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Serum vitamin D levels in relation to type-2 diabetes and prediabetes in adults: a systematic review and dose-response meta-analysis of epidemiologic studies

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ABSTRACT

Background: Findings of observational studies that investigated the relationship between vitamin D deficiency and abnormal glucose homeostasis were contradictory. This meta-analysis of epidemiologic studies evaluated the association of vitamin D status and risk of type-2 diabetes (T2D) and prediabetes in adults.

Methods: A systematic search was conducted on all published articles in five electronic databases (including MEDLINE/PubMed, EMBASE, Institute for Scientific Information, Scopus and Google scholar), up to August 2020. Twenty-eight prospective cohort and nested case-control studies and 83 cross-sectional and case-control investigations that reported relative risks (RRs) or odds ratios (ORs) with 95% confidence intervals (CIs) for abnormal glucose homeostasis in relation to serum vitamin D levels in adults were included in the analysis.

Results: In prospective studies, high versus low level of vitamin D was respectively associated with significant 35%, 30% and 51% decrease in risk of T2D (RR:0.65; 95%CI: 0.55–0.76; 27 effect sizes), combined T2D and pre-diabetes (RR:0.70; 95%CI: 0.52–0.95; 9 effect sizes) and pre-diabetes (RR:0.49; 95%CI: 0.26–0.93; 2 effect sizes). These inverse associations were significant in almost all subgroups. Dose-response analysis in prospective studies showed that each 10 ng/ml increase in serum vitamin D levels resulted in 12% and 11% reduced risk of T2D (RR:0.88; 95%CI: 0.83–0.94) and combined T2D and prediabetes (RR:0.89; 95%CI: 0.87–0.92), respectively. In cross-sectional and case-control studies, highest versus lowest level of serum vitamin D was linked to reduced odds of T2D (OR:0.64; 95%CI: 0.57–0.72; 42 effect sizes) and combined T2D and pre-diabetes (OR:0.79; 95%CI: 0.74–0.85; 59 effect sizes); but not pre-diabetes (OR:0.64; 95%CI: 0.17–2.37; 11 effect sizes).

Conclusion: This meta-analysis of epidemiologic studies disclosed that serum vitamin D level was reversely associated with the risk of T2D and combined T2D and prediabetes in adults, in a dose-response manner. However, the association was not remarkable for pre-diabetes.

KEYWORDS

Serum 25-hydroxy vitamin D; type 2 diabetes; prediabetes; meta-analysis; epidemiologic studies

Introduction

Diabetes mellitus (DM) is one of the most common chronic diseases which leads to disorders in the metabolism of carbohydrates, proteins and lipids (Baynes 2015). Type-2 diabetes (T2D), known as non-insulin dependent diabetes which accounts for about 90% of all diabetes (Baynes 2015; Eppens et al. 2006), is often associated with impaired glucose tolerance, insulin resistance, hyperglycemia, and is a risk factor for obesity and cardiovascular diseases (CVD), stroke, kidney and liver diseases and amputation (Baynes 2015; Eppens et al. 2006). These complications of T2D are highly prevalent worldwide (Kannel and McGee 1979; Manson et al. 1991). The number of people with diabetes is increasing every year and it is estimated that by 2030, 439 million adults will have diabetes around the globe (Shaw et al. 2010).

In recent years, we have witnessed a change in the quality of diseases (Cohen et al. 2017); previous studies have shown

that one of the important factors that cause disability and early death has changed from infectious and contagious diseases to chronic and degenerative diseases, such as T2D, that are mainly due to the changing lifestyle of people (Cohen et al. 2017; Mokdad et al. 2016). The interaction of genetic, environmental, behavioral factors, hormonal disorders, and the use of certain medications are risk factors for developing diabetes (Haffner 1998; Rawshani et al. 2018). One of these important environmental factors is serum 25-hydroxyvitamin D levels (Pittas et al. 2012). Circulating vitamin D levels can improve glycemic disorders by acting on calcium metabolism, increasing calcium concentration in the cell, stimulating the insulin receptor gene, and increasing glucose uptake by the muscle (Berridge 2017; Wimalawansa and Biology 2018; Wu et al. 2014).

