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Burden of micronutrient deficiency among patients with type 2 diabetes: systematic review and meta-analysis

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ABSTRACT

Background Micronutrient deficiencies are a significant issue worldwide, particularly in South Asia and sub-Saharan Africa. These deficiencies can impact glucose metabolism and insulin signalling pathways, potentially leading to the beginning and advancement of type 2 diabetes (T2D). This study is a comprehensive assessment of the burden of multiple micronutrient deficiencies among T2D patients. The aim of the study is to resolve conflicting evidence from previous studies that mainly focused on one specific micronutrient.

Methods The systematic review followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 guidelines and the Cochrane Handbook. This comprehensive literature search explored Embase, ProQuest, PubMed, Scopus, Cochrane Library, Google Scholar, LILACS and the grey literature, and studies that met the inclusion criteria. A pre-piloted data extraction sheet was used to extract data for relevant study outcomes and characteristics. Results were produced by R V.4.3.2 (R Core Team 2023 using general packages such as tidyverse, and specific packages such as meta and metafor.

Results The analysis included 132 studies with 52 501 participants. The pooled prevalence of multiple micronutrient deficiency (vitamins, minerals and electrolytes) was 45.30% (95% CI 40.35% to 50.30%) among T2D patients. The pooled prevalence (48.62%, 95% CI 42.55 to 54.70) was higher in women with T2D than in men. Vitamin D was the most prevalent micronutrient deficiency (60.45%, 95% CI 55% to 65%), followed by magnesium (41.95%, 95% CI 27% to 56%). B12 deficiency (28.72%, 95% CI 21.08% to 36.37%) was higher in the metformin consuming group. The prevalence of micronutrient deficiency varied across WHO regions.

Conclusions Micronutrient deficiencies were common in T2D patients, the most common being vitamin D deficiency. Women were more likely to be affected by micronutrient deficiency than men. These studies were hospital based and the findings of this systematic review may be used with caution due to inherent selection bias. Diversity of foods, lifestyle choices and cultural practices may contribute to geographic variations in micronutrient deficiency.

Trial registration PROSPERO CRD42023439780.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Researchers have paid little attention to the role of hidden hunger and micronutrient deficiency in type 2 diabetes (T2D), which may not manifest clinically in early deficiencies.
⇒ Preliminary review of the literature unveiled varied prevalence of micronutrient deficiencies and contradictory results in T2D, and a systematic review reported an 80.4% prevalence of vitamin D deficiency among T2D patients, while another reported a lower prevalence of 32.7%.
⇒ Several studies have reported the prevalence of individual micronutrient deficiency in T2D.

WHAT THIS STUDY ADDS

⇒ This study included multiple micronutrient deficiencies in T2D patients and all studies published in seven major databases between 1998 and 2023, regardless of country, economy or language, as well as reports and studies from the grey literature.
⇒ Pooled prevalence of micronutrient deficiency among patients with T2D are provided and the difference in the prevalence between geographic areas, sexes and time periods.
⇒ The trend in prevalence rate over the years is presented, and contradictory pieces of evidence are discussed.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ We have identified research gaps in our knowledge of the burden of micronutrient deficiencies in T2D patients, which will attract new research on the topic.
⇒ The study findings will help address the escalating issue of hidden hunger or micronutrient deficiencies among T2D patients and their long term medical consequences.
⇒ Programme managers and practitioners will be able to fine tune or amend their clinical practice of the management of T2D.

INTRODUCTION

Diabetes is a pervasive health issue globally due to the associated comorbidities, complications and premature deaths. In recent decades, a continuous increase in both the incidence and prevalence of diabetes has been seen.[1] Type 2 diabetes mellitus (T2D) is a multifactorial metabolic disorder characterised by elevated blood glucose levels resulting from insulin resistance, disruptions in insulin secretion regulation and a decrease in pancreatic beta cell mass.[2 3] In addition to a genetic predisposition to T2D development, various environmental factors, sedentary lifestyle, unhealthy dietary habits and obesity significantly contribute to its onset.[4]

T2D has multifactorial aetiologies. Numerous studies have suggested a significant role of micronutrients in influencing the development and pathophysiology of insulin resistance, a fundamental underlying factor of diabetes and various cardiometabolic disorders.[5] Deficiencies in specific micronutrients associated with insulin action may act as catalysts in the pathways leading to several diseases, including T2D.[6–8] Some studies have reported the significant physiological implications of essential micronutrients and demonstrated direct connections with diabetes mellitus and a higher risk of morbidity and mortality.[9 10]

About a third of the global population is estimated to have at least one essential micronutrient deficiency.[11] These essential micronutrient deficiencies might cause a deficit in insulin action due to oxidative stress or reduced activity of insulin associated enzymes.[6–8 12] The significance of various micronutrients as cofactors in the glucose metabolic pathways, pancreatic beta cell function and insulin signalling cascade suggests that their deficiency may contribute to the development of T2D.[13] Increasing clinical evidence supports the notion that a lack of micronutrients, such as biotin, chromium, thiamine, vitamin D and vitamin C, may have metabolic effects. Deficiency of these vitamins is notably prevalent among individuals who have both obesity and diabetes.[13] It is also well established that individuals with obesity are at a fourfold increased risk of developing T2D, which could be due to pancreatic beta cell dysfunction, genetics, behavioural traits, a heightened resistance to incretin hormones and oxidative stress. In addition, certain micronutrient deficiencies prevalent in obese individuals might also play a part in the development of T2D.[13]

The available scientific evidence provides a reliable source for estimating the burden of essential micronutrient deficiency or overload in T2D. However, the inconsistency in the prevalence reported in a multitude of studies poses a serious challenge for physicians and policy makers in establishing nutritional recommendations for diabetes management. Diverse inconsistencies led to the conceptualisation of our systematic review and meta-analysis of estimates of the prevalence of micronutrient deficiencies in T2D reported in many studies. We evaluated the overall prevalence of micronutrient deficiencies among T2D subjects to answer the research question, What is the burden of micronutrient deficiency among patients with T2D? This systematic review and meta-analysis will serve as a guide and provide foundational data for evidence to policy makers and other stakeholders in planning for effective prevention and intervention strategies for T2D mellitus. Also, this study will establish a baseline for researchers as a reference for future studies.

