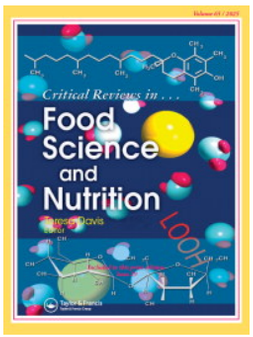

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REVIEW ARTICLE

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Association between vitamin D level and risk of type 2 diabetes: a systematic review of Mendelian Randomization studies

Kexin Sun[a], Yunan Chen[b], Hugh Simon Hung San Lam[a], Edmund Anthony Severn Nelson[a,c], Alice Pik-Shan Kong[d,e], Shiu Lun Au Yeung[f] and Lai Ling Hui[b]

[a]Department of Pediatrics, The Chinese University of Hong Kong, Hong Kong SAR, China; [b]Department of Food Science and Nutrition, The Hong Kong Polytechnic University, Hong Kong SAR, China; [c]School of Medicine, The Chinese University of Hong Kong, Shenzhen, Guangdong, China; [d]Department of Medicine & Therapeutics, The Chinese University of Hong Kong, Hong Kong SAR, China; [e]Li Ka Shing Institute of Health Science, The Chinese University of Hong Kong, Hong Kong SAR, China; [f]School of Public Health, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, China

ABSTRACT

This study aims to review the evidence from Mendelian randomization (MR) studies on the causal role of vitamin D in type 2 diabetes (T2D). A systematic search (registered on PROSPERO (CRD42024551731)) was performed in PubMed, Embase and Web of Science for publications up to June 2024. MR studies including vitamin D as the exposure and T2D as the outcome were included. Among the 22 studies included, which were mainly in European populations, half used single nucleotide polymorphisms (SNPs) located on vitamin D synthesis and metabolism genes, while others selected SNPs based on statistical thresholds. Negative associations implying that vitamin D protects against T2D were reported in three one-sample and three two-sample MR studies. The remaining studies reported null associations between genetically predicted circulating 25-hydroxyvitamin D and risk of T2D regardless of MR design, study population, data source or SNP selection. Findings from MR studies on circulating 25-hydroxyvitamin D and risk of T2D do not consistently support the causal role of vitamin D in T2D in the general population. Future MR studies to examine the non-linear association of vitamin D with T2D or disease progression from prediabetes are warranted to clarify the use of vitamin D in the prevention of T2D.

KEYWORDS

vitamin D supplementation; 25-hydroxyvitamin D; type 2 diabetes; Mendelian Randomization

Introduction

Vitamin D is an essential micronutrient primarily known for its role in bone health as well as calcium and phosphate homeostasis (Tsuprykov et al. 2018). However, there has been increasing research on its potential benefits in a wider spectrum of health outcomes, including type 2 diabetes (T2D) (Rosen et al. 2012). More than half of the patients with T2D were found to have vitamin D deficiency with poorer glycemic control and increased risk of other metabolic derangements (Taderegew et al. 2023) and complications such as diabetic retinopathy, endothelial dysfunction (Argano et al. 2023) and cardiovascular diseases (Iqhrammullah et al. 2024).

Recently, the Endocrine Society updated the clinical practice guideline to support the use of empiric vitamin D supplementation of 3500 IU/day for people with prediabetes for its potential to reduce progression to T2D (Demay et al. 2024). This is more than the recommended vitamin D intake for the general adult population (600–900 IU/day), and the Recommended Daily Allowance of 600–800 IU established by the former American Institute of Medicine, now the National Academy of Medicine (Del Valle et al. 2011). The latest recommendations from the Endocrine Society were based on a meta-analysis of 11 randomized controlled trials (RCTs) on vitamin D supplementation among prediabetic subjects (Barengolts et al. 2015; Bhatt et al. 2020; Davidson et al. 2013; Dutta et al. 2014; Jorde et al. 2016; Kawahara et al. 2022; Kuchay et al. 2015; Niroomand et al. 2019; Pittas et al. 2019; Zaromytidou et al. 2022), despite that individually only two of the studies reported significant protective effects on the progression to diabetes (Dutta et al. 2014; Niroomand et al. 2019). The strongest evidence for a protective effect of vitamin D against T2D came from a meta-analysis of individual patient data from three large RCTs on people with prediabetes. This analysis demonstrated that supplementation with vitamin D for two years reduced the risk of developing T2D among these high risk subjects by 15% (Pittas et al. 2023).