Serum vitamin D concentrations are influenced by environmental and lifestyle factors such as sun exposure and diet (Burnand et al. 1992). Vitamin D deficiency is more

common during the fall and winter due to less sun exposure (Burnand et al. 1992). However, the mechanism by which low vitamin D levels might increase the risk of T2D is not well understood (Alvarez and Ashraf 2010). Previous epidemiological studies have shown that low level of circulating 25-hydroxyvitamin D was related to insulin resistance which was accompanied by the destruction of beta cells and impaired glucose tolerance (Boucher et al. 1995; Kumar et al. 1994). In other words, low levels of vitamin D play a crucial role in abnormal glucose homeostasis and the development of T2D (Lucato et al. 2017). Although in some studies vitamin D deficiency was associated with a higher prevalence of diabetes, the association with glycemic profiles was not observed in other investigations (Boucher et al. 1995; Kumar et al. 1994; Lucato et al. 2017). Also, in some studies, the association of the vitamin with glucose levels was seen only in women or in men (Fu et al. 2019; Muldowney et al. 2011). As far as we know, there was no systematic review to summarize the relationship between serum vitamin D levels with T2D and prediabetes. So, this study aimed to systematically review and perform a meta-analysis on epidemiological studies that assessed the relationship between serum vitamin D concentrations with glycemic disorders (including T2D and prediabetes) in adults.

Methods and materials

Search strategy

We conformed to preferred reporting items for systematic reviews and meta-analyses (PRISMA) guideline in the report of this systematic review and meta-analysis. This study was registered at Prospero (<http://www.crd.york.ac.uk/Prospero: no.CRD42020205829>). A systematic search on all published articles was conducted in MEDLINE (PubMed), EMBASE, Institute for Scientific Information (ISI) (Web of sciences), Scopus, and Google scholar databases, up to August 2020. The following MeSH and non-MeSH (terms) including ("vitamin D" OR "25-hydroxyvitamin D" OR cholecalciferol OR "25-hydroxyvitamin D [25(OH)D]" OR hydroxycholecalciferols OR ergocalciferols OR "25-hydroxyvitaminD2" OR dihydroxycholecalciferols OR calcitriol) AND (diabetes OR prediabetes OR "insulin resistance" OR glucose OR "glycemic control" OR "FBS" OR "FBG" OR "FPS" OR "homeostasis model assessment" OR "Glucose Tolerance Test") were used. No language or time restriction was applied. Unpublished studies were not included in the search strategy. Duplicate citations were removed afterward. The article selection was independently carried out by 2 investigators (S.M. and Z.H.). Full texts of articles that were eligible to include in current study based on inclusion and exclusion criteria were obtained to extract required data.

Inclusion criteria

Studies with the following criteria were eligible for inclusion in the systematic review and meta-analysis: 1) all published observational studies with cross-sectional, cohort and case-

control design, (2) were conducted on adults (>18 years), regardless of their health status, (3) measured serum levels of 25-hydroxyvitamin D as the exposure, (4) reported the risk for T2D, prediabetes, impaired glucose tolerance or impaired fasting glucose as the outcomes, (5) reported odds ratios (ORs), relative risks (RRs), or hazard ratios (HRs) with corresponding 95% CIs for the association of vitamin D deficiency with abnormal glucose homeostasis.

Exclusion criteria

Details of more relevant studies that were excluded are presented in [Supplemental Table 1](#). Studies were excluded if they: (1) reported correlation coefficients, standard or unstandard regression coefficients, mean \pm SD for glucose homeostasis in different levels of serum vitamin D, (2) were conducted on children, (3) were review articles, comments, letters, randomized clinical trials studies or experimental studies, (4) considered gestational DM as the outcome, (5) reported the association between serum vitamin D levels with HOMA-IR, Insulin and HbA1c, (6) examined serum vitamin D levels as the outcome and abnormal glucose homeostasis as the exposure of interest, (7) Considered serum 1, 25 (OH) 2 D3 levels as the exposure.

In overall, our primary systematic search resulted in 21,838 reports. After removing duplicate studies, two investigators (S.M. and Z.H.) have independently screened the titles and abstracts in the first round of screening. Then, the full texts of 657 articles were assessed for eligibility in the second round of screening. Finally, 111 studies (28 prospective cohort and nested case-control studies and 83 cross-sectional and case-control investigations) were eligible to be included in the systematic review and meta-analysis. All procedures were administrated by the principal investigator (P.S.). Details of flow chart of search strategy and study selection are depicted in [Figure 1](#).