METHODS

This systematic review and meta-analysis assessed the estimates of the pooled prevalence of various micronutrient deficiencies in the T2D patient population reported in published studies. A comprehensive literature search was conducted using Embase, ProQuest, PubMed, Scopus, Cochrane Library, Google Scholar, LILACS and the grey literature, and studies that met the inclusion criteria were identified. A pre-piloted data extraction sheet was used to extract data for relevant study outcomes and characteristics.

The study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[14] and the guidelines stated in the Cochrane Handbook of Systematic Reviews.[15] The study protocol was published previously.[16]

Search strategy

Initially, a search string was developed for Embase; subsequently, we modified the search keywords/terms to build search strings for various electronic databases. Keywords for the study were developed using various medical subject headings (MESH)/non-MESH/Emtree terms, combining them with Boolean operators. A distinct search strategy was put forward to conduct a grey literature search using Embase, ProQuest, Google Scholar and Scopus; institutional repositories such as the international diabetes federation and other international associations/organisations related to micronutrients and diabetes were also explored. A list of reproducible search keywords such as 'Hidden hunger' OR 'micronutrient deficiency' OR 'multiple vitamin deficiencies' OR 'multiple trace element deficiencies' OR 'micro-mineral deficiencies' AND 'Type 2 diabetes mellitus' OR 'T2D' OR 'non-insulin-dependent diabetes' OR 'adult-onset diabetes' AND 'Prevalence OR incidence OR burden' was prepared for all of the databases, including the grey literature, before the initial keyword search on 31 July 2023 and later on 1 January 2024 to update the search with studies from 1 August 2023 to 31 December 2023 (online supplemental file 1). These search criteria were mutually decided by the study authors (DKM, NS, AKP, DG and KCS) and peer reviewed using the PRESS Evidence Based Checklist to evaluate the adequacy of the search strategy[17] (online supplemental file 2).

Study eligibility

The review included observational studies (ie, cross sectional and cohort studies) to assess the prevalence/burden/incidence of micronutrient deficiency of minerals/electrolytes (zinc, chromium, iron, copper, fluoride, selenium, iodine, manganese, calcium, phosphorus, molybdenum, potassium, folic acid, magnesium, sodium) and vitamins (vitamins A, B1, B2, B3, B5, B6, B7, B9, B12, C, D, E and K) in patients with T2D. All studies published between 1998 and 2023, irrespective of demography, country, language or economy, grounded on sound methodology in terms of defined inclusion and exclusion criteria were included in the review.[16] Also, grey literature studies and reports were included. Expert opinions, newspaper reports, case reports, narrative reviews, editorials, conference abstracts and posters were excluded.

Inclusion and exclusion criteria

Inclusion criteria were: T2D patients with or without complications, aged ≥18 years, of all sexes and ethnicities; T2D patients with micronutrient deficiency; and cross sectional, longitudinal and cohort studies, and randomised controlled trials. Exclusion criteria were: patients with type 1 diabetes mellitus, gestational diabetes and T2D in individuals aged <18 years; and supplementation of micronutrients, case reports, case series, reviews and ecological studies.

Selection of studies

After the study search, the titles and abstracts of all of the pertinent research articles and unpublished reports were retrieved using the search strategy and other additional sources. All of the selected studies were imported to Rayyan software to check for duplicates and screening (NS).[18] A manual search was also performed to check for duplicate articles (NS).

A comprehensive screening process was undertaken by two independent reviewers at each stage, including article title and abstract screening (NS and KCS) and full text screening (NS and DKM) using Rayyan software.[18] Two reviewers (NS and KCS) independently screened the titles and abstracts to find studies that fitted the inclusion and exclusion criteria. Google translator was used to translate articles published in languages other than English. All decisions on the inclusion or exclusion of studies were documented using Rayyan software. Eligible citations were retrieved after screening titles and abstracts, and the full texts were sought and imported. The selected full text articles were screened (NS and DKM). Any reviewer disagreement was resolved through discussion with a third reviewer (SDG). We contacted the authors to request the complete text if the full text article was not available. A specific reason for removal accompanied each exclusion. Cross references were also searched for potential studies (NS) and specific study investigators were contacted to obtain further details (DKM). We excluded articles if the full text was not available after three consecutive follow-ups. The selected articles were compiled for risk of bias assessment before data extraction.

Data extraction

A pre-piloted data extraction sheet prepared in MS Excel was used. In the data extraction sheet, we compiled information on the study characteristics, type and name of micronutrients, diagnostic criteria for diagnosing T2D and micronutrient deficiency, and the respective cut-off values for deficiency (online supplemental file 3). Two authors (NS and DG) independently extracted the data; any conflict was resolved by discussion with a the third member (DKM). Data from the included studies were extracted to estimate the pooled prevalence of micronutrient deficiency among T2D patients. However, the cut-off values for some of the micronutrients varied across the selected articles. Therefore, we considered the participants (i) who were already categorised as deficient/sufficient, (ii) between unit measurements, consistency was preserved (online supplemental file 3) and the information was extracted accordingly.

