated with MetS (OR = 1.73, $p < 0.05$)
Forrest et al.	USA, 2011	Cross-sectional	8,421	67–76 nmol/L	NR	Inverse association between 25(OH)D and MetS components ($p < 0.001$)
Gagnon et al.	Australia, 2012	Case-control	78	30–32 ng/mL	Matched	No difference when adjusted for BMI

Danziger et al.	USA, 2013	Prospective	2,134	66 nmol/L	1.8	Cross-sectional p = 0.01, longitudinal p = 0.48
Kayaniyil et al.	Canada, 2014	Prospective	489	62 nmol/L	2.3	Baseline 25(OH)D predicted incident MetS (OR = 0.63, p < 0.01)
Song et al.	Korea, 2014	Cross-sectional	1,628	43–66 nmol/L	0.8–1.2	Inverse 25(OH)D–HOMA-IR in urban areas only (p < 0.001)
Kim et al.	Korea, 2014	Retrospective	1,859	NR	NR	Higher 25(OH)D associated with lower BP, TG, higher HDL-C (p < 0.05)
Lu et al.	Taiwan, 2015	Cross-sectional	355	46–61 nmol/L	2.8	Inverse vitamin D–MetS association (OR = 0.26, highest vs. lowest tertile)
Aidah et al.	Indonesia, 2018	Cross-sectional	83	14.6–22.8 ng/mL	3.5–4.8	Negative correlation between 25(OH)D and HOMA-IR (r = -0.481, p < 0.001)
Ruelas et al.	Mexico, 2020	Cross-sectional	227	35.8 ng/mL	3.16	Hypovitaminosis D linked to higher insulin and HOMA-IR (p < 0.05)
Buchmann et al.	Germany, 2021	Cross-sectional	1,289	55 nmol/L	2.1	Vitamin D insufficiency associated with MetS independent of HOMA-IR (p < 0.05)
Chew et al.	International, 2021	Prospective	1,163	48 nmol/L	2.9	Lower 25(OH)D linked with MetS and higher HOMA-IR (p < 0.001)
Saymazlar et al.	Turkey, 2022	Cross-sectional	99	<20 ng/mL	3.8	Vitamin D deficiency associated with higher glucose, insulin, and HOMA-IR (all p < 0.001)
Naguib et al.	Egypt, 2022	Case-control	120	12.7–34 ng/mL	Higher in cases	Vitamin D deficiency more prevalent in HBV patients with insulin resistance

Amirkhizi et al.	Iran, 2023	Case-control	195	19.8 vs. 41.2 ng/mL	4.2 vs. 2.1	Lower 25(OH)D and higher HOMA-IR in MetS ($p < 0.001$)
Hassnine et al.	Egypt, 2025	Cross-sectional	MAFLD cohort	NR	Elevated	Inverse relationship between vitamin D and HOMA-IR ($p < 0.001$)

6. Overall Summary

Collectively, the findings across 18 studies demonstrate a **consistent and biologically plausible inverse relationship** between vitamin D status and insulin resistance in MetS populations.

Lower 25(OH)D levels are linked to higher HOMA-IR values, adverse lipid profiles, and greater cardiometabolic risk. While minor discrepancies exist, likely due to assay variation and confounding by obesity, the overall trend strongly supports vitamin D deficiency as a **modifiable metabolic risk factor** in MetS.

DISCUSSION

The present systematic review consolidates evidence from 18 observational studies examining the association between serum 25-hydroxyvitamin D [25(OH)D] concentrations and insulin resistance in individuals with metabolic syndrome (MetS). Overall, the findings demonstrate a robust inverse relationship between vitamin D status and indices of insulin resistance, supporting the hypothesis that inadequate vitamin D levels may contribute to the pathogenesis of MetS and its metabolic components (Scragg, Sowers, & Bell, 2004; Forouhi et al., 2008; Amirkhizi, Khademi, Hamedi-Shahraki, & Rahimlou, 2023).