Data extraction

The following information was extracted from each eligible investigation: first author's last name, publication date, study design, research location, participants' age and gender, number of participants, biomarkers of serum vitamin D levels, vitamin D deficiency and insufficiency cutoff points, unit of serum vitamin D levels, methods used for assessing serum vitamin D levels, ORs or RRs or HRs and their 95% confidence intervals for serum vitamin D and cutoff points for abnormal glucose homeostasis, representativeness of study population, health status of subjects and adjustments for confounders. For dose-response meta-analysis, we collected the following information from each eligible study: the number of cases and total number of participants for each category, the RRs with 95% CIs for all exposure levels for linear dose-response analysis and at least three exposure categories for nonlinear dose-response analysis, and the mean or median serum vitamin D levels for each category. Data extraction was separately conducted by 2 researchers (S.M.

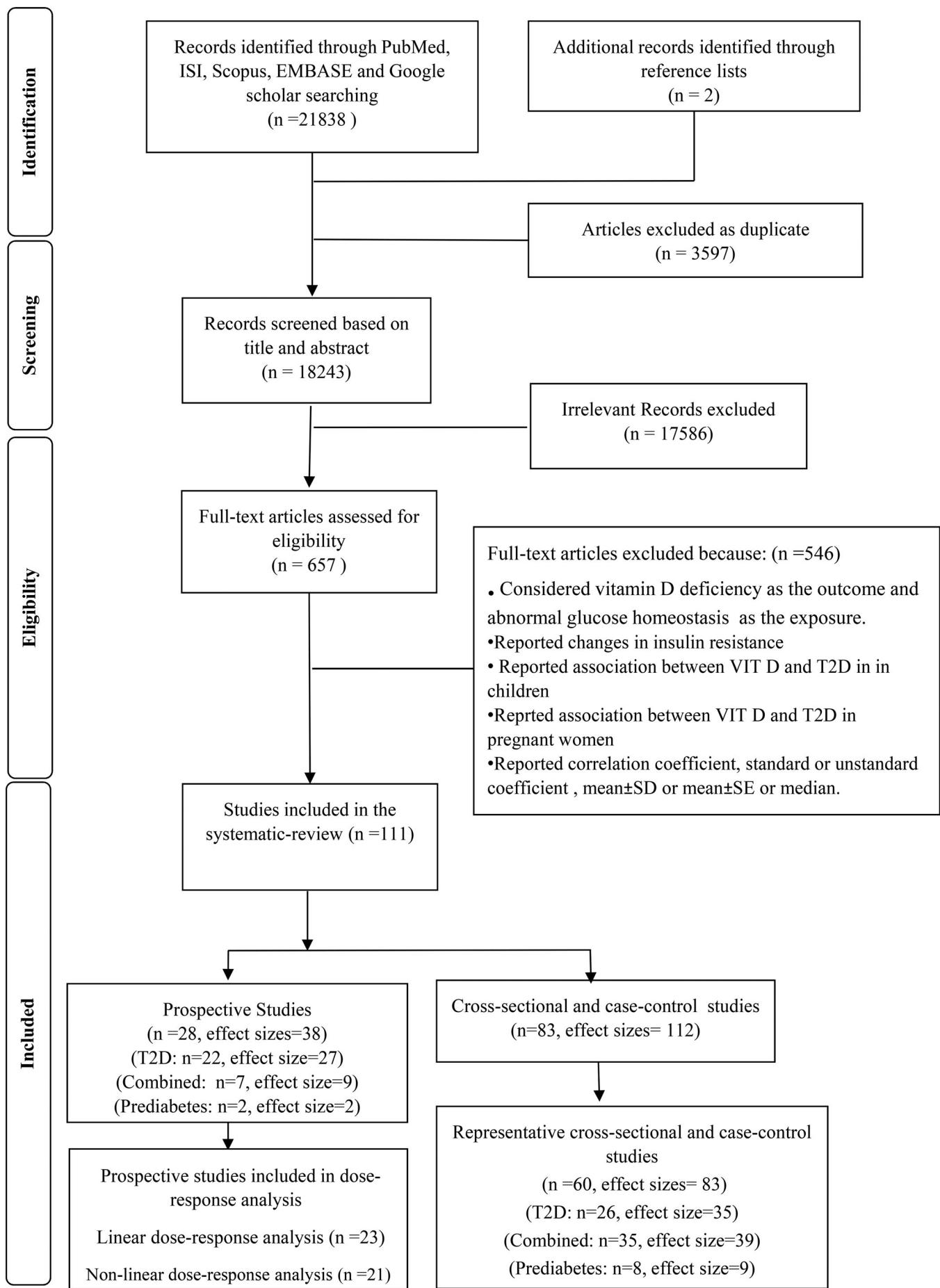


Figure 1. Flowchart of the study selection process.

and Z.H.) and any disagreements were resolved by consultation with the principal investigator (P.S.).