Quality assessment and level of evidence

The quality of the studies was assessed using the Joanna Briggs Institute Critical Appraisal Checklist.[19] This tool comprises nine questions for prevalence studies, eight for analytical cross sectional studies, 11 for systematic reviews and meta-analyses, and 11 for cohort studies. For each question, the answer options were yes, indicating higher quality, no, indicating low quality, unclear or not applicable. Two authors (NS and DKM) assessed the methodological quality of the selected articles. Any discrepancies in judgments regarding inclusion were resolved by the third author (SDG). We generated the risk of bias plot using Excel. The result of the quality assessment was further utilised during sensitivity analysis. Prevalence studies were categorised as high risk (grade 0–3), unclear (4–6) and low risk (7–9) of bias.

Statistical methods

The statistical layout of the study was multifold. Using proportions and numbers, we outlined the study characteristics and provided an overview of the relevant literature. The sample of studies included micronutrients such as vitamins A, B1, B6 and E (k=1) (k=number of studies selected for the meta-analysis), vitamin B12 (k=36), vitamin C (k=2), vitamin D (k=67), iodine (k=1), iron (k=3), magnesium (k=16), potassium (k=1) and zinc (k=2). The pooled prevalence was estimated using a random effects model under mathematical and statistical transformations (that is, logit, double arcsine and generalised linear model approach for variance stabilising purposes.[20–22] We estimated pooled prevalence for all micronutrients and each of the micronutrients for which we had three or more studies on prevalence[23–25] (ie, vitamin D, vitamin B12, magnesium and iron). Model assessment was done by computing Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) values under no transformation, logit transformation, double arcsine transformation, and generalised linear model to identify which transformation was better for stabilising the variance. Subgroup analysis, sensitivity analysis and meta-regression were also performed to strengthen the process of generating statistical evidence.

We used the random effects model to calculate the pooled effect size. The inverse of the total variance of the study was used to weigh each study. To determine if there were significant differences between the groups, we used p values or 95% CIs. Many studies did not report 95% CIs. Hence, as a standard practice, in the meta-analysis, 95% CIs were estimated from the reported cases (ie, number of persons with micronutrient deficiency) and totals (sample, ie, number of patients with T2D) for each study. The standard error (SE) and 95% CI were calculated for each of the studies included in the meta-analysis using popular software packages (eg, meta and metafor} and functions in R software.

Every statistical test used a two sided design, with the p value fixed at 0.05. Results were produced through R V.4.3.2 (R Core Team 2023) using general packages, such as tidyverse, and specific packages, such as meta and metafor, built exclusively for conducting meta-analysis in R environment.

Test of heterogeneity and publication bias

Given that the studies were conducted in several world regions with varying demographic characteristics, we expected heterogeneity. Assessment of statistical heterogeneity was captured using a random effects model under each type of transformation through the measure of between study heterogeneity (r^2) and proportional heterogeneity (I^2).[26] Publication bias was assessed using Egger's regression test for asymmetry and illustrated with a funnel plot. A p value of 0.05 was considered statistically significant.

Subgroup analysis

Subgroup analysis assessed statistical heterogeneity across all micronutrients collectively and individually. For subgroup analysis, we estimated the pooled prevalence for men and women, population with diabetic complications, community/hospital based studies, WHO regions (classified as Americas, Europe, Eastern Mediterranean, South East Asia, Western Pacific and Africa), diabetic

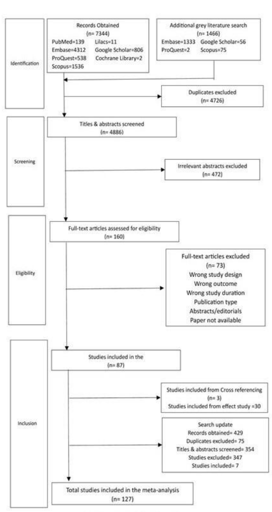

Figure 1 Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flowchart. SRMA, systematic review and meta-analysis.

Table 1 Summary characteristics of studies included in the systematic review

Characteristics	No of studies (n=132)*
WHO region	
Americas	8
Europe	19
Eastern Mediterranean	41
South East Asia	29
Western Pacific	23
Africa	7
Total	127
Missing data	5
Diabetic complications	
Deficient population with complications	26
Year of publication	
1998–2015	35
2016–23	96
Total	131
Missing data	1
Metformin group	
Vitamin B12 deficiency among T2D patients on metformin therapy	3
Study design	
Cross sectional	94
Cross sectional analytical	17
Cohort	1
Retrospective	4
SRMA	1
Total	117
Missing data	15
Study approach	
Hospital based	124
Community based	5
Total	129
Missing data	3
Language	
Bulgarian	1
English	128
German	1
Portuguese	1
Turkish	1
Total	132

*Number of studies selected for meta-analysis.
SRMA, systematic review and meta-analysis; T2D, type 2 diabetes.

patients who had received metformin therapy and years of studies (time periods 1998–2015 (k=96) and 2016–23 (k=36)).

Meta-regression

Meta-regression was conducted, taking publication year as an independent variable to study the pattern of deficiency prevalence for overall and individual micronutrients over time. We prepared bubble plots to visualise the prevalence of multiple micronutrient deficiencies.

Sensitivity analysis

Sensitivity analysis was conducted in two steps. In the first analysis, studies with a weight >10% were excluded from assessing changes in the pooled prevalence of micronutrient deficiency. The second analysis assessed the effect size by removing the outliers identified by computing standardised residuals.

