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Review

Serum Zinc Concentrations in Saudi Adults With Type 2 Diabetes: A Systematic Review and Meta-Analysis of Observational Studies

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Abstract

Background: Zinc deficiency has been linked to the onset and progression of type 2 diabetes (T2D), and zinc plays a role in glucose regulation. Notably, the role of zinc in insulin synthesis, secretion, and signaling is reasonably well documented; however, to our knowledge, no review has specifically synthesized the Saudi Arabia-based evidence, despite Saudi Arabia possessing a high burden of T2D. While several local studies report lower serum zinc in diabetic adults, these have not been examined collectively. **Objective:** Therefore, this systematic review and meta-analysis assessed serum zinc concentrations in adults from Saudi Arabia with T2D and explored the molecular pathways that may underlie this association. **Method:** A literature search was conducted on September 9, 2025, across PubMed, Cochrane CENTRAL, ClinicalTrials.gov, and Google Scholar. Eligible studies were observational and cross-sectional, compared adults with T2D with healthy controls, and reported serum zinc data as the mean ± standard deviation (SD). Studies of type 1 or gestational diabetes, those using hair zinc, and those without standard mean values were excluded. Standardized mean differences (SMDs) were pooled using a random-effects model. Heterogeneity was assessed and presented using forest and funnel plots. **Results:** Six cross-sectional studies met the criteria, including 1407 participants (752 with T2D and 655 healthy controls). Serum zinc was lower in the T2D group than in controls in five of the six included studies, with one study reporting no difference between groups. The pooled SMD was –1.29 (95% confidence interval (CI): –1.40 to –1.17) under the common-effect model and –1.62 (95% CI: –2.66 to –0.59) under the random-effects model. The pooled estimate favored lower serum zinc in T2D, although one study contributed a null estimate. The estimate should be interpreted with caution due to very high heterogeneity ($I^2 = 97.4\%$), likely reflecting differences in assay techniques, sample sizes, and study designs across the included studies. **Conclusion:** Serum zinc concentrations were generally lower in adults from Saudi Arabia with T2D than in controls across the included observational studies. However, the high between-study heterogeneity, cross-sectional design of all included studies, and one null study mean that the findings should be interpreted as evidence of an association rather than a precise or causal effect. Larger prospective and interventional studies with standardized zinc assessment and better control of dietary, renal, and treatment-related confounders are needed to clarify the biological pathways and determine whether serum zinc has clinical relevance in this population. **Registration:** This research is in line with PRISMA 2020. The meta-analysis is pre-specified but not confidential (e.g., PROSPERO). Registration Number: CRD420251101587 (https://www.crd.york.ac.uk/PROSPERO/view/CRD420251101587).

Keywords: type 2 diabetes; serum zinc; meta-analysis; trace elements; glycemic control; Saudi Arabia

1. Introduction

Type 2 diabetes (T2D) is a chronic metabolic disorder characterized by progressive β-cell dysfunction, insulin resistance, and impaired cellular glucose uptake. In the Kingdom of Saudi Arabia (KSA), the prevalence of type 2 diabetes has increased significantly over the past few decades, currently affecting approximately 25% of the adult population. These figures are expected to rise further, a trend attributed to changes in diet, sedentary lifestyles, and genetic susceptibility [1]. The resulting clinical burden on the national healthcare system is considerable, much of it tied to secondary complications such as nephropathy, retinopathy, neuropathy, and cardiovascular disease [2]. Alongside the established focus on macronutrients, there has been growing interest in how micronutrients, and trace elements like zinc in particular, contribute to glucose regulation. Zinc is involved in stabilizing insulin receptors, in insulin production, and in the body's antioxidant defenses. Observational evidence has linked zinc status or zinc intake with the risk and progression of T2D, although these findings should be interpreted as associations rather than evidence of a causal relationship [3]. At the mechanistic level, zinc regulates several enzymes connected to carbohydrate metabolism and oxidative stress defense, among them metallothioneins and superoxide dismutase (SOD) [4,5]. Ahmad et al. [6] (2024) recently added to this picture, describing the part zinc plays in protecting pancreatic β-cells, supporting insulin synthesis, and reducing systemic oxidative stress. A substantial literature reports that serum zinc concentrations are lower in patients with T2D than in healthy controls, and several studies have linked this depletion to poor glycemic control, dyslipidemia, and the progression of diabetic nephropathy

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[7,8]. Several mechanisms may explain the lower serum zinc concentrations observed in individuals with type 2 diabetes. First, dietary zinc intake may be inadequate in this population. A systematic review and meta-analysis reported significantly lower dietary zinc intake among individuals with type 2 diabetes compared with healthy controls [9], suggesting that habitual dietary patterns may not consistently meet zinc requirements. Second, gastrointestinal zinc absorption may be impaired. Chronic hyperglycemia can disrupt intestinal mucosal function and reduce absorptive efficiency [10], thereby limiting the entry of dietary zinc into the systemic circulation. Third, urinary zinc excretion is often increased in patients with type 2 diabetes. Diabetes-related renal dysfunction, including reduced tubular zinc reabsorption, may contribute to hyperzincuria and progressive depletion of circulating zinc stores, even when dietary intake is adequate [11]. Collectively, reduced dietary intake, impaired gastrointestinal absorption, and increased renal zinc loss may act together to produce a sustained zinc deficit, which may be further exacerbated by the broader metabolic dysregulation associated with type 2 diabetes. The clinical data, however, are scattered. The included Saudi studies varied in study location and analytical method used for zinc measurement, highlighting the need to synthesise the available Saudi observational evidence. As a result, the epidemiological picture of zinc status in this population is still not well defined. More recent molecular work has concentrated on the zinc transporter proteins, specifically the solute carrier family 39 (SLC39A/ZIP) zinc importers and solute carrier family 30 (SLC30A/ZnT) zinc exporters, and their part in maintaining intracellular zinc homeostasis, which is relevant to T2D pathophysiology [12]. By regulating the movement of zinc into and out of cells, these transporters influence insulin secretion, signal transduction, and cellular stress responses.

At the mechanistic level, ZIP7 regulates endoplasmic reticulum (ER) stress and downstream insulin signaling [13], while ZIP14 supports glucose-stimulated insulin secretion in pancreatic β-cells [14]. Additionally, ZnT7 is implicated in cardiac muscle glucose utilization [15]. Despite the clinical importance of these pathways, data specific to the Saudi Arabian population remain limited. To bridge this gap, the present systematic review and meta-analysis consolidates the available evidence on serum zinc in Saudi adults with T2D and weighs the methodological factors that shape it.

2. Methods

2.1 Protocol and Registration

This meta-analysis was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 [16]. The protocol was prespecified and registered in the PROSPERO International Prospective Register of Systematic Reviews (Registration ID: CRD420251101587).