Assessment the quality of studies

The quality of included studies was evaluated by using the Newcastle-Ottawa Scale (NOS) for observational studies (Wells et al. 2000). For cohort study, the NOS assigns a maximum of 9 points to each report: 4 for selection and assessment of exposure, 2 for comparability, and 3 for assessment of outcomes. The NOS for cross-sectional articles allocates a maximum of 10 points to each study: 5 for selection, 2 for comparability, and 3 points for assessment of outcomes. For case-control study, the NOS considers a maximum of 9 points to each report: 4 for selection of cases and controls, 2 for comparability, and 3 for ascertainment of exposure. Studies which have received more than median points (≥ 6 for prospective studies and ≥ 8 for cross-sectional and case-control studies) were considered to be relatively high quality; otherwise, the investigations were deemed to be low quality. Results from the quality assessment of studies included in the meta-analysis are presented in Supplemental Table 2.

Statistical analysis

All reported ORs, RRs, or HRs and their 95% CIs for the relation of highest vs. lowest level of serum 25(OH) D and T2D, combined T2D and prediabetes, or prediabetes were used to calculate log ORs, RRs, or HRs and their standard errors. Since RRs and HRs should be reasonable approximations of each other, we analyzed them together and then conducted a subgroup analysis based on the reported estimates (RRs vs. HRs). For those studies that reported OR/RR for the lowest vs. the highest level of serum 25(OH) D, we inverted OR/RR and its lower and upper limits to compute the estimate for the highest vs. the lowest levels. Using the random effects model that takes between-study heterogeneity into account, the overall effect size was calculated. We calculated both Q-statistic and I^2 as indicators of heterogeneity. In case of significant between-study heterogeneity, we performed subgroup analysis based on categorical variables to find possible sources of heterogeneity. Between-subgroup heterogeneity was assessed by fixed effect model. Sensitivity analysis was used to explore the extent to which inferences might depend on a specific study. Publication bias was assessed by visual inspection of funnel plots. Formal statistical assessment of funnel plot asymmetry was done with Begg's and Egger's regression asymmetry tests.

For the dose-response analysis, a previously described method by Greenland and Longnecker (Greenland and Longnecker 1992) and Orsini et al (Orsini, Bellocchio, and Greenland 2006) was used. The natural logs of the RRs or HRs and 95% CIs across categories of serum vitamin D were used to compute study specific slopes (linear trends) and 95% CIs for 10 ng/ml (or 25 nmol/l) which is the difference between severe deficiency (<10 ng/ml), deficiency (10–20 ng/ml), insufficiency (20–30 ng/ml) and sufficiency

(>30 ng/ml) of serum vitamin D. In this method, the mean or median level of serum vitamin D in each category was assigned to the corresponding RR for each study. For studies that reported the serum 25(OH) D levels as ranges, we estimated the midpoint in each category by calculating the average of the lower and upper bound. When the highest category was open-ended, the length of the open-ended interval was assumed to be the same as that of the adjacent interval. When the lowest category was open-ended, the lower boundary for 25(OH) D was set to zero. Restricted cubic splines (3 knots at fixed percentiles of 10%, 50%, and 90% of the distribution) were used to examine potential nonlinear dose-response associations between serum vitamin D and risk of T2D or prediabetes. Statistical analyses were conducted by using Stata version 14.0 (Stata Corp, College Station, TX). P -values less than 0.05 were considered statistically significant.