RESULTS

A total of 7344 records were identified during the initial literature search. After screening of the title, abstract and full paper, we identified 127 studies that met the inclusion and exclusion criteria (online supplemental file 4). Three studies reported the prevalence of multiple micronutrient deficiencies, making a total of 132 datasets (n=52 501) for quantitative evidence synthesis. The PRISMA flowchart[14] was prepared to document the process and enable replication (figure 1 and online supplemental file 3). The overall characteristics of the included studies are given in table 1.

Summary of study characteristics

From a total of 132 identified datasets for quantitative evidence synthesis, 94 were cross sectional studies, 124 were hospital based studies, 128 were reported in English, 26 were for individuals with diabetic complications and 30 were for people in the metformin group with vitamin B12 deficiency. All studies reported on WHO regions except five.[27–31] All studies reported on hospital based or community based studies except three.[28 32 33]

We extracted and analysed the data on outpatients and inpatients included in hospital based studies. Outpatients were included as study participants in 37 (29.8%) studies; the remaining were inpatients or not specified.

Risk of bias assessment

The quality of the studies was assessed using the Joanna Briggs Institute Critical Appraisal Checklist.[19] Of 132 selected studies for quantitative evidence synthesis, 96 were prevalence studies, of which 82 (85.41%) did not discuss the sampling frame appropriately (figure 2). More than half of the studies did not address the sampling technique (53.12%) or the sample estimation method (52.1%).

Interestingly, most prevalence studies had a low risk of bias based on other critical appraisal questions. Of the 29 cross sectional studies, 21 (72.41%) did not evaluate the confounding factors or clearly state strategies for dealing with them. For the other questions, most studies were classified as having a low risk of bias. There was one systematic review and meta-analysis (SRMA) and one cohort study with a low and medium risk of bias, respectively.[28 34] Study specific biases are presented in online supplemental file 5.

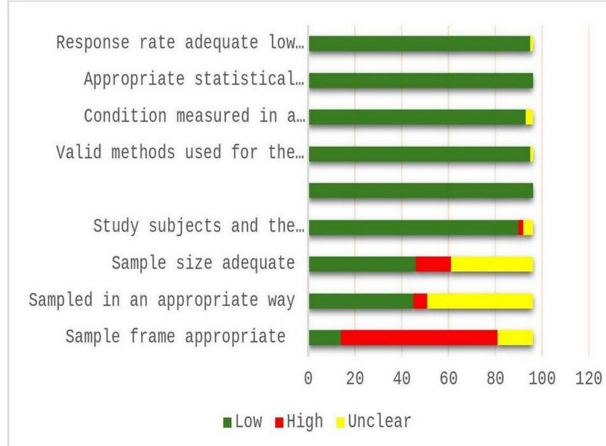

Figure 2 Critical appraisal of prevalence studies based on risk of bias assessment.

Pooled prevalence

The analysis was made up of 132 studies (n=52 501). Figure 3A shows a corresponding forest plot. Double arcsine transformation for stabilising the variance of prevalence across studies was found to be the best fit because AIC (49.6546) and BIC (55.3742) were observed to be the lowest compared with other transformations. Based on the random effects model, the pooled prevalence of micronutrient deficiency was 45.30% (95% CI 40.35%–50.30%) (table 2). Significant heterogeneity was observed among the studies (I^2=99%; p=0). The sensitivity analysis post-removal of studies with higher weight showed no significant change in the pooled prevalence obtained with random effects models (47%, 95% CI 42% to 51%). The unweighted Egger's test showed a significantly asymmetrical funnel plot (z=2.0269, p=0.0427) (figure 3B). The limit estimate after trim-and-fill was quantified as 0.6211 (95% CI 0.4973 to 0.7450).

Subgroup

The results of the subgroup analysis are summarised in tables 2 and 3 and as forest plots (online supplemental file 6).

a. **Prevalence of micronutrient deficiency among men and women:** All of the studies that reported prevalence for men and women were considered. Meta-analysis for the prevalence of micronutrient deficiency for men and women was conducted separately. There were 62 studies for men and 63 for women. Results showed that the prevalence of micronutrient deficiency was marginally lower for men (42.53%, 95% CI 36.34% to 48.72%) than for women (48.62%, 95% CI 42.55% to 54.70%) (table 2). Pooled prevalence under no transformation for stabilising the variance was found to be a best fit model for both men (AIC=6.5045, BIC=10.7262) and women (AIC=4.9191 and BIC=9.1734). Forest plots for analysis of micronutrient deficiency among men and women presented significant differences in prevalence across all studies (p<0.001) and statistical heterogeneity with 99% and 100% for men and women, respectively.