2.2 Eligibility Criteria

A study qualified on four conditions: conduct entirely within KSA; enrollment of adults (aged ≥18 years) with diagnosed T2D under established criteria such as those of the American Diabetes Association (ADA) or WHO; inclusion of a control or comparison group of non-diabetic individuals; and reporting of serum zinc as mean and standard deviation (SD). Observational cross-sectional designs met the eligibility criteria for this review. Studies of type 1 or gestational diabetes were excluded, as were those without a suitable control group. Interventional trials were left out where baseline zinc measurements were not reported. Secondary literature, including systematic reviews, editorials, commentaries, and conference abstracts, was also excluded, along with publications in languages other than English. That last exclusion reflected limited translation resources rather than any judgment of quality. To structure the synthesis systematically, studies were categorized by methodology, zinc assessment technique, and geographic region within Saudi Arabia. Predefined subgroup analyses were set up across these categories to examine possible sources of heterogeneity. After full-text screening, eligible studies were grouped by assay method, region, and sample size, with only those reporting sufficient quantitative data carried forward to the meta-analysis. A characteristics table then confirmed their fit with the planned synthesis groups.

2.3 Search Strategy

The aim was to examine the relationship between zinc deficiency and type 2 diabetes in Saudi Arabia. The literature search covered PubMed, Cochrane CENTRAL, and ClinicalTrials.gov, with Google Scholar used as a supplementary source. Google Scholar was helpful here because it picked up local publications not indexed in PubMed or CENTRAL, which broadened coverage, though its limitations as a search tool are recognized. Grey literature, such as theses, conference abstracts, and local reports, was not included. The final search was run on 09 September 2025.

2.3.1 PubMed Search String

("Type 2 Diabetes Mellitus" [MeSH] OR "T2DM" OR "Type 2 Diabetes") AND ("Zinc" [MeSH] OR "Zinc Deficiency" OR "Zinc Transporters") AND ("Saudi Arabia") AND ("Cross-sectional")

Filters applied: Humans, Adults (≥18 years), English language, publication years 2000–2025.

2.3.2 Cochrane CENTRAL

("Type 2 Diabetes Mellitus" OR T2DM OR "Non-insulin dependent diabetes") AND (Zinc OR "Zn" OR "Zinc Sulfate" OR "Zinc Gluconate") AND ("Cross-sectional")

Filters: 2000–2025.

2.3.3 ClinicalTrials.gov

Type 2 Diabetes AND Zinc AND Saudi Arabia

Filters: Completed studies, observational cross-sectional design, 2000–2025.

2.3.4 Google Scholar

Keywords: "Type 2 Diabetes" AND "Zinc Deficiency" AND "Saudi Arabia AND "Cross-sectional"

Restricted to 2000–2025. Embase, Scopus, and Web of Science were weighed but left out. Regional and Arabic-language databases were also excluded, in both cases because institutional access was not available, which is noted here for transparency. With no translation resources on hand, the review was restricted to English-language publications. This introduces a possible language bias, which is taken up again in the limitations. Every search string, filter, and inclusion or exclusion rule was recorded following the PRISMA 2020 guidelines so that the process can be reproduced.

2.4 Selection Process

All retrieved records entered EndNote X9 (Clarivate Analytics, Philadelphia, PA, USA), where de-duplication followed. Two reviewers independently screened titles and abstracts against a standardized protocol, and both then assessed the full texts for eligibility. An automation tool (Rayyan QCRI, version 2025 (Qatar Computing Research Institute, Doha, Qatar; https://www.rayyan.ai)) was used to support the first pass over titles and abstracts. The tool flagged duplicates, highlighted keywords, and tagged likely exclusions. It never made the final call, though—every inclusion and exclusion rested with the human reviewers. This double-review step, adopted to curb bias and error, follows the PRISMA 2020 guidelines.

2.5 Data Collection Process

Data were extracted independently by two reviewers using a standardized collection form, and any discrepancies were resolved by consensus. For each eligible study, the following variables were recorded: first author and year of publication; geographic location within Saudi Arabia and overall study design; sample sizes of the diabetic and control groups; mean serum zinc concentration and SD for both groups, reported in the original unit and converted to µmol/L; the analytical method used to measure zinc; and any reported associations with glycaemic markers, lipid profile, or diabetic complications where available.

2.6 Data Items

2.6.1 Primary Outcomes

The primary outcome stayed constant throughout. This was serum zinc concentration in patients with T2D and in healthy controls. Serum zinc values from both groups were used in the quantitative synthesis, and all eligible results were included regardless of assay technique or geographic setting. Where a study offered several time points or subgroups, only the baseline or cross-sectional figures entered, for consistency. Where a value appeared in more than one form, the most complete version prevailed. Studies that failed to report serum zinc as mean ± SD were set aside. This kept the pooled estimates statistically comparable.

2.6.2 Secondary Outcomes and Other Variables

Several secondary variables added context to the primary outcome. Participant detail ran thin—sample size was usually all a study reported, with demographics noted only here and there. Each study's design and location entered the record. This included its cross-sectional or case-control form and the region of Saudi Arabia it covered. The zinc assay method entered too, since technique drives variation. The methods used across the set were inductively coupled plasma mass spectrometry (ICP-MS), inductively coupled plasma optical emission spectrometry (ICP-OES), graphite furnace atomic absorption spectrometry (GFAAS), and colorimetric assay.

Several studies reported associations between serum zinc and glycaemic or renal markers, including inverse correlations with glycated haemoglobin (HbA1c) and albumin-to-creatinine ratio; however, the type of analysis and the clinical variables reported varied across studies [8].

2.6.3 Handling of Missing or Ambiguous Data

Every included study reported both the mean and the SD for serum zinc, so no imputation was needed. The concentrations were reported in a mix of units (µg/dL, mg/L, µmol/L, and mcg/dL) and were all converted to µmol/L for cross-study comparison. Participant characteristics such as age, sex distribution, and diabetes duration were reported unevenly across studies and were therefore not used as exclusion criteria. The numeric reporting, by contrast, ran clear and complete; no author needed contacting, and no study entered on qualitative grounds alone. Leave-one-out sensitivity analyses tested the robustness of the pooled estimates. The results remained consistent. This confirmed that no single study swayed the overall estimate.

2.7 Study Risk of Bias Assessment

Both reviewers judged each study's risk of bias independently, using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Analytical Cross-Sectional Studies suited to this design [17]. The Supplementary Material lays out the checklist's domains.

2.8 Effect Measures

The primary outcome was serum zinc. For it, the effect measure was the standardized mean difference (SMD) between patients with T2D and healthy controls. Each study's raw mean ± SD in µmol/L became a unitless SMD. The common unit (µmol/L) served descriptive reporting,

but the SMD did the real comparative work, absorbing differences in assay methodology and measurement scale from one study to the next. Each SMD carried a 95% confidence interval (CI), pooled under a random-effects model to accommodate heterogeneity. The approach set studies side by side even when their zinc assays and reporting units differed.

2.9 Synthesis Methods

Anticipating clinical and methodological heterogeneity, the synthesis fitted a random-effects model using restricted maximum likelihood (REML) to estimate between-study variance (τ^2) [18], with all analyses run in R version 4.5.1 (R Foundation for Statistical Computing, Vienna, Austria) using the meta (v6.0-0), metafor (v4.0-0), and dmetar (v0.1.0) packages.