Mendelian randomization (MR) involves the use of genetic variants, typically single nucleotide polymorphisms (SNPs), as instrumental variables to improve causal inference from observational data. Based on Mendel's laws of inheritance, genotypes are randomly allocated at conception, which resembles

CONTACT Lai Ling Hui connie.hui@polyu.edu.hk; Shiu Lun Au Yeung ayslryan@hku.hk
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the randomization process in RCTs (Sanderson et al. 2022). Therefore, MR studies are less susceptible to common confounding by lifestyle factors and socioeconomic status (Smith et al. 2007), and tend to give more consistent findings with RCTs compared to conventional observational studies. For example, although lower serum 25(OH)D level was associated with higher fracture risk in observational studies (Melhus et al. 2010), null associations of vitamin D supplementation and serum 25-hydroxyvitamin D (25(OH)D) levels on fracture risk were found in RCT (LeBoff et al. 2022) and MR (Trajanoska et al. 2018) studies, respectively. MR studies have three important assumptions: relevance, independence, and exclusion restriction (Sanderson et al. 2022). The increasing availability of genome wide association studies (GWAS) in recent years has contributed to a surge in the use of MR to assess the causality of vitamin D in T2D. Four genes with well-established roles in the biological pathways of vitamin D have been identified and widely applied in MR studies. DHCR7/NADSYN1 (7-dehydrocholesterol reductase/nicotinamide adenine dinucleotide synthase 1) is responsible for vitamin D synthesis in the skin. CYP2R1 (cytochrome P450, family 2, subfamily R, polypeptide 1) is responsible for 25-hydroxylation in the liver. DBP/GC (vitamin D binding protein/group-specific component) is responsible for vitamin D transport. CYP24A1 (cytochrome P450, family 24, subfamily A, polypeptide 1) is responsible for vitamin D catabolism. It is generally accepted that DHCR7 and CYP2R1 represent vitamin D synthesis, while GC and CYP24A1 represent vitamin D metabolism (Z. Ye et al. 2015).

So far, more than 20 MR studies on vitamin D and T2D have been published. There have been some reviews summarizing results from only one to 17 MR studies published before 2023, and they reported insignificant (Fang et al. 2024; D. Liu, Meng, et al. 2022) and negative associations between vitamin D and risk of T2D (Yuan and Larsson 2020). Given that more MR studies with large sample sizes in different populations have been published since then, we set out to systematically summarize the current evidence from MR studies on the association between vitamin D levels and the risk of developing T2D in the general population.

Methods

A systematic search was conducted in PubMed, Embase and Web of Science for publications from inception up to 30 June 2024 using the following key search terms: ("vitamin D" OR "25-hydroxyvitamin D") AND ("diabetes") AND ("mendelian randomization") (see details in Table S1). MR studies including vitamin D levels as the exposure and T2D as the outcome were included. Studies were excluded if they are reviews, commentaries, did not implement an MR design, not having vitamin D levels as the exposure or not having T2D as the outcome. Two review authors (K.S. and Y.C.) independently screened the title and abstract of all records retrieved and assessed all potentially relevant articles in full text. References of relevant articles were assessed manually for potential additional studies.

For studies fulfilling all eligible criteria, the following data were extracted using standard data extraction templates: first author, year of publication, study population, MR design (one-sample or two-sample), data sources (i.e., the GWAS used for vitamin D levels and T2D), sample size, number of SNPs used as genetic instruments, proportion of variance explained, unit of effect estimate, main analytical methods and results. We also summarized how studies addressed strength of genetic instruments and potential pleiotropy. One review author (K.S.) extracted relevant information from the included studies, which was double-checked by another review author (Y.C.), and any discrepancies were resolved by discussion with a corresponding author (L.L.H.).

A narrative synthesis was performed to assess the effects of genetically predicted vitamin D levels on the risk of developing T2D. Meta-analysis of the MR results was not feasible due to the heterogeneous analytical methods and substantially overlapping GWAS populations. Two review authors (K.S. and Y.C.) independently assessed the risk of bias according to the relevant items from the Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization (STROBE-MR) checklist (Skrivankova et al. 2021).

Only published data were sought for this review and ethical approval was not needed. This systematic review was registered on International Prospective Register of Systematic Reviews (PROSPERO) (ID: CRD42024551731).

Results

Result of search

Initial search obtained 362 studies in total from PubMed ($n = 84$), Embase ($n = 161$) and Web of Science ($n = 117$), and 208 were left after removing duplicates. One hundred and ninety-two studies were excluded after screening by title and abstract because they were reviews ($n = 62$), editorials/commentaries/abstracts ($n = 17$), not in MR design ($n = 15$), MR studies not involving vitamin D as exposure and/or not involving T2D as outcome ($n = 98$). One MR study on vitamin D was further removed after reading in full text, because it does not have T2D as one of the outcomes (Chen et al. 2019). Manual search of the reference lists identified seven additional relevant MR studies (Buijsse et al. 2013; Jiang, Ge, and Chen 2021; Jorde et al. 2012; Kang et al. 2024; H. Liu, Meng, et al. 2022; Revez et al. 2020; J. Xu et al. 2023). Therefore, a total of 22 studies published between 23 May 2012 and 17 May 2024 were included in this review (Figure 1) (Afzal et al. 2014; Bejar et al. 2021; Buijsse et al. 2013; De La Barrera and Manousaki 2023; Jiang, Ge, and Chen 2021; Jorde et al. 2012; Kang et al. 2024; H. Liu, Meng, et al. 2022; Lu et al. 2018; Meng et al. 2019; Niu, Aierken, and Feng 2024; Revez et al. 2020; Wang et al. 2020; Xiao et al. 2021; J. Xu et al. 2023; Y. Xu et al. 2020; Y. Ye et al. 2021; Z. Ye et al. 2015; Yuan et al. 2019; Zanetti et al. 2020; Zhao et al. 2024; Zheng et al. 2020). Details of each study were summarized in Table 1. Additional information on MR design, details of SNPs and validation of strength and pleiotropy, variance explained, description of the GWAS for vitamin D and T2D, mean 25(OH)D level and results using different SNPs were shown in Table S2.