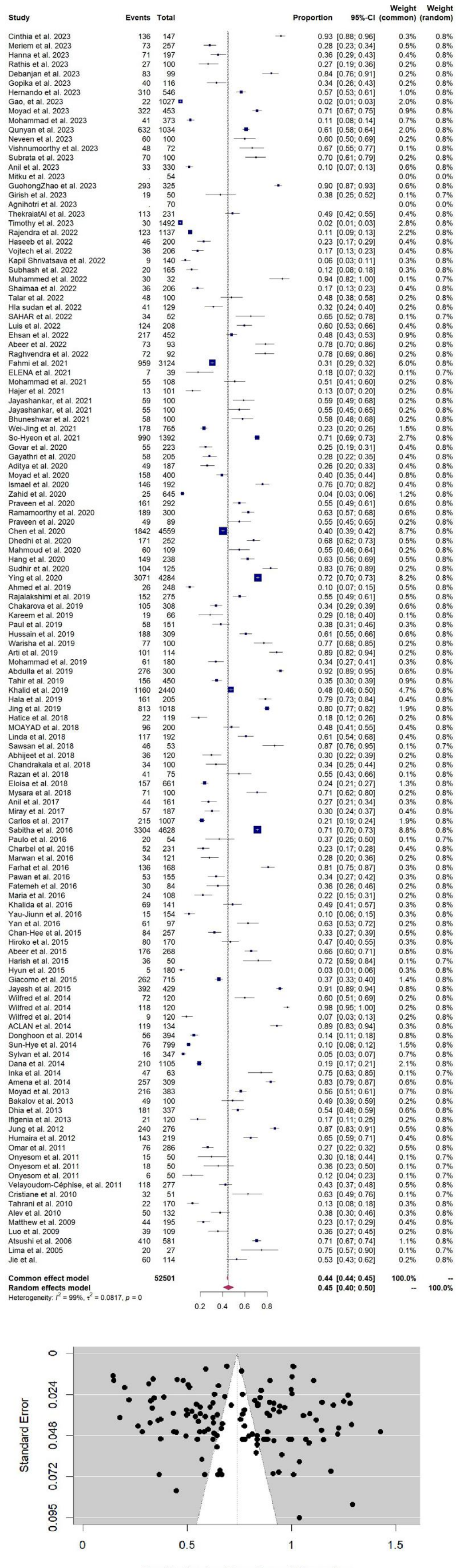

Figure 3 (A) Forest plot for meta-analysis of pooled prevalence of micronutrient deficiency among patients with type 2 diabetes. (B) Funnel plot.

No publication bias was present in the meta-analysis of the prevalence of individual micronutrients.

b. **Prevalence of micronutrient deficiency for a population with diabetic complications:** Table 2 showed that micronutrient deficiency was prevalent in 40% (95% CI 29.38% to 50.28%) of the population with diabetic complications (k=26). Variance stabilisation was not especially important for prevalence in this case, as AIC=9.5914 and BIC=12.0291 being the lowest under no transformation. Heterogeneity indicators were estimated as τ^2=0.0715, I^2=99.5% (p<0.001).
c. **Geographic WHO regions and years (time periods) 1998–2015 and 2016–23:** The estimated pooled prevalence was highest (54.04%, 95% CI 35.03% to 72.48%) in Americas among all WHO regions (figure 4). The analysis showed a similar estimated pooled prevalence of 45% for the time periods 1998–2015 and 2016–23 (table 3).
d. **Community/hospital based studies:** The estimated pooled prevalence of micronutrient deficiency in hospital based studies (k=124, n=43 367) was higher (46%, 95% CI 41% to 51%) than in community based studies (k=5, n=8839), which had a prevalence of 22% (95% CI 6% to 46%).
e. **Prevalence of vitamin B12 deficiency among T2D subjects on metformin therapy:** The prevalence of vitamin B12 deficiency (k=30) among the metformin group (28.72%, 95% CI 21.08% to 36.37%), was marginally higher than the overall prevalence of vitamin B12 deficiency (23.78%) (table 2).
f. **Vitamin D, vitamin B12, magnesium and iron:** The analysis included a total of 66 studies (n=27 169) for vitamin D, 34 studies (n=14 433) for vitamin B12, 16 studies (n=3210) for magnesium and three studies (n=1887) for iron. Double arcsine transformation for stabilising the variance of prevalence across studies was found to be the best fit, as AIC and BIC were observed to be the lowest under double arcsine transformation among all micronutrients. Based on a random effects model, pooled prevalence of deficiency under double arcsine transformation was found to be different for all vitamins, being highest for vitamin D (60.45%, 95% CI 55% to 65%), magnesium (41.95%, 95% CI 27% to 56%), iron (27.81%, 95% CI 7% to 55%) and vitamin B12 (22.01%, 95% CI 16.5% to 27%) (table 2).

Meta-regression

Meta-regression estimates are summarised as bubble plots for overall micronutrients (figure 5) and individual micronutrients (online supplemental file 7). The bubble plot for analysing prevalence over time for all micronutrients did not indicate any significant trend but a weak trend increasing in prevalence over time (0 0003, p=0 967). Bubble plots for meta-regression also showed a slight non-significant increase in prevalence over time for vitamin D (0 0112, p=0 1027) and vitamin B12 (0 0065, p=0 4612) but a decreasing trend for magnesium (–0 0098, p=0 5133).