Studies with insufficient summary statistics, such as a missing SD, were dropped, and nothing was imputed. Because the included studies reported zinc in several units (µg/dL, mg/L, and µmol/L), all values were converted to µmol/L before analysis. A shared unit did not remove every difference, since the studies relied on different techniques (ICP-OES, ICP-MS, GFAAS, and colorimetric assays), each with its own measurement spread. The SMD therefore served as the primary effect measure, and the random-effects model carried the expected methodological and clinical heterogeneity.

The Cochran Q-test ($p < 0.10$) and the I^2 statistic gauged heterogeneity, with 25%, 50%, and 75% read as low, moderate, and high [19]. Where the data allowed, subgroup analyses ran by assay method, study region, and sample size. To test the stability of the pooled estimate, a leave-one-out sensitivity analysis dropped one study at a time. Notably, each grouping targeted a possible source of heterogeneity.

A forest plot displayed the pooled effect. To screen for publication bias, a funnel plot was used. In the Results section, each subgroup outcome was presented next to the relevant study characteristics, including assay technique, region, sample size, and participant demographics. Reporting these details together was intended to help with interpreting the subgroup comparisons. The synthesis followed PRISMA 2020 guidance throughout.

2.10 Reporting Bias Assessment

Funnel plots were used to assess publication bias visually, and Egger's regression test was applied to test for asymmetry. A threshold of $p < 0.05$ was used to identify potential small-study effects.

2.11 Certainty Assessment

The certainty of evidence for the primary outcome was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework. This assessment took into account risk of bias, inconsistency, indirectness, imprecision, and publication bias. Each outcome was then rated as high, moderate, low, or very low certainty.

3. Results

3.1 Study Selection

The search identified 3097 records: 2998 from PubMed, 33 from Cochrane CENTRAL, and 66 from Google Scholar. After removal of 19 records before screening (5 duplicates, 7 records flagged by automation tools, and 7 records removed for other reasons), 3078 records proceeded to title and abstract screening.

Six studies remained for the systematic review and meta-analysis. Fig. 1 lays out the PRISMA 2020 flow diagram for the selection process.

3.2 Study Characteristics

The six studies were published between 2013 and 2021. All were observational and cross-sectional, conducted in several regions of Saudi Arabia, including Riyadh and Jeddah, with a combined total of 1407 participants (752 patients with T2D and 655 healthy controls). The assays used to measure zinc differed across studies: one used ICP-OES, three used ICP-MS, one used GFAAS, and one used colorimetry. Full study characteristics are given in Table 1 (Ref. [20,21,22,23,24,25]).

3.3 Risk of Bias in Studies

Risk of bias was assessed using a modified version of the JBI Critical Appraisal Checklist for Analytical Cross-Sectional Studies, as described in the Methods. The domain-level judgments and overall ratings are reported in Table 2 (Ref. [20,21,22,23,24,25]), with each rating based on the JBI checklist completed for the individual studies (**Supplementary Material**).

3.4 Pooled Meta-Analysis of Serum Zinc Levels

Six Saudi cross-sectional studies were included in the meta-analysis, with a combined total of 752 patients with type 2 diabetes and 655 controls. The individual studies reported serum zinc in µmol/L (Table 1), whereas the pooled effect is expressed as an SMD, which is unitless. This conversion allows studies with different scales and variances to be compared, while the study-level data remain based on the original µmol/L values. All but one of the studies reported lower serum zinc in patients with type 2 diabetes than in controls. The exception was Yakout et al. [22] (2021), which reported identical means in the T2D and control groups (26.01 ± 6.12 µmol/L) and therefore contributed a null estimate to the pooled result. The common-effect model gave a pooled SMD of –1.29 (95% CI: –1.40, –1.17), and the random-effects model gave –1.62 (95% CI: –2.66, –0.59). Between-study heterogeneity was high (I^2 = 97.4%, τ^2 = 1.64, $p < 0.0001$; Fig. 2). The pooled effect favoured lower serum zinc in type 2 diabetes than in

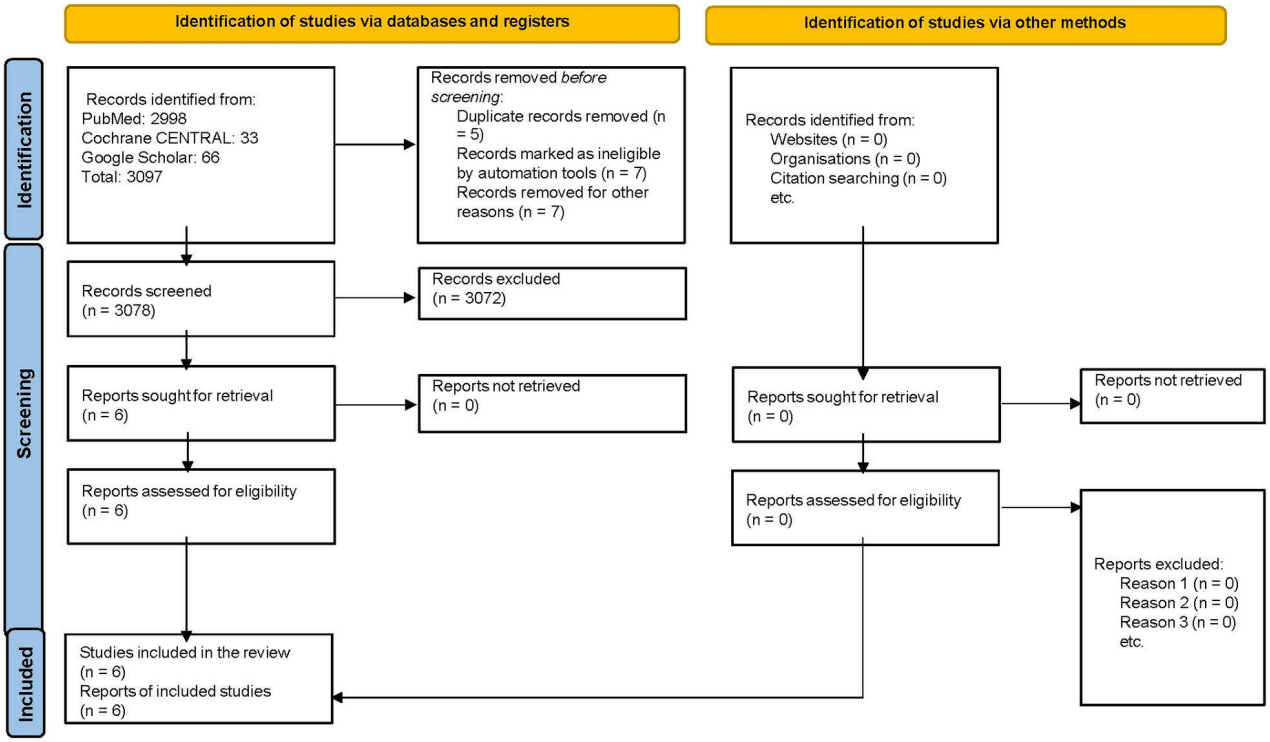


Fig. 1. PRISMA 2020 flow diagram of the study selection process. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 1. Overview of six cross-sectional Saudi studies of zinc in T2D, using diverse assay techniques.