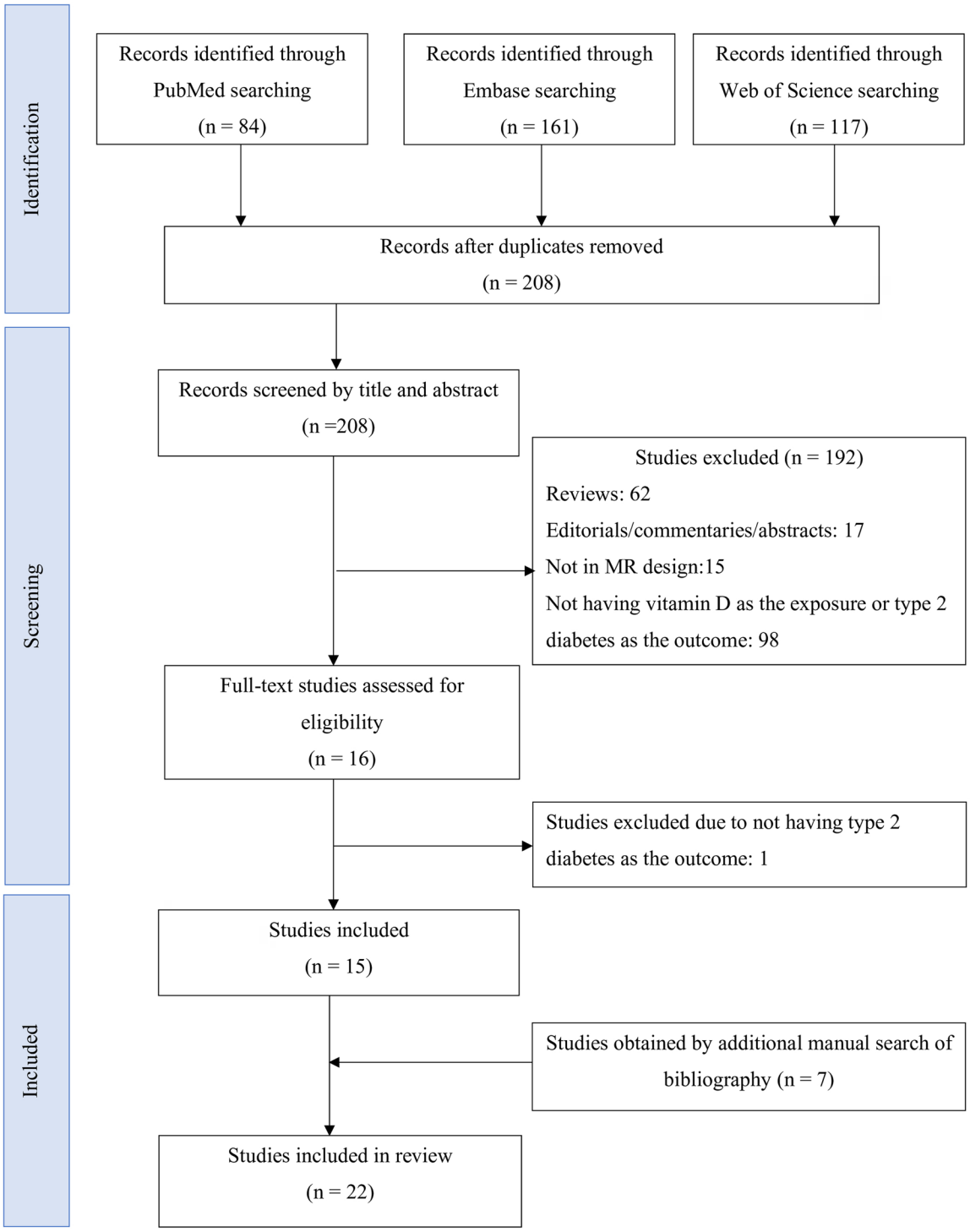

Figure 1. Flowchart of study selection in this review.