Table 2 Meta-analysis under different variance stabilising transformations

Statistical model	Heterogeneity	Pooled prevalence	95% CI	AIC, BIC
Meta-analysis for pooled prevalence of micronutrient deficiency				
No transformation	$\tau^2 = 0 \cdot 0226, I^2 = 99 \cdot 16\%$	0.4598	0.4156 to 0.5041	69.10, 84.82
Logit transformation	$\tau^2 = 1 \cdot 8233, I^2 = 99 \cdot 24\%$	0.4424	0.3854 to 0.5009	454.07, 459.79
Double arcsine transformation	$\tau^2 = 0 \cdot 0817, I^2 = 99 \cdot 23\%$	0.4530	0.4035 to 0.5030	49.65, 55.37
Generalised linear model	$; cap\tau^2 = 1 \cdot 8719, I^2 = 98 \cdot 6\%$	0.4428	0.3852 to 0.5021	76.43, 81.45
Meta-analysis for prevalence of micronutrient deficiency for men				
No transformation	$\tau^2 = 0 \cdot 0592, I^2 = 98 \cdot 77\%$	0.4253	0.3634 to 0.4872	26.50, 30.72
Logit transformation	$\tau^2 = 1 \cdot 4110, I^2 = 98 \cdot 40\%$	0.4055	0.3346 to 0.4805	204.21, 208.43
Double arcsine transformation	$\tau^2 = 0 \cdot 0699, I^2 = 98 \cdot 73\%$	0.4160	0.3496 to 0.4840	17.73, 21.95
Generalised linear model	$\tau^2 = 1 \cdot 4710, I^2 = 97 \cdot 8\%$	0.4049	0.3329 to 0.4813	48.93, 56.21
Meta-analysis for prevalence of micronutrient deficiency for women				
No transformation	$\tau^2 = 0 \cdot 0579, I^2 = 99 \cdot 6\%$	0.4862	0.4255 to 0.5470	4.91, 9.17
Logit transformation	$\tau^2 = 1 \cdot 2471, I^2 = 98 \cdot 20\%$	0.4795	0.4090 to 0.5508	209.55, 213.80
Double arcsine transformation	$\tau^2 = 0 \cdot 0739, I^2 = 98 \cdot 54\%$	0.4902	0.4211 to 0.5596	20.62, 24.87
Generalised linear model	$\tau^2 = 1 \cdot 6744, I^2 = 97 \cdot 6\%$	0.4970	0.4159 to 0.5781	32.87, 36.78
Meta-analysis of prevalence for micronutrient deficiency among cases with complications				
No transformation	$\tau^2 = 0 \cdot 0715, I^2 = 99 \cdot 5\%$	0.3983	0.2938 to 0.5028	19.59, 32.02
Logit transformation	$\tau^2 = 2 \cdot 0088, I^2 = 98 \cdot 19\%$	0.3613	0.2440 to 0.4979	95.75, 98.19
Double arcsine transformation	$\tau^2 = 0 \cdot 0915, I^2 = 98 \cdot 55\%$	0.3852	0.2723 to 0.5047	16.05, 18.49
Generalised linear model	$\tau^2 = 2 \cdot 1461, I^2 = 98\%$	0.3623	0.2419 to 0.5029	72.45, 76.64
Meta-analysis of prevalence for micronutrient deficiency among hospital based studies				
No transformation	$\tau^2 = 0 \cdot 0651, I^2 = 99 \cdot 38\%$	0.4681	0.4226 to 0.5137	18.73, 24.33
Logit transformation	$\tau^2 = 1 \cdot 7695, I^2 = 99 \cdot 12\%$	0.4550	0.3968 to 0.5145	426.49, 432.10
Double arcsine transformation	$\tau^2 = 0 \cdot 0811, I^2 = 99 \cdot 11\%$	0.4630	0.4121 to 0.5143	9.34, 16.74
Generalised linear model	$\tau^2 = 1 \cdot 8202, I^2 = 98 \cdot 5\%$	0.4556	0.3966 to 0.5158	89.90, 130.56
Meta-analysis of prevalence for micronutrient deficiency among community based studies				
No transformation	$\tau^2 = 0 \cdot 0499, I^2 = 99 \cdot 87\%$	0.2575	0.0614 to 0.4537	3.38, 2.15
Logit transformation	$\tau^2 = 2 \cdot 5808, I^2 = 99 \cdot 12\%$	0.1814	0.0513 to 0.4761	19.17, 17.94
Double arcsine transformation	$\tau^2 = 0 \cdot 0789, I^2 = 99 \cdot 79\%$	0.2249	0.0598 to 0.4555	2.20, 3.17
Generalised linear model	$\tau^2 = 2 \cdot 0749, I^2 = 99 \cdot 5\%$	0.1810	0.0586 to 0.4394	29.90, 67.56
Meta-analysis of the prevalence of vitamin B12 deficiency among patients with metformin therapy				
No transformation	$\tau^2 = 0 \cdot 0446, I^2 = 99 \cdot 5\%$	0.2872	0.2108 to 0.3637	13.15, 9.42
Logit transformation	$\tau^2 = 1 \cdot 5230, I^2 = 98 \cdot 66\%$	0.2452	0.1720 to 0.3370	99.54, 102.28
Double arcsine transformation	$\tau^2 = 0 \cdot 0602, I^2 = 98 \cdot 80\%$	0.2685	0.1932 to 0.3512	5.64, 8.37
Generalised linear model	$\tau^2 = 1 \cdot 4991, I^2 = 97 \cdot 3\%$	0.2437	0.1713 to 0.3344	24.78, 28.56
Meta-analysis of prevalence for deficiency of vitamin D deficiency				
No transformation	$\tau^2 = 0 \cdot 0402, I^2 = 98 \cdot 78\%$	0.5971	0.5479 to 0.6463	–18.70, –14.36