Study (author, year)	Region	Study design	T2D (n)	Mean ± SD (µmol/L)	Controls (n)	Mean ± SD (µmol/L)	Assay method
(Khan et al., 2015) [20]	Riyadh	Cross-sectional	76	5.13 ± 2.74	75	14.76 ± 1.96	ICP-OES
(Farooq et al., 2020) [21]	Riyadh	Cross-sectional	252	9.26 ± 1.63	188	11.70 ± 1.48	ICP-MS
(Yakout et al., 2021) [22]	Riyadh	Cross-sectional	119	26.01 ± 6.12	95	26.01 ± 6.12	ICP-MS
(Hasanato, 2020) Riyadh [23]		Cross-sectional	50	9.90 ± 2.70	50	15.00 ± 3.20	ICP-MS
(Farid & Abulfaraj, 2013) Jeddah [24]		Cross-sectional	55	14.72 ± 3.72	55	19.92 ± 4.90	GFAAS
(Farooq, 2019) Riyadh [25]		Cross-sectional	200	10.18 ± 1.73	192	12.64 ± 1.87	Colorimetric

Note: All six included studies used a cross-sectional design and were conducted in Riyadh or Jeddah, Saudi Arabia. Zinc was measured by ICP-OES in one study, ICP-MS in three, GFAAS in one, and a colorimetric assay in one. The total enrollment comprised 752 patients with T2D and 655 healthy controls. All serum zinc values were converted to µmol/L before analysis. For Hasanato [23] (2020), the value of 9.9 ± 2.7 µmol/L refers to the HbA1c <6.5% T2D subgroup (n = 50), which was used in the primary meta-analysis. The HbA1c >6.5% subgroup was not pooled because it was reported separately and included microalbuminuria, which may independently influence serum zinc through renal zinc loss; this subgroup is reported descriptively in the supplementary material. Abbreviations: T2D, type 2 diabetes; SD, standard deviation; ICP-OES, inductively coupled plasma optical emission spectrometry; ICP-MS, inductively coupled plasma mass spectrometry; GFAAS, graphite furnace atomic absorption spectrometry; µmol/L, micromoles per litre; KSA, Kingdom of Saudi Arabia; HbA1c, glycated haemoglobin.

controls; however, one study contributed a null estimate, and the high degree of heterogeneity indicates that effect sizes varied considerably between studies. This variation reduces the precision of the pooled estimate and may reflect methodological differences between studies, particularly in the assay methods used. The findings should therefore be interpreted as descriptive rather than definitive.

3.5 Heterogeneity Analysis

As Fig. 2 shows, between-study heterogeneity was pronounced (I^2 = 97.4%; τ^2 = 1.64; $p < 0.0001$). Exploratory subgroup analyses were conducted by assay method and study region, but neither analysis could reliably explain the heterogeneity. Assay-specific estimates varied, whereas no robust conclusion could be drawn regarding regional differences because one regional subgroup contained only a single study. The direction of the association was

Table 2. Risk of bias assessment of included studies using the JBI Checklist (domain-level judgments).

Study (year)	Selection & allocation	Exposure measurement	Outcome measurement	Confounders identified	Confounder strategies	Statistical validity	Reporting	Overall RoB judgment
(Farid & Abulfaraj, 2013) Jeddah [24]	Yes — clear inclusion criteria; objective diagnosis (T2D, HbA1c, serum zinc)	Unclear	Yes — validated assays	Yes (limited)	Partial — basic adjustment	Yes — descriptive, *t*-test, correlation	Yes — detailed subjects & setting	Moderate
(Farooq 2019) Riyadh [25]	Yes — clear criteria; T2D, HbA1c defined	Yes — zinc measured with a validated kit	Yes — validated methods	Yes (age, sex, BMI, BP, FBS, HbA1c, lipids)	Yes — statistical adjustment	Yes — descriptive, *t*-test, correlation	Yes — comprehensive reporting	Moderate
(Farooq et al., 2020) Riyadh [21]	Yes — HbA1c cut-offs, zinc deficiency <10 µmol/L	Yes — validated assay	Yes — validated methods	Yes (age, sex, BMI, marital status, socioeconomic status, hypertension, dyslipidemia)	Yes — regression models	Yes — correlation, logistic & multivariate regression	Yes — detailed eligibility, demographics, lab methods	Serious
(Hasanato 2020) Riyadh [23]	Yes — OGTT diagnosis, HbA1c, zinc ICP-MS	Yes — validated ICP-MS	Yes — validated methods	Yes (age, sex, illness duration, treatment, complications, lifestyle)	Partial	Yes — descriptive, *t*-test, correlation	Yes — comprehensive reporting	Moderate
(Khan et al., 2015) Riyadh [20]	Yes — ≥5 years T2D, proteinuria, controls	Yes — validated assays	Yes — validated methods	Yes (age, sex, duration, HbA1c, proteinuria; diet/ medications not addressed)	Partial	Yes — ANOVA, Tukey, Pearson	Yes — detailed demographics & labs	Moderate
(Yakout et al., 2021) Riyadh [22]	Yes — WHO FBG thresholds (T2D, prediabetes, controls)	Yes — ICP-MS validated	Yes — validated methods	Yes (age, sex, BMI, BP, waist-hip ratio, lifestyle; residual confounding)	Partial — adjusted *p*-values	Yes — descriptive, ANOVA/ Kruskal-W allis, correlation	Yes — comprehensive reporting, ethics approval	Moderate

Abbreviations: JBI, Joanna Briggs Institute; RoB, risk of bias; OGTT, Oral Glucose Tolerance Test; FBG, Fasting Blood Glucose; BMI, Body Mass Index; BP, Blood Pressure; FBS, Fasting Blood Sugar.