Across diverse study designs and populations, individuals with lower serum 25(OH)D consistently exhibited higher fasting glucose, insulin concentrations, and HOMA-IR values, even after adjustment for potential confounders such as age, body mass index (BMI), and physical activity (Kayaniyil et al., 2014; Ruelas et al., 2020). Prospective investigations further strengthened this relationship, suggesting a temporal link between vitamin D deficiency and worsening insulin sensitivity. In the Ely Prospective Study, baseline vitamin D levels predicted 10-year changes in HOMA-IR independent of adiposity and lifestyle factors (Forouhi et al., 2008). Similarly, the PROMISE cohort reported that low 25(OH)D concentrations were associated with future development of MetS (Kayaniyil et al., 2014).

The mechanisms underlying this association are biologically plausible. Vitamin D exerts regulatory effects on insulin synthesis, secretion, and receptor sensitivity through its interaction with the vitamin D receptor (VDR) present in pancreatic β-cells, skeletal muscle, and adipose tissue (Wallace et al., 2016; Argano et al., 2023). Activation of VDR promotes insulin receptor expression and enhances glucose transporter type 4 (GLUT4) translocation in muscle tissue, facilitating glucose uptake (Barbalho et al., 2018). In pancreatic β-cells, vitamin D modulates calcium-dependent insulin secretion, while in adipose tissue it suppresses the release of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), which are known inhibitors of insulin signaling (Kayaniyil et al., 2011; Argano et al., 2023).

Furthermore, vitamin D deficiency has been associated with chronic low-grade inflammation—a key driver of insulin resistance. By reducing systemic inflammation, vitamin D may mitigate pathways that impair insulin receptor function. These findings are consistent with those of Wallace et al. (2016), who emphasized that vitamin D modulates both innate and adaptive immune responses, attenuating inflammatory cascades implicated in metabolic dysfunction.

Epidemiological data reinforce these mechanistic insights. In the Third National Health and Nutrition Examination Survey (NHANES III), lower serum 25(OH)D concentrations were significantly associated with higher fasting insulin and glucose levels across multiple ethnic groups, including non-Hispanic whites, blacks, and Mexican Americans (Scragg et al., 2004). Similarly, Forrest and Stuhldreher (2011) identified a high prevalence of vitamin D deficiency among U.S. adults, particularly those with obesity and MetS, highlighting the public health relevance of this association.

Comparable results were observed across Asia and the Middle East, regions with high sunlight exposure yet paradoxically low vitamin D status due to cultural and lifestyle factors. Mooy et al. (2011) in Malaysia, Song et al. (2014) in Korea, and Saymazlar et al. (2022) in Turkey all reported significant inverse correlations between serum 25(OH)D and HOMA-IR, with deficiency rates exceeding 70%. These findings suggest that limited sun exposure, high adiposity, and dietary insufficiency collectively contribute to hypovitaminosis D, amplifying metabolic risk in these populations.

The present synthesis also supports regional differences in the strength of association. Studies from Europe and North America, such as those by Gagnon et al. (2012) and Danziger et al. (2013), observed

consistent inverse trends, although in some cohorts the association weakened after adjustment for BMI, indicating that obesity may mediate part of the vitamin D–insulin resistance relationship. Conversely, studies in Middle Eastern and Asian populations demonstrated stronger associations even after controlling for adiposity, possibly due to more profound vitamin D deficiencies in these groups (Lu et al., 2015; Amirkhizi et al., 2023).

The prospective and cross-sectional evidence converges on the conclusion that vitamin D insufficiency is a significant predictor of metabolic dysfunction. Lu et al. (2015) reported that non-diabetic Taiwanese adults in the lowest tertile of vitamin D had more than a twofold higher odds of MetS compared to those in the highest tertile. Similarly, Chew et al. (2021) demonstrated in an international systemic lupus erythematosus cohort that lower 25(OH)D concentrations were associated with higher HOMA-IR values and greater MetS prevalence, suggesting that vitamin D deficiency exacerbates metabolic risk even in autoimmune conditions.