Continued

Table 2 Continued

Statistical model	Heterogeneity	Pooled prevalence	95% CI	AIC, BIC
Logit transformation	$\tau^2 = 0 \cdot 9067,\ I^2 = 98 \cdot 63\%$	0.6127	0.5558 to 0.6668	186.48, 190.83
Double arcsine transformation	$\tau^2 = \ 0 \cdot 0465,\ I^2 = 98 \cdot 63\%$	0.6045	0.5517 to 0.6560	–8.38, –4.03
Generalised linear model	$\tau^2 = 0 \cdot 9185,\ I^2 = 97 \cdot 7\%$	0.6146	0.5574 to 0.6688	370.48, 374.86
Meta-analysis of prevalence of vitamin B12 deficiency				
No transformation	$\tau^2 = \ 0 \cdot 0226,\ I^2 = 99 \cdot 16\%$		0.1870 to 0.2886	–26.96, –23.90
Logit transformation	$\tau^2 = \ 1 \cdot 1006,\ I^2 = 98 \cdot 32\%$	0.1983	0.1479 to 0.2605	104 99, 108.04
Double arcsine transformation	$\tau^2 = \ 0 \cdot 0358,\ I^2 = 98 \cdot 24\%$	0.2201	0.1693 to 0.2757	–11.68, –8.62
Generalised linear model	$\tau^2 = 1 \cdot 0858,\ I^2 = 97 \cdot 5\%$	0.1965	0.1468 to 0.2578	193.82, 196.93
Meta-analysis of the prevalence of magnesium deficiency				
No transformation	$\tau^2 = \ 0 \cdot 0751,\ I^2 = 98 \cdot 94\%$	0.4141	0.2671 to 0.5781	8.043, 9.45
Logit transformation	$\tau^2 = \ 1 \cdot 8413,\ I^2 = 98 \cdot 17\%$	0.4139	0.2644 to 0.5812	56.32, 57.74
Double arcsine transformation	$\tau^2 = \ 0 \cdot 0898,\ I^2 = 98 \cdot 48\%$	0.4195	0.2768 to 0.5693	10.80, 12.22
Generalised linear model	$\tau^2 = 1 \cdot 7682;,\ I^2 = 97 \cdot 4\%$	0.4141	0.2671 to 0.5781	83.60, 85.15
Meta-analysis of prevalence of Iron deficiency				
No transformation	$\tau^2 = \ 0 \cdot 8677,\ I^2 = 98 \cdot 3\%$	0.2607	0.1082 to 0.5062	3.72, 1.11
Logit transformation	$\tau^2 = \ 1 \cdot 3143,\ I^2 = 98 \cdot 96\%$	0.2621	0.0876 to 0.5676	10.26, 7.65
Double arcsine transformation	$\tau^2 = \ 0 \cdot 0620,\ I^2 = 99 \cdot 17\%$	0.2781	0.0704 to 0.5557	4.17, 1.55
Generalised linear model	$\tau^2 = 0 \cdot 8677,\ I^2 = 98 \cdot 43\%$	0.2607	0.1082 to 0.5062	22.19, 20.39

AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Overall quality of evidence

The level of certainty of evidence was assessed for the overall pooled prevalence of micronutrient deficiency among the T2D patients (table 4). The certainty of evidence was generated using GRADEPro.[35 36] The certainty of the evidence was deemed moderate due to the asymmetrical distribution of the study effect size, which was confirmed with Egger's test, suspecting publication bias.

Table 3 Subgroup analysis for different WHO regions and year groups 1998–2015 and 2016–23

Region or year group	No of studies*	Pooled prevalence	95% CI
Region			
Americas	8	0.5404	0.3503 to 0.7248
Eastern Mediterranean	41	0.4694	0.3880 to 0.5517
Europe	19	0.3982	0.2726 to 0.5309
South East Asia	28	0.4973	0.3888 to 0.6060
Western Pacific	23	0.3921	0.2578 to 0.5352
Africa	7	0.4054	0.2392 to 0.5833
Not specified	4	0.5092	0.3053 to 0.7115
Year group			
2016–23	94	0.4533	0.3974 to 0.5098
1998–2015	36	0.4523	0.3492 to 0.5575

*Number of studies selected for meta-analysis.

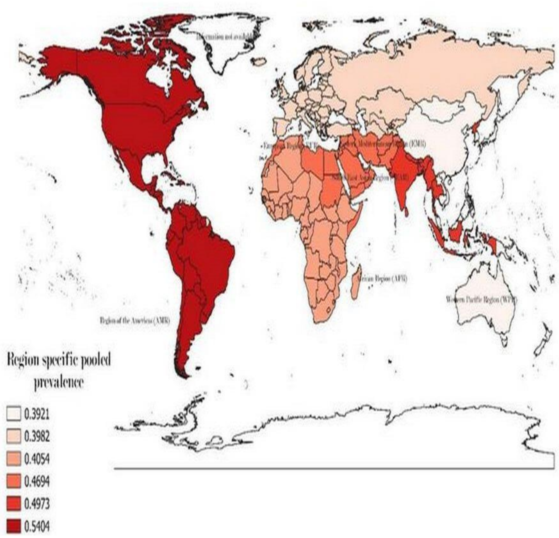

Figure 4 Spatial distribution of prevalence of micronutrient deficiency across WHO regions.

DISCUSSION

Our study showed that almost half of the T2D population had multiple micronutrient deficiencies, with a pooled prevalence of 45 30% (95% CI 40 35% to 50 30%). This evidence had a moderate certainty of evidence. The pooled prevalence varied across WHO regions, and 40% of the subjects with diabetic complications had micronutrient deficiency.

Women were more likely to be affected by micronutrient deficiencies than men. Among the individual micronutrients, vitamin D deficiency was the most common deficiency, with a prevalence as high as 60.45% (95% CI 55% to 65%), followed by magnesium deficiency (41 95%, 95% CI 27% to 56%). The next in order was vitamin B12 deficiency in a subgroup of T2D patients on metformin.

Multiple micronutrients are involved in the metabolic processes in the human body. Micronutrient deficiencies may influence glucose metabolism and insulin signalling pathways, leading to the onset and progression of T2D.[5 13] The global rise in the disease burden of diabetes, essentially a metabolic disorder, has aroused the interest of the scientific community in exploring the role of micronutrients and their association with diabetes in recent years. This SRMA presents the pooled prevalence of multiple micronutrient deficiencies (vitamins/minerals/electrolytes) in the T2D population, as reported in the past two decades, highlighting the link between the hidden hunger with micronutrients and globally rising public health problem of diabetes

The findings of the studies included in the SRMA were grossly inconsistent, as revealed by the forest plot. Most of these studies were cross sectional and hence it was difficult to establish causality, whether the micronutrient deficiency preceded the poor glycaemic control or was a sequelae of the disease. Moreover, all studies were hospital based, with inherent selection bias. Further, none of the studies considered evaluating the effect of various confounding factors arising from place, person and time distribution of T2D patients. We also assessed the risk of bias in the included studies in our SRMA arising from response rate, sample size, selection of subjects and statistical analysis approaches, and found that all studies were at the elevated risk of bias, thus posing serious threats to validity of the estimates of the prevalence of micronutrient deficiencies.