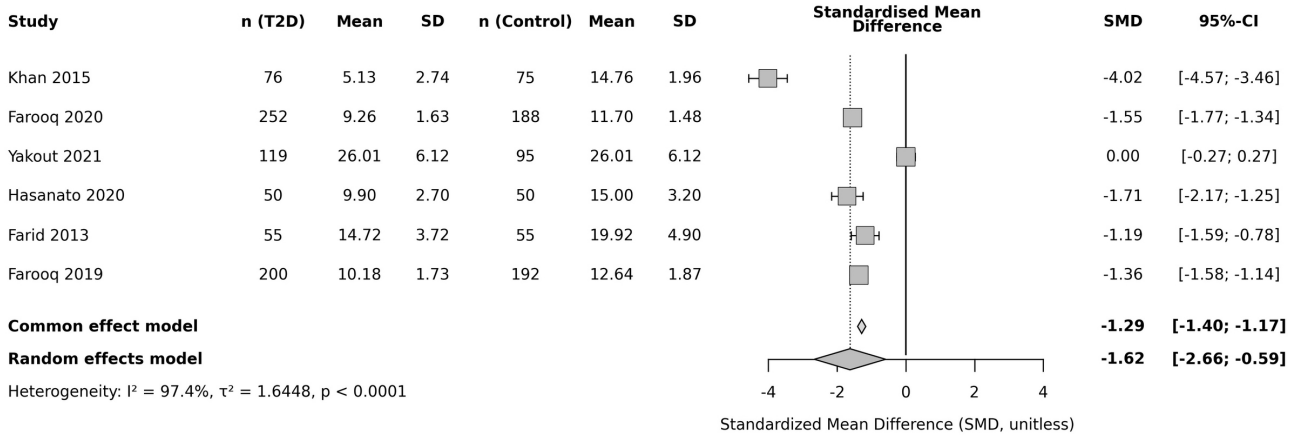


Fig. 2. Forest plot of standardized mean differences (SMDs) in serum zinc concentrations between individuals with type 2 diabetes and controls. Study-level data are reported in µmol/L (Table 1), whereas pooled estimates are expressed as standardized mean difference (SMD), which are unitless. Squares represent individual study estimates, horizontal lines represent 95% confidence intervals, and the diamond represents the pooled random-effects estimate. Negative SMD values indicate lower serum zinc in the T2D group. CI, confidence interval; SMD, standardized mean difference; T2D, type 2 diabetes.

negative in five of the six studies. Yakout et al. [22] (2021) was the exception, as it reported identical serum zinc values in both groups and therefore contributed a null estimate.

Measurement procedure likely fed the heterogeneity as well. ICP-MS delivered tighter, more accurate readings, while the less sensitive colorimetric assays drifted more from one study to the next. Such methodological unevenness may have inflated the between-study variability [26].

3.5.1 Assay and Region Subgroups

To explore possible sources of heterogeneity, subgroup analyses were carried out by assay method and study region. As shown in Fig. 3, assay-specific estimates varied, with ICP-OES showing the largest reduction in serum zinc (SMD = –4.02, 95% CI: –4.57 to –3.46), while ICP-MS, GFAAS, and colorimetric assays showed smaller reductions (SMD range: –1.08 to –1.36). However, the test for subgroup differences was not statistically significant ($\chi^2 = 4.00$, df = 3, $p = 0.2617$), indicating that assay method could not be confirmed as a source of heterogeneity. Because only six studies were included, with some assay subgroups represented by a single study, these subgroup findings should be interpreted as exploratory only.

Subgrouping by region showed no statistically significant difference between Riyadh and Jeddah studies ($\chi^2 = 0.14$, df = 1, $p = 0.7120$). Fig. 4 shows the Riyadh studies pooling to –1.72 (95% CI: –2.97 to –0.46), while the single Jeddah study gave –1.19 (95% CI: –1.59 to –0.78). Because the Jeddah subgroup contained only one study, no robust conclusion can be drawn regarding geographic variation.

3.5.2 Sample Size Subgroups

A further analysis grouped the studies by sample size to explore whether larger and smaller studies contributed differently to the observed heterogeneity. The larger studies (total sample size >150) pooled to an SMD of –1.72 (95% CI: –3.34 to –0.10), with very high heterogeneity ($I^2 = 98.4\%$). The smaller studies (total sample size ≤150) pooled to an SMD of –1.44 (95% CI: –1.95 to –0.93), with lower but still substantial heterogeneity ($I^2 = 64.2\%$). However, the difference between the two subgroups was not statistically significant ($\chi^2 = 0.06$, df = 1, $p = 0.8134$). These findings suggest that study size alone did not explain the between-study heterogeneity observed in the meta-analysis, as Fig. 5 indicates.

3.5.3 Exploratory Subgroup Analyses

Table 3 (Ref. [20,21,22,23,24,25]) summarizes how the six studies reported potential moderators. Age was reported in all six studies. HbA1c was reported in five studies; Yakout et al. [22] (2021) used fasting glucose criteria only and did not report HbA1c. Therefore, subgroup analyses by glycaemic control were interpreted cautiously. Diabetes duration was available in four studies. Complications such as proteinuria and microalbuminuria, along with renal indices, appeared in only two, which was too few to support a subgroup analysis. Assay type and sample handling were reported across all six studies, though the techniques used differed, including ICP-OES, ICP-MS, GFAAS, and colorimetric methods. Taken together, the available evidence is most consistent with assay methodology being the main contributor to the heterogeneity, with age, HbA1c, and diabetes duration as possible additional factors. The data on complications and renal function were too limited to allow any assessment.

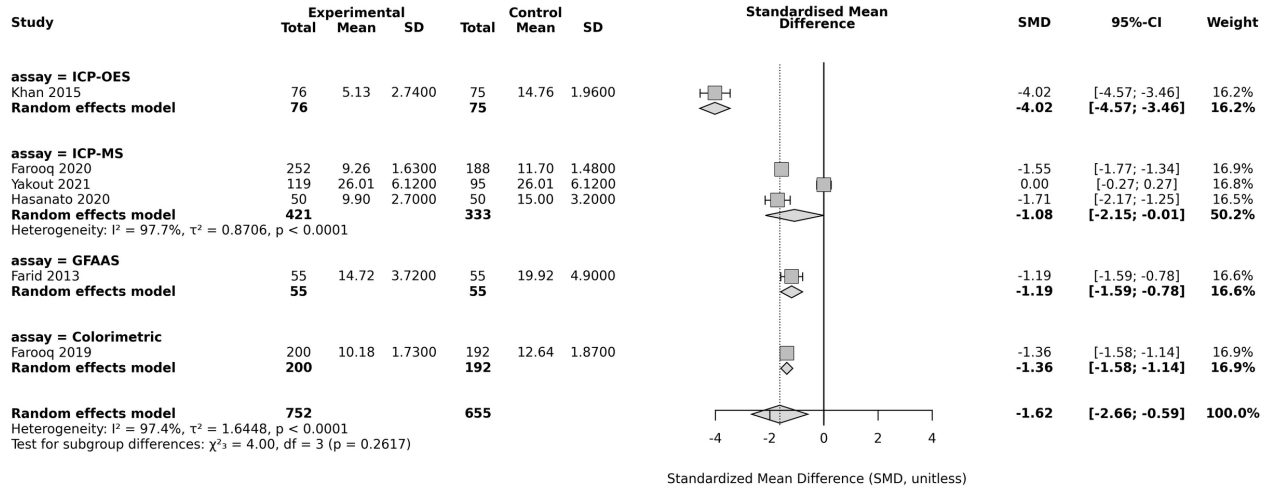


Fig. 3. Subgroup analysis by assay method.