Data sources for MR analysis

Vitamin D status was proxied by total serum 25(OH)D concentration in all included studies. Zheng et al.'s study additionally measured 25(OH)D_3, the major fraction of 25(OH)D, and C3-epi-25(OH)D_3, a metabolite of 25(OH)D (Zheng et al. 2020). Seven included studies conducted one-sample MR analyses (Afzal et al. 2014; Bejar et al. 2021; Buijsse et al. 2013; Jorde et al. 2012; Lu et al. 2018; Wang et al. 2020; Xiao et al. 2021) and the rest employed two-sample design (De La Barrera and Manousaki 2023; Jiang, Ge, and Chen 2021; Kang et al. 2024; H. Liu, Meng, et al. 2022; Meng et al. 2019; Niu, Aierken, and Feng 2024; Revez et al. 2020; J. Xu et al. 2023; Y. Xu et al. 2020; Y. Ye et al. 2021; Z. Ye et al. 2015; Yuan et al. 2019; Zanetti et al. 2020; Zhao et al. 2024; Zheng et al. 2020). Most studies were conducted in adults only, except for one study that focused on pediatric T2D cases (De La Barrera and Manousaki 2023). Three large GWAS on vitamin D and/or T2D were used multiple times in the included MR studies: The Study of Underlying Genetic Determinants of Vitamin

Table 1. Characteristics of mendelian randomization (MR) studies on vitamin D and type 2 diabetes included in this review.

Publication	Population	Cases/controls[a]	SNPs[&]	Effect estimates	Unit	Association
Jorde et al. (2012)	Norwegian	1,092 (total)	rs10741657* rs3794060* rs7041[#] s2298850[#] rs6013897[#]	1.01 (0.86, 1.20)[b]	Highest vs lowest quartile	Null
Buijsse et al. (2013)	German	3,359 (total)	rs12785878* rs10741657* rs2282679[#] rs10877012[#]	0.98 (0.89, 1.08)[b]	per 5 nmol/L increase	Null
			rs12785878* rs10741657* rs2282679[#] rs6013897[#] rs10877012[#]	0.99 (0.91, 1.06)[b] 1.00 (0.93, 1.07)[b]	per allele increase	
Afzal et al. (2014)	Danish	96,423 (total)	rs7944926* rs11234027* rs10741657* rs12794714*	1.51 (0.98, 2.33)[c] 1.02 (0.75, 1.37)[c]	per 20 nmol/L reduction	Null
Ye et al. (2015)	European	28,144/76,344	rs12785878* rs10741657* rs4588[#] rs17217119[#]	1.01 (0.75, 1.36)[d]	per 25 nmol/L reduction	Null
			rs12785878* rs10741657* rs4588[#] rs17217119[#]	1.16 (0.84, 1.60)[d] 0.95 (0.59, 1.52)[d]		
Lu et al. (2018)	European & Chinese	32,796/248,629	rs12785878* rs10741657* rs2282679[#] rs6013897[#]	0.92 (0.84, 1.01)	per 25 nmol/L increase	Null
		58,312/370,592	rs12785878* rs10741657*	**0.86 (0.77, 0.97)**		**Negative**
Meng et al. (2019)	European	15,958/323,298	rs12785878* rs10741657* rs3755967[#] rs17216707[#] rs10745742[#] rs8018720[#]	0.97 (0.85, 1.12)	per SD increase in log-transformed level	Null
Yuan et al. (2019)	European	74,124/824,006	rs10741657* rs117913124* rs12785878* rs3755967[#] rs17216707[#] rs10745742[#] rs8018720[#]	**0.94 (0.88, 0.99)**	per SD increase	**Negative**
			rs10741657* rs117913124* rs12785878*	**0.90 (0.83, 0.98)**		
Revez et al. (2020)	European	62,892/596,424	161^	1.00 (0.94, 1.05)[e]	per unit increase in rank-based inverse-normal transformed level	Null
Wang et al. (2020)	Chinese	1,565/9,090	rs12785878* rs10741657* rs2282679[#] rs6013897[#]	0.99 (0.94, 1.03)[c]	per GRS unit reduction	Null
			rs12785878* rs10741657* rs2282679[#] rs6013897[#]	0.98 (0.90, 1.06)[c] 0.99 (0.94, 1.05)[c]		
Xu et al. (2020)	European	74,124/824,006	180^ rs12785878* rs10741657*	**0.95 (0.91, 0.99)**[f] **0.89 (0.82, 0.98)**	per 21.14 nmol/L increase	**Negative**
Ye et al. (2021)	European	26,676/132,532	91^	1.00 (0.98, 1.03)	per SD increase	Null
Zanetti et al. (2020)	North European	34,840/114,981	29^	1.07 (0.77, 1.37)	per 21.11nmol/L increase	Null
Zheng et al. (2020)	European	80,983/842,909	rs116970203* rs12785878* rs17216707[#] rs3755967[#] rs3213737[#] rs8018720[#] rs11203339[$] rs7529325[$] rs17862870[$] rs9304669[$]	0.96 (0.89, 1.03)	per SD increase	Null
			rs116970203* rs12785878* rs3755967[#] rs17216707[#]	0.96 (0.87, 1.05) 0.97 (0.85, 1.11)		

(*Continued*)

Table 1. Continued.