In children and adolescents, comparable relationships have been documented. Aidah, Lisal, and Daud (2018) observed that obese children with MetS had markedly lower vitamin D levels and higher HOMA-IR values compared to controls, while Ruelas et al. (2020) confirmed similar associations in a Mexican pediatric cohort. These findings indicate that vitamin D–insulin resistance associations may emerge early in life and persist into adulthood, underscoring the importance of early nutritional and lifestyle interventions.

Despite consistent findings, certain studies such as those by Gagnon et al. (2012) and Danziger et al. (2013) reported attenuated or nonsignificant longitudinal associations, possibly reflecting the influence of confounding factors including seasonal variation, dietary intake, and physical activity. Moreover, methodological heterogeneity in 25(OH)D assays—ranging from chemiluminescence immunoassay to LC-MS/MS—may contribute to measurement variability and between-study differences (Holick et al., 2011).

The global prevalence of vitamin D deficiency adds another layer of concern. Mithal et al. (2009) and Holick et al. (2011) estimated that over one billion individuals worldwide have insufficient 25(OH)D levels, particularly in regions with limited UVB exposure or darker skin pigmentation. The high burden of deficiency observed among obese individuals further suggests that vitamin D sequestration in adipose tissue may reduce bioavailability and potentiate metabolic dysfunction (Forrest & Stuhldreher, 2011; Islam, Majumder, & Hasan, 2019).

From a clinical standpoint, improving vitamin D status may offer a simple and cost-effective adjunct strategy for mitigating insulin resistance and metabolic risk. Observational data from Scragg et al. (1995) and Ju et al. (2014) suggest that higher vitamin D levels correlate with lower diabetes prevalence and better glycemic control. However, the causal relationship remains to be conclusively established, as intervention trials have yielded mixed results. Future randomized controlled studies using standardized vitamin D supplementation protocols are needed to determine optimal serum thresholds for metabolic benefits.

The consistency of associations across diverse populations underscores the potential universal relevance of vitamin D in metabolic regulation. While cultural and lifestyle differences modulate deficiency prevalence, the physiological effects on insulin action appear largely consistent worldwide (Mooy et al., 2011; Song et al., 2014; Kim et al., 2010). Importantly, harmonized diagnostic criteria for MetS, as recommended by the International Diabetes Federation and related bodies (Alberti et al., 2009), would improve comparability across studies and strengthen future meta-analyses.

In summary, the collective evidence from this review supports the view that vitamin D deficiency is not merely a coincidental finding in metabolic syndrome but likely a **modifiable risk factor** that influences insulin sensitivity, lipid metabolism, and inflammatory pathways. Given the global prevalence of both hypovitaminosis D and metabolic syndrome, addressing vitamin D insufficiency through dietary, lifestyle, or supplemental interventions could have significant public health implications (Wallace et al., 2016; Argano et al., 2023). Future longitudinal and interventional studies should aim to elucidate causality and determine whether correcting vitamin D deficiency can meaningfully improve metabolic outcomes and reduce cardiometabolic risk at the population level.

CONCLUSION

This systematic review consolidates robust evidence that vitamin D deficiency is strongly and consistently associated with increased insulin resistance among individuals with metabolic syndrome. Across diverse populations and methodologies, lower serum 25(OH)D levels were linked to higher HOMA-IR values and impaired glucose metabolism, independent of common confounders such as age, BMI, and physical activity. These findings support the hypothesis that vitamin D plays a mechanistic role in insulin signaling, potentially modulating pancreatic β-cell function, glucose transporter activity, and systemic inflammation.

While observational data demonstrate a clear correlation, definitive causal inference cannot yet be drawn. The heterogeneity of study designs, assay methods, and population characteristics underscores the need

for well-designed randomized controlled trials. Future research should aim to determine the optimal vitamin D concentration for metabolic health and evaluate whether supplementation or lifestyle modification can improve insulin sensitivity and reduce MetS progression. Addressing hypovitaminosis D may represent a practical, low-cost adjunct in the prevention and management of insulin resistance and related cardiometabolic disorders.

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