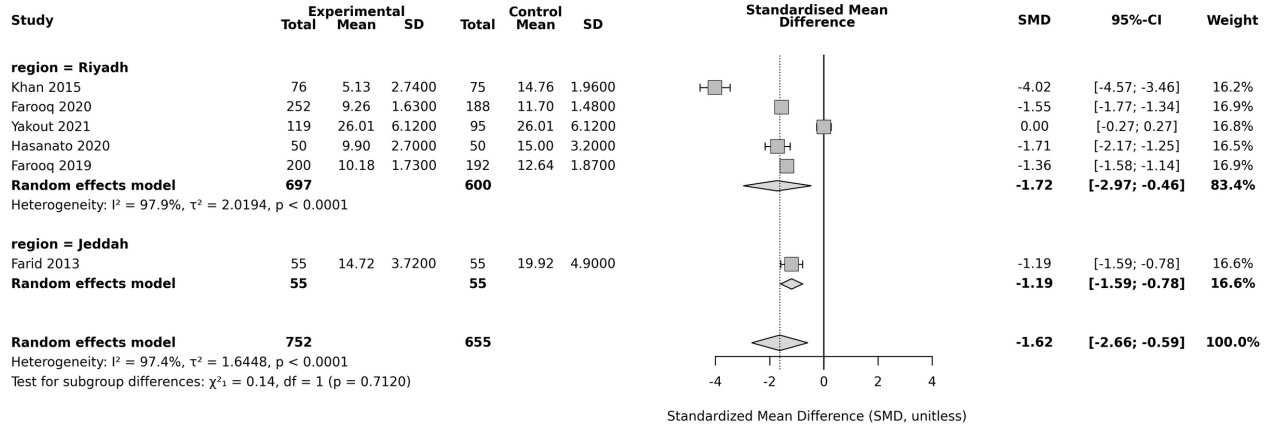


Fig. 4. Subgroup analysis by study region (Riyadh vs. Jeddah).

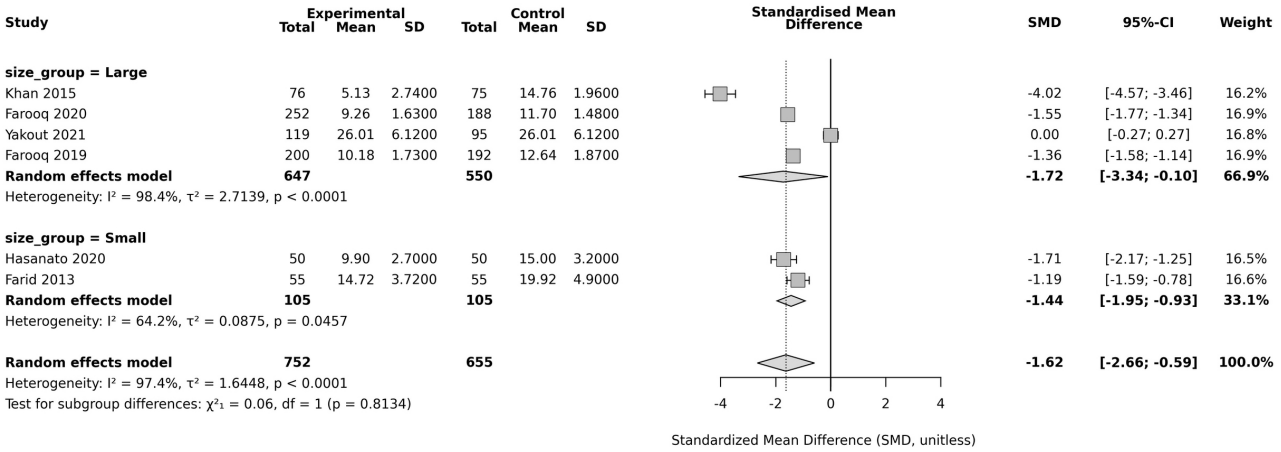


Fig. 5. Subgroup analysis by sample size (large vs. small studies).

3.5.4 Exploratory Reporting-Completeness Analyses

Beyond assay type, region, and sample size, several additional exploratory analyses were conducted to examine whether the availability of key study-level information differed across the included studies. These analyses grouped studies according to whether age, diabetes duration, glycaemic control as measured by HbA1c, complications, and renal function were reported. The results are presented in

Table 3. Reporting of key moderators across the six included studies.

Study	Age reported	Diabetes duration	HbA1c (glycemic control)	Complications reported	Renal function data	Sample collection/ processing
Khan et al., 2015 (Riyadh) [20]	Yes (30–90 yrs; tertiles)	Yes (≥5 yrs)	Yes (HbA1c 8.2% in T2DM + proteinuria, 7.1% in T2DM)	Yes (proteinuria)	Yes (creatinine, CrCl, UAE, ACR)	Yes (fasting blood, serum stored at –80 °C, urine dipstick/turbidimetric)
Farooq et al., 2020 (Riyadh) [21]	Yes (<50 vs. >50 yrs)	No	Yes (HbA1c mean 8.1% vs. 5.6% controls; poor control >7%)	No	Exclusion criteria only (<30 CrCl), no renal indices	Yes (fasting blood, HbA1c resin method, zinc ICP-MS with QC)
Yakout et al., 2021 (Riyadh) [22]	Yes (mean ages: 40.9, 46.7, 52.2 yrs)	No	No (glycemic status by fasting glucose only)	No	No (renal disease excluded)	Yes (fasting blood, serum digested with nitric acid/ H_2O_2, centrifuged, stored at 4 °C)
Hasanato, 2020 (Riyadh) [23]	Yes (mean ages 55–58 yrs)	Yes (8.7–10.4 yrs)	Yes (HbA1c stratified: <6.5% vs. >6.5%)	Yes (microalbuminuria in 26% of the poor control group)	Limited (microalbuminuria only)	Yes (venous blood, serum stored at –80 °C, nitric acid calibration, dilution 1:50)
Farid & Abulfaraj, 2013 (Jeddah) [24]	Yes (45–65 yrs; mean ~60)	Yes (mean 5.3 yrs)	Yes (HbA1c mean 9.18% vs. 5.27% controls; stratified <8% vs. >8%)	No (acute complications excluded)	No	Yes (fasting blood, serum stored at –70 °C)
Farooq, 2019 (Riyadh) [25]	Yes (mean ~52 yrs)	Yes (>2 yrs)	Yes (HbA1c mean 9.7% vs. 4.5% controls; stratified <7% vs. >7%)	No	Exclusion criteria only (<30 CrCl), no renal indices	Yes (12-h fasting blood, HbA1c resin method, zinc measured colorimetrically)

Abbreviations: ACR, albumin-to-creatinine ratio; CrCl, creatinine clearance; HbA1c, glycated haemoglobin; UAE, urinary albumin excretion; T2DM, Type 2 Diabetes Mellitus; QC, quality control.

Supplementary Figs. 1–5. Because these groupings were based on reporting status rather than the actual measured levels of these variables among participants, they should not be interpreted as clinical moderator analyses. Overall, the pooled effects generally pointed toward lower zinc levels in type 2 diabetes; however, heterogeneity remained high. Therefore, these supplementary analyses are presented as descriptive reporting-completeness analyses only, and no firm conclusions can be drawn regarding the contribution of these variables to the observed heterogeneity.

3.5.5 Sensitivity Analysis

Influence analyses tested how firmly the pooled estimate stood. In the leave-one-out checks, dropping any single study barely moved the overall standardized mean difference, which stayed negative at every step. Heterogeneity persisted (I^2 >95%), but the direction and size of the effect did not budge—no single study was steering the result. **Supplementary Fig. 6** carries the leave-one-out forest plots.