Publication	Population	Cases/controls[a]	SNPs[&]	Effect estimates	Unit	Association
Bejar et al. (2021)	Indian	4,234 (total)	rs12785878* rs12794714* rs2282679[#]	1.00 (1.00, 1.01)	per 3.1nmol/L reduction	Null
			rs2282679[#]	**1.09 (1.02, 1.17)**	per 11nmol/L reduction	**Negative**
	European & Indian	44,927 (total)	rs12785878* rs12794714* rs2282679[#]	1.00 (1.00, 1.01)	per 2.1nmol/L reduction	Null
		58,338 (total)	rs12785878*	**1.05 (1.00, 1.11)**	per 4.2nmol/L reduction	**Negative**
Jiang, Ge, and Chen (2021)	European	62,892/596,424	31^	0.99 (0.90, 1.09)[f]	per SD increase in log-transformed level	Null
Xiao et al. (2021)	Chinese	2,393 (total)	rs12785878* rs10741657* rs2282679[#] rs6013897[#]	0.92 (0.70, 1.02)[c]	per 25 nmol/L reduction	Null
			rs12785878* rs10741657*	**1.10 (1.02, 1.45)**[c]		**Negative**
			rs2282679[#] rs6013897[#]	0.91 (0.60, 1.36)[c]		Null
Liu, Meng, et al. (2022)	European	40,250/170,615	41^	0.94 (0.79, 1.12)	per SD increase in log-transformed level	Null
	Japanese		2^	**0.53 (0.32, 0.86)**		**Negative**
	Indian		14^	1.01 (0.90, 1.13)		Null
De La Barrera and Manousaki (2023)	Multi-ethnic[+]	3,006/6,061	49^	1.04 (0.96, 1.13)	per 40.9 nmol/L increase	Null
Xu et al. (2023)	European	74,124/824,006	70^	0.98 (0.89, 1.07)	per unit reduction	Null
Kang et al. (2024)	European	80,154/853,816	338^	0.94 (0.90, 0.99)‖	per unit increase	Null
Niu, Aierken, and Feng (2024)	European	74,124/824,006	74^	0.95 (0.85, 1.06)	per 20 nmol/L increase	Null
Zhao et al. (2024)	European	895,649	48^	0.99 (0.98, 1.00)	per unit increase	Null

[a] Total sample size in case number of cases and controls were not provided.
SNP, single nucleotide polymorphism. GRS, genetic risk score.
Effect estimates are produced by inverse-variance weighting unless otherwise specified.
[b] by Cox regression, [c] by Wald-type estimator, [d] by Bayesian likelihood method, [e] by Generalized summary-based mendelian randomization, [f] by MR-pleiotropy residual sum and outlier.
[&] The number of SNPs is presented if the specific SNPs analyzed are not mentioned in the original paper or if the number of SNPs is high.
* SNPs from vitamin D synthesis genes, # SNPs from vitamin D metabolism genes, $ SNPs from other genes in vitamin D pathways, ^ SNPs selected by statistical thresholds.
‖ Not significant after adjusting for multiple testing.
[+] Including non-Hispanic White, Hispanic and African American in the United States.

D and Highly Related Traits (SUNLIGHT) consortium (Meng et al. 2019; Yuan et al. 2019; Zheng et al. 2020), UK Biobank (UKBB) (De La Barrera and Manousaki 2023; Jiang, Ge, and Chen 2021; Kang et al. 2024; H. Liu, Meng, et al. 2022; Lu et al. 2018; Meng et al. 2019; Niu, Aierken, and Feng 2024; Revez et al. 2020; J. Xu et al. 2023; Y. Xu et al. 2020; Y. Ye et al. 2021; Zanetti et al. 2020; Zhao et al. 2024; Zheng et al. 2020) and different versions (Mahajan et al. 2022; Mahajan et al. 2018; Morris et al. 2012; Scott et al. 2017) of DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) consortium (Jiang, Ge, and Chen 2021; Kang et al. 2024; Lu et al. 2018; Niu, Aierken, and Feng 2024; Revez et al. 2020; J. Xu et al. 2023; Y. Xu et al. 2020; Y. Ye et al. 2021; Z. Ye et al. 2015; Yuan et al. 2019; Zanetti et al. 2020; Zheng et al. 2020). Some MR studies shared the same data sources for both vitamin D and T2D: two studies utilized SUNLIGHT and DIAGRAM (Yuan et al. 2019; Zheng et al. 2020) and five studies utilized UKBB and DIAGRAM (Niu, Aierken, and Feng 2024; Revez et al. 2020; Y. Xu et al. 2020; Y. Ye et al. 2021; Zanetti et al. 2020). Majority of the included studies ($n = 16$) used data from people of European descent only (Afzal et al. 2014; Buijsse et al. 2013; Jiang, Ge, and Chen 2021; Jorde et al. 2012; Kang et al. 2024; Meng et al. 2019; Niu, Aierken, and Feng 2024; Revez et al. 2020; J. Xu et al. 2023; Y. Xu et al. 2020; Y. Ye et al. 2021; Z. Ye et al. 2015; Yuan et al. 2019; Zanetti et al. 2020; Zhao et al. 2024; Zheng et al. 2020). Data from Chinese (Lu et al. 2018; Wang et al. 2020; Xiao et al. 2021), Indians (Bejar et al. 2021; H. Liu, Meng, et al. 2022), Japanese (H. Liu, Meng, et al. 2022), Hispanic Americans and African Americans (De La Barrera and Manousaki 2023) were used in some studies.