Results

Systematic review

Details of 28 included prospective studies in this review are presented in Table 1. These publications were reported between 2007 and 2019. Among them, 22 researches were cohorts and six others were nested case-controls. The range of follow-up was between 3 and 29 years. These cohort and nested case-cohort studies have included a total of 127,980 participants, with a range of 351 -as the least- and 41,504 -as the most- number of participants. Twenty-six of these studies were accomplished in developed countries (Afzal, Bojesen, and Nordestgaard 2013; Akter et al. 2020; Anderson et al. 2010; Buijsse et al. 2013; Deleskog et al. 2012; Forouhi et al. 2012; Gagnon et al. 2012; Gagnon et al. 2011; González-Molero et al. 2012; Grimnes et al. 2010; Husemoen, Thuesen, et al. 2012; Kayaniyil et al. 2011; Knek et al. 2008; Lim et al. 2013; Liu, Tan, and Jeynes 2011; Mattila et al. 2007; Napoli et al. 2016; Park et al. 2018; Pilz et al. 2012; Pittas et al. 2010; Robinson et al. 2011; Schafer et al. 2014; Schmitt et al. 2018; Schottker et al. 2013; Thorand et al. 2011; Veronese et al. 2014) and two other studies were carried out in developing societies (Gao et al. 2018; Tohidi et al. 2013). Five of them were conducted in USA (Anderson et al. 2010; Liu, Tan, and Jeynes 2011; Pittas et al. 2010; Schafer et al. 2014), three in Denmark (Afzal, Bojesen, and Nordestgaard 2013; Husemoen, Thuesen, et al. 2012; Husemoen, Thuesen, et al. 2012) and Germany (Buijsse et al. 2013; Schottker et al. 2013; Thorand et al. 2011), two in Italy (Napoli et al. 2016; Veronese et al. 2014), Australia (Gagnon et al. 2012; Gagnon et al. 2011), South Korea (Lim et al. 2013; Park et al. 2018), Finland (Knek et al. 2008; Mattila et al. 2007) and one in China (Gao et al. 2018), Iran (Tohidi et al. 2013), Sweden (Deleskog et al. 2012), Netherlands (Pilz et al. 2012), Spain (González-Molero et al. 2012), Japan (Akter et al. 2020), Canada (Kayaniyil et al. 2011). The age range of participants was between 30 and 75 years. The relation between serum vitamin D levels and abnormal glucose homeostasis in twenty-one included studies were studied in both genders

Table 1. Main characteristics of included cohort and nested case-control studies examined the association between serum vitamin D levels and abnormal glucose homeostasis in adults.