3.5.6 Prediction Intervals

To map the uncertainty more fully, prediction intervals were calculated alongside the random-effects model. The pooled random-effects estimate favoured lower serum zinc in type 2 diabetes (SMD = –1.62, 95% CI: –2.66 to –0.59); however, the prediction interval was much wider (–5.19 to 1.94). This indicates that, although the average effect was negative, a future study could plausibly show a very large negative effect, a smaller effect, or no effect. This wide interval reflects the very high between-study heterogeneity (I^2 = 97.4%) and supports cautious interpretation of the pooled estimate. **Supplementary Fig. 7** shows the prediction interval within the forest plot.

3.6 Publication Bias

Publication bias was assessed visually using a funnel plot and formally using Egger's regression test (Fig. 6). The funnel plot appeared asymmetric, with one study showing an extreme negative effect size. However, because only six studies were included, both visual assessment of funnel plot asymmetry and Egger's regression test are underpowered and should be interpreted with caution. Therefore, publication bias could not be reliably assessed, and larger, methodologically rigorous studies are needed to clarify whether small-study effects or selective reporting influenced the pooled estimate.

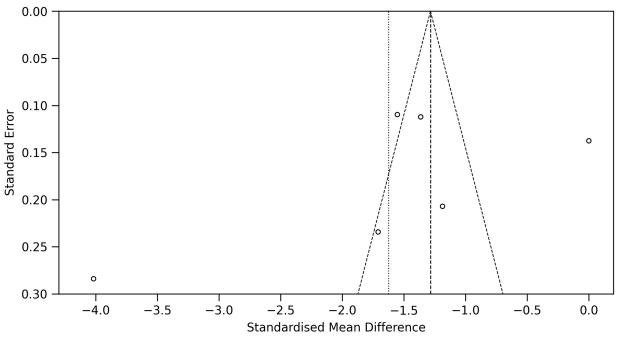


Fig. 6. Funnel plot of the included studies showing visual asymmetry, including one study with an extreme negative effect size. Given the small number of included studies, publication bias could not be reliably assessed.

3.7 Certainty of Evidence

The GRADE framework graded the certainty of evidence for zinc deficiency in Saudi adults with type 2 diabetes. Risk of bias rated serious. Notably, the studies were cross-sectional and hospital-based, with loose control of confounders such as diet, treatment regimen, and comorbidity. Inconsistency was also rated serious because between-study heterogeneity was very high. In the primary meta-analysis, five study comparisons [20,21,23,24,25] showed lower serum zinc in adults with T2D than in controls, while Yakout et al. [22] reported identical zinc values in both groups and therefore contributed a null estimate.

Indirectness held its ground, since every study examined Saudi adults and clinically meaningful outcomes (serum zinc, HbA1c, and proteinuria). Precision slipped, however: the larger studies estimated well, but small samples and subgroup splitting drained confidence. Given the single-center designs, exploratory analyses, and missing protocol registration, publication bias looked possible as well.

Overall, the certainty of evidence was rated as low. Most studies confirm that zinc deficiency travels with type 2 diabetes and its complications. Heterogeneity and methodological gaps, however, hold confidence in the pooled estimate down. Therefore, the case for well-designed prospective and interventional studies, ones that can pin zinc to glycemic control and diabetic complications, is hard to miss.

Detailed study-specific JBI risk-of-bias judgments and methodological concerns are provided in **Supplementary Tables 2–7**. The GRADE certainty assessment was conducted only at the body-of-evidence level and is presented in Table 4 (Ref. [20,21,22,23,24,25]). Therefore, both underpin the summary judgments in Table 4 of the main text.

4. Discussion

This meta-analysis found that serum zinc was generally lower in Saudi adults with type 2 diabetes than in healthy controls, although one included study reported no difference between groups. The pooled effect was large (common-effect model: –1.29; random-effects model: –1.62), yet the heterogeneity was striking (I^2 = 97.4%) and tempers any strong reading. The findings stand as exploratory rather than settled. They sit comfortably beside the global literature on zinc deficiency in diabetes. Notably, methodological and contextual limits keep firm conclusions out of reach.

Several frameworks try to explain why zinc deficiency tracks T2D. The first is dietary. Saudi Arabia's nutritional transition, urbanization and westernized eating, has cut intake of zinc-rich foods such as legumes, seafood, and dairy, leaving a subclinical shortfall that turns clinically relevant under the metabolic stress of diabetes; this places the present findings within the broader account of diet-induced micronutrient imbalance in chronic disease [7,21]. Diet is not the whole story. Chronic hyperglycemia stokes systemic inflammation that shunts zinc into hepatic tissue through IL-6-mediated metallothionein expression [4], and the resulting deficiency cripples antioxidant enzymes like superoxide dismutase, sharpening oxidative stress and insulin resistance [5]. That feedback loop supplies a mechanism for the observed association. Renal loss adds another route: diabetic nephropathy drives urinary zinc excretion upward and serum zinc downward [8], tying the deficiency to both metabolic dysfunction and the nephropathy and proteinuria seen in Saudi cohorts. Low zinc also tends to accompany poor glycemic control—no surprise, given zinc's part in insulin synthesis, crystallization, and receptor signaling [24,25]. These pathways suggest plausible biological links between zinc status and T2D pathophysiology, but the available observational evidence cannot determine whether lower zinc is a cause, consequence, or marker of metabolic dysregulation.

Diet and excretion aside, the molecular dysregulation of zinc transporters offers a way to explain why individuals differ. Experimental models show that transporter dysfunction, especially across the ZIP and ZnT families, disturbs insulin signaling and glucose metabolism [27]. None of the included Saudi studies measured zinc transporter expression. Therefore, future Saudi studies could consider whether zinc transporter pathways have relevance to serum zinc changes in T2D. Genetic and epigenetic differences in transporter activity may be why zinc deficiency varies between populations, and why two people with the same diet and disease course can be metabolically worlds apart.

The steady finding of lower serum zinc in Saudi adults with T2D suggests the deficiency may feed poor glycemic control, oxidative stress, and the march of complications such as nephropathy and dyslipidemia. The data are associative, yet they hint that zinc could work as a biomarker for

Table 4. Overall certainty of evidence for zinc deficiency in type 2 diabetes across six Saudi studies, assessed using GRADE domains.

Domain	Evidence across studies	Overall assessment
Risk of bias	All six studies are cross-sectional, hospital-based, with limited control for confounding (dietary intake, treatment regimens, comorbidities).	Serious — downgrades certainty.
Inconsistency	Five studies [20,21,23,24,25] consistently reported hypozincemia in T2DM, while one study [22] reported a null finding.	Serious — heterogeneity reduces confidence.
Indirectness	The populations are Saudi adults, directly relevant to the review question. Outcomes (serum zinc, HbA1c, proteinuria) are clinically meaningful.	Not serious — no downgrading.
Imprecision	Larger studies [21,22,25] provide robust estimates. Smaller samples [23,24] and subgroup analyses reduce precision.	Serious — some downgrading warranted.
Publication bias	Possible across all studies due to single-center designs, exploratory analyses, and emphasis on positive findings without protocol registration.	Possible — caution required.
Overall certainty (GRADE)	In the primary meta-analysis, five of the six study comparisons showed lower serum zinc in adults with T2D, while one study reported identical zinc values in T2D and controls. However, the evidence was limited by cross-sectional designs, methodological limitations, very high heterogeneity, and possible publication bias.	Low Certainty

Abbreviations: GRADE, Grading of Recommendations Assessment, Development and Evaluation.

metabolic risk stratification. Further prospective studies are required to determine whether serum zinc measurement has prognostic or clinical utility in patients with T2D. Caution still applies, the evidence is observational and methodologically mixed, and affected by very high heterogeneity.