SNP selection and MR analysis

Half of the studies used 2–10 SNPs as genetic instruments for they selected genes in the biological pathways of vitamin D ("biologically motivated strategy" (Burgess and Cronjé 2024)), including the four well-established genes (DHCR7, CYP2R1, GC, CYP24A1) (Afzal et al. 2014; Bejar et al. 2021; Buijsse et al. 2013; Jorde et al. 2012; Lu et al. 2018; Meng et al. 2019; Wang et al. 2020; Y. Xu et al. 2020; Z. Ye et al. 2015; Yuan et al. 2019; Zheng et al. 2020) and other genes (Buijsse et al. 2013; De La Barrera and Manousaki 2023; Meng et al. 2019; Zheng et al. 2020). The other half adopted a "genome-wide strategy (Burgess and Cronjé 2024)" based on statistical thresholds for genome-wide significance and linkage equilibrium, as such they usually utilized tens or over a hundred of SNPs (De La Barrera and Manousaki 2023; Jiang, Ge, and Chen 2021; Kang et al. 2024; H. Liu, Meng, et al. 2022; Niu, Aierken, and Feng 2024; Revez et al. 2020; Xiao et al. 2021; J. Xu et al. 2023; Y. Xu et al. 2020; Y. Ye et al. 2021; Zanetti et al. 2020; Zhao et al. 2024) as instruments.

Most studies used inverse-variance weighting (IVW) as the main analytical method (Bejar et al. 2021; De La Barrera and Manousaki 2023; Kang et al. 2024; H. Liu, Meng, et al. 2022; Lu et al. 2018; Meng et al. 2019; Niu, Aierken, and Feng 2024; J. Xu et al. 2023; Y. Xu et al. 2020; Y. Ye et al. 2021; Yuan et al. 2019; Zanetti et al. 2020; Zhao et al. 2024; Zheng et al. 2020) and sensitivity analyses were often conducted with consistent results obtained (De La Barrera and Manousaki 2023; Jiang, Ge, and Chen 2021; Kang et al. 2024; H. Liu, Meng, et al. 2022; Lu et al. 2018; Meng et al. 2019; Niu, Aierken, and Feng 2024; Revez et al. 2020; Xiao et al. 2021; J. Xu et al. 2023; Y. Xu et al. 2020; Y. Ye et al. 2021; Yuan et al. 2019; Zanetti et al. 2020; Zhao et al. 2024; Zheng et al. 2020). (Table S2).

Assessment of reporting quality

Results of quality assessment using STROBE-MR checklist (Skrivankova et al. 2021) is presented in Table S3. Most studies covered over 70% of the items in the checklist (Afzal et al. 2014; Bejar et al. 2021; De La Barrera and Manousaki 2023; Jiang, Ge, and Chen 2021; Lu et al. 2018; Meng et al. 2019; Niu, Aierken, and Feng 2024; Revez et al. 2020; Xiao et al. 2021; Y. Xu et al. 2020; Z. Ye et al. 2015; Yuan et al. 2019; Zanetti et al. 2020; Zhao et al. 2024; Zheng et al. 2020). The reporting rates of most items were above 50%, except for two items: only six out of 15 two-sample MR studies provided information on sample overlap between the exposure and outcome GWAS (item 10dii) (Jiang, Ge, and Chen 2021; H. Liu, Meng, et al. 2022; Y. Ye et al. 2021; Z. Ye et al. 2015; Zanetti et al. 2020; Zheng et al. 2020), and only seven studies assessed reverse causation (item 13c) by performing a bi-directional MR analysis (Bejar et al. 2021; Revez et al. 2020; Wang et al. 2020; J. Xu et al. 2023; Y. Xu et al. 2020; Zhao et al. 2024) or Steiger test (Kang et al. 2024). (Table S3).