There were no valid population based studies on prevalence estimates of micronutrient deficiencies, so comparisons between T2D patients and the general population could not be done. There is a need for well designed population based studies to estimate the burden of micronutrient deficiencies in the general population and patients with T2D. Case control and cohort studies could be conducted to establish cause-and-effect relationships and the ultimate evidence derived from randomised

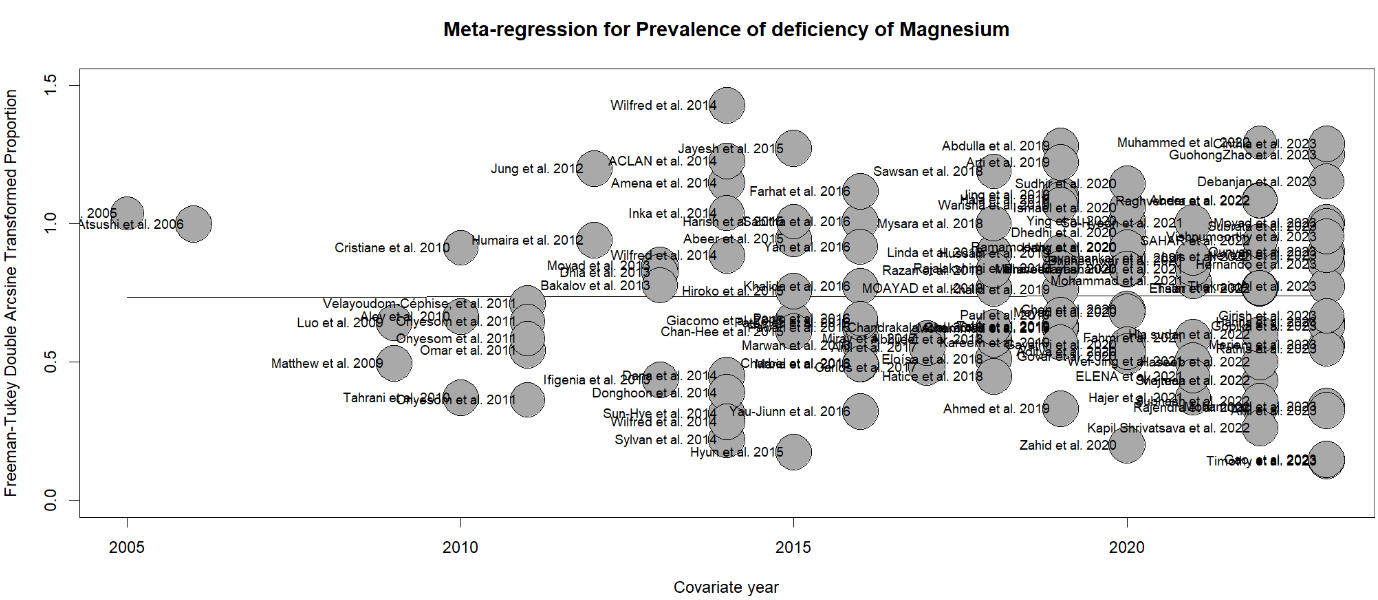

Figure 5 Bubble plot for meta-regression for overall micronutrients.

Table 4 GRADE summary of findings for prevalence of micronutrient deficiency in patients with type 2 diabetes mellitus

	Certainty assessment						Effect			
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No of events	No of individuals	Rate (95% CI)	Certainty
127	Cross sectional, cohort, retrospective	Not serious	Not serious	Not serious	Not serious	Publication bias is strongly suspected*	23 855	52 501	Event rate 45.3% (40.35 to 50.3)	⊕⊕⊕◯ Moderate

*Selected studies showed an asymmetrical distribution with an Egger's test suspecting publication bias.

controlled trials. Nevertheless, our SRMA indicated a high prevalence of various micronutrients in T2D worldwide and would necessitate the attention of physicians and policy makers to explore micronutrient supplementation's role in preventing comorbidity and complications, and disease management.

Strengths and limitations

This study analysed multiple micronutrient deficiencies among T2D patients. This study's main strength was its thorough, comprehensive search strategy, which included searching through several databases, considering studies published between 1998 and 2023 and not being limited by language or geography. We conducted risk of bias for all the studies in the SRMA to assess the certainty of evidence. Another crucial strength was using a statistically sound double arcsine transformation method for assessing pooled prevalence. A predesigned protocol and a thorough search strategy were used to reduce the associated bias.

The limitations were: (1) most of the studies in this SRMA were hospital based, cross sectional studies and were inevitably biased; (2) lack of community based studies on prevalence estimates of micronutrient deficiencies among T2D patients impeded the comparison between the prevalence of micronutrient deficiencies among the general population and T2D patients; and (3) some studies might have been missed despite following all the standard processes for conducting the comprehensive SRMA.

CONCLUSIONS

The pooled prevalence for deficiency of all micronutrients among T2D patients was 45.30%. Of all of the micronutrients, the prevalence of vitamin D deficiency was highest (60.45%), followed by the prevalence of magnesium deficiency (41 95%). Most of the data in the analysis came from hospital based, cross sectional studies. Hence the results cannot be generalised to the general population. Despite being a thorough review, there is a chance that some studies were overlooked or missed and might influence the results.

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Competing interests FA declares potential conflicts of interest as an employee of Abbott, the study sponsor.

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