The implications run in two directions, clinical and scientific. In clinical practice, monitoring serum zinc in patients with poor glycemic control and nephropathy might help identify those at greater risk of complications. Trials that adapt supplementation to Saudi dietary patterns could then examine whether correcting zinc levels reduces HbA1c and lessens oxidative stress. On the research side, future work should pair clinical zinc measurement with molecular profiling of transporter expression. In doing so, it would sort dietary shortfall from renal loss and from intracellular dysregulation. Standardized assays would cut heterogeneity and improve reproducibility. In addition, longitudinal designs would put causal claims on firmer ground.

The high heterogeneity points to limitations that are both methodological and contextual. Variation in assay methods, incomplete control of confounders such as diet and medication, and the use of cross-sectional designs all weaken any causal interpretation. The pooled estimate should therefore be read with caution. Most studies carried a moderate risk of bias; the field needs sturdier ones. The scale of the heterogeneity here ($I^2 = 97.4\%$) almost certainly reflects factors the subgroup analyses could not fully catch participant mix, diabetes duration, glycemic control, the prevalence of complications, nutritional status, dietary zinc intake, and coexisting illness among them. Variation in recruitment setting, laboratory method, and study design probably played a part too. Because the studies reported these factors so unevenly, their influence escaped direct testing. Even so, the direction of the association is consistent, which is why the findings are best read as hypothesis-generating rather than conclusive. The analysis provides preliminary evidence that zinc deficiency occurs alongside type 2 diabetes in Saudi adults, which is in keeping with the broader literature. This is compatible with the proposed mechanisms of nutritional transition, oxidative stress, renal loss, and transporter dysregulation. The methodological heterogeneity and the moderate quality of the included studies, though, mean the results fall short of proof. Determining whether zinc deficiency is a modifiable risk factor or contributes to the development of diabetes will require clinical, dietary, and molecular data considered together.

5. Limitations

Several limitations bound the evidence gathered here. First, all of the included studies were cross-sectional, so the analysis can address association but not causation. In the absence of longitudinal or mechanistic data, it remains unclear whether zinc deficiency precedes type 2 diabetes, results from it, or instead reflects poor glycemic control and its complications. Second, the studies were conducted exclusively in Saudi populations, which limits how readily the findings extend to groups with different diets, genetic backgrounds, or health systems. Third, between-study heterogeneity was very high ($I^2 = 97.4\%$), and the differences in assay methods across ICP-MS, ICP-OES, GFAAS, and colorimetric techniques likely contributed to it. Other factors may also have affected the pooled estimate, including participant characteristics, diabetes duration, glycemic control, nutritional status, and clinical setting, so the overall effect size should be interpreted cautiously. Fourth, common confounders such as dietary zinc intake, systemic in-

flammation, and medication use were unmeasured or unadjusted in a number of the studies, which may bias the reported associations. Finally, none of the studies measured zinc transporter expression, so the mechanistic evidence is limited, and the molecular pathways remain separate from the epidemiological finding.

The review process carried limits of its own. The search reached only PubMed, Cochrane CENTRAL, ClinicalTrials.gov, and Google Scholar. Although this strategy captured indexed literature and additional records through Google Scholar, it did not include Embase, Scopus, or Web of Science because of institutional access limitations. This may have increased the possibility of missed studies. During revision, a targeted supplementary check of accessible records was performed using key concepts related to zinc, type 2 diabetes, and Saudi Arabia, and no additional eligible studies were identified. To support transparency and reproducibility, all search strings and filters were recorded in accordance with PRISMA 2020 guidelines. Two reviewers screened and extracted independently and settled disagreements by consensus, trimming selection and extraction bias. All serum zinc values also moved to μmol/L, and leave-one-out analyses tested the pooled estimates. None of this erases the limitations. Notably, it does strengthen the case that the association survives across different study conditions.

6. Future Perspectives

This meta-analysis points consistently toward lower zinc levels in Saudi adults with T2D. The mechanism underlying this finding, and in particular the part played by zinc transporters, is still not well understood. A reasonable next step would be functional and genetic research on how the major zinc transporters are expressed and regulated in the Saudi T2D population. Examining how these transporters change under diabetic conditions in insulin-sensitive tissues such as the liver, skeletal muscle, and pancreas could be informative. Work of this kind has the potential to provide mechanistic insight as well as candidate biomarkers of disease progression.

Given their hand in insulin signaling, ER stress regulation, and β-cell function, ZIP7 and ZIP14 stand out as targets. Experimental models already tie their dysfunction to glucose intolerance and cardiac abnormalities [28]. Whether the same holds in human populations, particularly high-burden ones like Saudi Arabia, is still an open question.

An integrated design would help most clinical zinc measurement paired with molecular profiling of transporter gene expression and activity. These findings point to a transporter-related form of functional zinc deficiency, one that may appear even when dietary intake is adequate and renal function is normal. Pairing genomic and epigenetic data with dietary and metabolic measures could help identify the patients most likely to benefit from individualized efforts to restore zinc status, and clarify whether those efforts have any effect on glycemic control. Characterizing the zinc–diabetes relationship will probably require a multi-omics approach that brings together clinical, molecular, and environmental data; without it, statements about prevention or treatment stay tentative.

7. Conclusion

This meta-analysis found that serum zinc concentrations were generally lower in Saudi adults with type 2 diabetes than in controls, but the pooled estimate warrants caution because of severe between-study heterogeneity (I^2 = 97.4%) and the observational, cross-sectional design of all included studies. The findings support an association between T2D and lower serum zinc in most Saudi studies, but they do not establish causality or justify clinical recommendations.

The results add to a global body of work linking trace element imbalance to metabolic disease, and they make the case for tougher study designs in Saudi populations. What is needed now is longitudinal research with standardized zinc measurement, capable of telling whether zinc deficiency helps drive the disease or merely mirrors its metabolic disorder.

Zinc transporters (ZIPs and ZnTs) make an appealing mechanistic hypothesis and a possible biomarker, yet the evidence so far is indirect and speculative. They merit serious experimental and genetic study; on the current data, they cannot yet be called an established explanation.

This review provides a foundation for further clinical and molecular research on the observed association between lower serum zinc concentrations and type 2 diabetes in Saudi adults, while emphasizing the need for prospective studies to clarify causality and clinical relevance.

Availability of Data and Materials

The data will be made available upon request. The data supporting the findings of this study are available within the paper. If any raw data files are needed, they are available from the corresponding author upon reasonable request.

Author Contributions

AMA conceptualization, methodology, formal analysis, writing—original draft, AHA formal analysis, writing—review & editing. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/IJVNR53277.

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