Association between vitamin D level and the risk of T2D

Sixteen out of the 22 included MR studies reported null associations between genetically predicted circulating total serum 25(OH)D concentration and risk of T2D regardless of MR design, study population, the GWAS used and SNP selection criteria (Buijsse et al. 2013; De La Barrera and Manousaki 2023; Jiang, Ge, and Chen 2021; Jorde et al. 2012; Kang et al. 2024; Meng et al. 2019; Niu, Aierken, and Feng 2024; Revez et al. 2020; Wang et al. 2020; J. Xu et al. 2023; Y. Ye et al. 2021; Z. Ye et al. 2015; Zanetti et al. 2020; Zhao et al. 2024; Zheng et al. 2020). Negative associations were reported in six one-sample (Bejar et al. 2021; Lu et al. 2018; Xiao et al. 2021) or two-sample (H. Liu, Meng, et al. 2022; Y. Xu et al. 2020; Yuan et al. 2019) MR studies with different choices of SNPs. The association between vitamin D and risk of T2D varied by choice of SNPs in some (Bejar et al. 2021; Lu et al. 2018; Xiao et al. 2021) but not in other studies (Y. Xu et al. 2020; Yuan et al. 2019). Lu et al. (Lu et al. 2018), Xiao et al. (Xiao et al. 2021) and Bejar et al. (Bejar et al. 2021) (in the combined Indian and European population) identified a negative association when using SNPs from vitamin D synthesis genes, but the association was not evident when using SNPs from vitamin D metabolism genes (Xiao et al. 2021) or all four well-established, biologically relevant genes (Lu et al. 2018; Xiao et al. 2021). However, Yuan et al. (Yuan et al. 2019) and Xu et al. (Y. Xu et al. 2020) showed consistent negative associations regardless of SNP choices.

Discussion

This systematic review of 22 MR studies found mixed results on the associations between genetically predicted total circulating 25(OH)D levels and risk of T2D, with some reporting negative associations implying that vitamin D protects against T2D and the majority reporting null associations. Therefore, the evidence from the existing MR studies does not consistently support the causal role of 25(OH)D in T2D development in the general populations.

Our findings from 22 MR studies are consistent with two previous reviews on vitamin D and health outcomes, one including three MR studies on vitamin D and T2D (D. Liu, Meng, et al. 2022), and the other including 17 MR studies (Fang et al. 2024). An earlier review of MR studies on the risk factors of T2D (Yuan and Larsson 2020) identified circulating vitamin D as a protective factor mediated by body mass index, but this was based on only one MR study conducted by the same group (Yuan et al. 2019). Therefore, the null associations from the majority of MR studies reviewed do not align with the protective effect of vitamin D supplementation against new-onset T2D among adults with prediabetes observed in some RCTs (Dutta et al. 2014; Niroomand et al. 2019) and a recent meta-analysis of three RCTs (Pittas et al. 2023). However, results from RCTs on vitamin D supplementation were also mixed, and the majority did not find vitamin D supplementation significantly reduced risk of T2D in people with prediabetes (Barengolts et al. 2015; Bhatt et al. 2020; Davidson et al. 2013; Jorde et al. 2016; Kawahara et al. 2022; Kuchay et al. 2015; Misra et al. 2021; Pittas et al. 2019; Zaromytidou et al. 2022). We cannot rule out the presence of methodological limitations in some RCTs that contributed to the mixed findings, even among the prediabetic individuals. Nevertheless, comparing the differences on the design and methodology between existing RCTs and MR studies will shed lights on the applicability of the existing MR studies and the directions of further MR studies.

Assuming there is a protective effect of vitamin D against the development of T2D in high-risk populations as shown in some RCTs, prediabetes status, baseline vitamin D concentrations, and other characteristics of the study populations may partly explain the null findings obtained from most MR studies. MR studies used data from the general populations, while RCTs could specifically recruit participants with prediabetes (Barengolts et al. 2015; Bhatt et al. 2020; Davidson et al. 2013; Dutta et al. 2014; Jorde et al. 2016; Kawahara et al. 2022; Kuchay et al. 2015; Niroomand et al. 2019; Pittas et al. 2019; Zaromytidou et al. 2022; Misra et al. 2021). As such, MR studies are more comparable to

RCTs among non-prediabetic individuals. A recent RCT conducted on 2271 healthy elderly without prediabetes showed that different doses of vitamin D_3 supplementation did not reduce the risk of T2D after a mean follow-up of 4.2 years (Virtanen et al. 2024). Sub-group analyses of RCTs showed that the protective effect of vitamin D supplementation on progression of prediabetes was more prominent in those with baseline vitamin D deficiency (25(OH)D < 30nmol/L), aged 62.1 years or above or with a body mass index below 30 kg/m^2 (Pittas et al. 2023). However, most included MR studies did not have sub-group analyses. Only one early MR study conducted sub-group analyses on those with a relatively lower 25(OH)D level (< 45nmol/L), which had a limited sample size (n < 2,000) and reported null associations in this sub-group (Buijsse et al. 2013).

The range of serum 25(OH)D concentrations of the study populations may also contribute to some differences in the findings by study design. RCT design allows for assessing the disease risks among the very high and low levels of vitamin D where their associations may be more prominent. Sub-group analyses of RCTs revealed that the benefits of vitamin D supplementation was observed in those with baseline vitamin D deficiency (25(OH)D < 30nmol/L), and the largest protective effect occurred in those with a post-intervention serum 25(OH)D level ≥ 125nmol/L (Pittas et al. 2023). As for the MR studies included in this review, the average serum 25(OH)D level in the vitamin D GWAS varied from 31 to 78 nmol/L (Table S2), and the magnitude of difference in serum 25(OH)D levels, usually expressed as standard deviations, was much smaller (mostly 20–25 nmol/L) than that between intervention and control groups in RCTs.

The choice of genetic instruments and MR design (one-sample or two-sample) could play an important role in MR results. SNPs selected based on biological pathways are generally less vulnerable to horizontal pleiotropy than those including all SNPs selected from the entire genome which may have pleiotropic effects independent of vitamin D. A previous systematic review of MR studies on vitamin D and T2D concluded that the inverse associations with risk of T2D were more evident when using SNPs from vitamin D synthesis pathway compared to when using SNPs related to metabolism pathway or combination of pathways (Fang et al. 2024). However, for the MR studies included in our review, this conclusion seems true in some (Lu et al. 2018; Xiao et al. 2021), but not the others (Afzal et al. 2014; Y. Xu et al. 2020; Yuan et al. 2019; Zheng et al. 2020). Two-sample MR using large-scale GWAS consortia improves statistical power compared to one-sample MR (Lawlor 2016). However, results from the included two-sample MR studies were still mixed, with some reporting negative (Y. Xu et al. 2020; Yuan et al. 2019) and others reporting null associations (Jiang, Ge, and Chen 2021; Kang et al. 2024; H. Liu, Meng, et al. 2022; Meng et al. 2019; Niu, Aierken, and Feng 2024; Revez et al. 2020; J. Xu et al. 2023; Y. Ye et al. 2021; Z. Ye et al. 2015; Zanetti et al. 2020; Zhao et al. 2024; Zheng et al. 2020). Weak genetic instruments may explain null MR results in two-sample MR studies (Lawlor 2016). Although the genetic instruments for vitamin D in the included studies explained only 1.1–5.3% of the variance of 25(OH)D concentration Table S2), this is usual and expected for MR studies. More importantly, most studies ensured F statistics > 10, which is not considered as weak. These indicate that the mixed findings may not be solely explained by different genetic instruments and MR design.

Observational analysis suggested a non-linear relationship between vitamin D and T2D (Buijsse et al. 2013). However, the approach used in the included MR studies assumed linearity. Recently, there have been MR studies implementing non-linear MR methods (e.g., residual method and doubly ranked method). The doubly ranked method has been applied to address the dose-response association between vitamin D and risk of cardiovascular and all-cause mortality after obtaining implausible results using the residual method, and yet the study identified null associations overall and in different strata of 25(OH)D concentrations ranging from below 30 nmol/L to above 70 nmol/L (Sofianopoulou et al. 2024). Further MR studies on vitamin D and T2D may potentially consider using a doubly ranked method with caution and perform additional sensitivity analyses (Hamilton et al. 2024). In case vitamin D has different effects on the initiation and progression of T2D, similar to the role of folate in colon cancer (Kim 2003), existing MR studies cannot detect these differences. However, currently there is a general lack of appropriate MR techniques and GWAS data on disease progression (Paternoster, Tilling, and Davey Smith 2017), which limits the investigation of vitamin D levels and disease progression from prediabetes to T2D using the MR approach.

Our review has some limitations. First, the included MR studies were predominantly conducted in people of European ancestry, with limited studies in other populations using large consortia. Therefore, their findings may not generalize to other ethnicities, which may have varying underlying characteristics modifying the relation of vitamin D and risk of T2D. Second, we were unable to conduct meta-analyses on the MR results due to the heterogeneous analytical methods and overlapping GWAS populations. Third, the included MR studies did not consider any potential confounding epigenetic effects, i.e., non-Mendelian, heritable changes in gene expression that occur without directly altering nucleotide sequences, such as DNA methylation (Ogbuanu, Zhang, and Karmaus 2009). For example, the methylation status of CYP2R1 and CYP24A1 may contribute to the variation in 25(OH)D levels (Forouhari et al. 2023), and such increased DNA methylation could be a risk factor in T2D development (Wahl et al. 2017). Fourth, the validity of the findings from most two-sample MR studies relied heavily on the quality of the summary statistics from GWAS. The presence of misclassification of phenotypes in electronic health records (Bollaerts et al. 2020), inappropriate covariable adjustments biasing genetic associations (Hartwig et al. 2021) and potential selection bias (Schoeler et al. 2023) may affect the findings in different directions. Finally, potential publication bias toward significant findings may be present. Given more than two thirds of the MR studies included in this review reported null associations, it is unlikely that MR studies showing significant associations were systematically excluded. As such, publication bias is less likely in our review.

Conclusions

Findings from 22 MR studies did not consistently show negative linear association between total serum 25(OH)D and risk of T2D in the general population. However, results from existing MR studies may not directly apply to populations with prediabetes or vitamin D deficiency. Further MR studies to examine the non-linear associations of vitamin D with T2D or disease progression from prediabetes will clarify the use of vitamin D in the prevention of T2D.

Author contributions

All authors contributed to manuscript revision and approved the final version. Specifically, L.L. Hui conceived the review. K. Sun prepared the original draft including tables and figures, which was reviewed and revised by Y. Chen, S.L. Au Yeung, H.S.H.S. Lam, E.A.S. Nelson, A.P. Kong and L.L. Hui.

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