First Author (Year)	Study design /name study	Age range / Mean age	Country	No. Participants	Sex	25(OH)D Levels, nmol/L	RR or HR (95% CI)	Method of 25(OH)D assessment (Exposure)	Subject	Definition (Outcome)	Adjustments
1 Aker 2020	Nested-case-control	Japan	34–69	Men 1004 (336 Cases/ 668 Controls)		<20 ng/mL 20–29 >30	1.00 (Ref) 0.52 (0.31–0.86) 0.37 (0.12–1.11)	LC-MS/MS	T2D (FPG ≥ 126 mg/dL / HbA1c ≥ 6.5% / BG ≥ 200 mg/dL / Current medical treatment For DM)	Matching factors: sex, age date of blood drawing Adjustments: leisure time physical activity, occupational physical activity, smoking, alcohol drinking, shift work, sleep duration, family history of diabetes, hypertension, BMI, fasting blood glucose	
2 Gao 2018	Cohort (4-year follow-up)	China	20–74	Both	490	Q1(13.93–33.56) nmol/l Q2 (33.57–40.11) Q3 (40.12–46.38) Q4 (46.39–80.30)	5.61 (1.73–18.27) 2.12 (0.64–7.02) 1.77 (0.48–6.58) 1.00 (Ref)	E/A	Adults	T2D (FPG ≥ 7 mmol/L or a 2h-PG ≥ 11.1 mmol/L or treatment with insulin or oral hypoglycemic agents) Prediabetes (IFG or IGT)	Matching factors: sex, age date of blood drawing Adjustments: leisure time physical activity, occupational physical activity, smoking, alcohol drinking, shift work, sleep duration, family history of diabetes, hypertension, BMI, fasting blood glucose
3 Park 2018	Cohort	South-Korea	74	Both	903	<30 ng/ml 30–39 40–49 ≥50	1.00 (Ref) 0.44 (0.20–0.95) 0.47 (0.22–1.00) 0.36 (0.14–0.90)	PBA and CLA	Diabetes Prediabetes	T2D (FPG ≥ 126 mg/dL or 70 mmol/L) Pre diabetes (FPG:100–125, 2-OGTT:140–200 mg/dl)	Age, sex, race, hypertension, smoking history, resting pulse, parental history of DM and anthropometric characteristics such as height, waist, weight and plasma glucose, triglyceride, HDL cholesterol and uric acid in fasting state
4 Napoli 2016	Cohort (follow-up 6.4 ± 1.0 year)	Italy	≥65 73.3 ± 5.7	Both (51% Women; 67.9 ± 5.7 years)	1939 482 492 480 485 2227	3.13–20.89 ng/ml 20–90–25.63 25.64–30.59 30.60–74.77 per 1 SD increase <25 nmol/L 25–50 50–75 >75	1.00 (Ref) 1.43 (0.89–2.30) 1.62 (0.99–2.64) 1.07 (0.61–1.89) 1.03 (0.85–1.25) 1.37 (0.87–2.16) 1.44 (0.95–1.98) 1.05 (0.76–1.45) 1.00 (Ref)	LC-MS/MS	Adults	T2D (FPG ≥ 7 mmol/L self-reported DM or use of medication to treat DM)	Age, sex, race, season, BMI, and calcium intake (diet and supplement)
5 Veronese 2014	Cohort (follow-up of 4.4 years)	Italy	≥65 65–103	Both (51% Women)	761	For change of 1 nmol/L	0.99 (0.997–1.002)	R/A	Older adults	T2D (FPG 70 nmol/L HbA1c > 6.5% use of glucose lowering drugs, or a 2-h PG > 11.1 mmol/L)	Age, gender, and baseline waist circumference, hypertension, formal education, monthly income, smoking habits, eGFR, and serum levels of FPG, HbA1c and total cholesterol
6 Schafer 2014	Cohort (follow-up of 8.6 ± 4.4 years)	US	≥65 76.5	Women	5463	<20 ng/ml 20–29 ≥30	1.00 (Ref) 0.89 (0.69–1.14) 0.88 (0.64–1.20)	LC-MS/MS	Adults	T2D (self-report based on physician diagnosis or anti-diabetic medication use)	Age, clinic site, BMI, self-reported health and hypertension
7 Tohid 2013	Nested case-control (follow-up 3.6 year) T1GS	Iran	20–83	Both	761	T1 2.82–11.0 ng/ml T2 11.03–21.80 T3 ≥ 21.82	1.00 (Ref) 0.54 (0.29–1.00) 0.40 (0.22–0.75)	E/A	Adults	T2D (FBG concentration 7.0 mmol/l and/or 2-h triglyceride-to-HDL (continued)	Family history of diabetes, baseline systolic blood pressure, triglyceride-to-HDL

**Table 1.** Continued.

First Author (Year)	Study design / name study	Age range / Mean age	Country	No. Participants	Sex	25 (OH)D Levels, nmol/L	RR or HR (95% CI)	Method of 25 (OH) D assessment (Exposure)	Subject	Definition (Outcome)	Adjustments
8 Schottker 2013	Cohort (8 years of follow-up)	Germany	50–74	Both Women Men	7791 972 1068	Q1 (28.2–30) nmol/l Q2 (34.7–39.1) Q3–5	1.36 (1.12–1.59) 1.26 (1.04–1.48) 1.00 (Ref)	IA LC–MS/MS	Adults	T2D (diagnoses documented by the GPs, use of antidiabetic drugs according to the GPs' medical records and HbA1c > 6.5)	PG > 11.1 mmol/l to-height ratio, and fasting plasma glucose. Age, sex and season of blood draw, intake of multi-vitamin supplements, frequent fish consumption, BMI, HbA1c family history of diabetes, education, physical activity, smoking, hypertension, renal dysfunction, CRP and fasting triglycerides
9 Afzal 2013	Cohort (29 year follow-up)	Denmark	20–100	Both	9841	≥ 20 ng/ml 10–19.9 5–9.9 <5 ≥20 10–19.9 10 ng/ml	1.00 (Ref) 1.22 (1.03, 1.44) 1.30 (1.06, 1.59) 1.22 (0.85, 1.74) 1.00 (Ref) 2.06 (1.22–3.49) 3.23 (1.66–6.30)	DiAScorin Liaison 25(OH)D Total assay (IA) LC–MS/MS	Adults	T2D (self-reported use of antidiabetic medicine, BG > 198 mg/dL)	Sex, age, smoking status, BMI, income, physical activities and month of blood sampling
10 Lim 2013	Cohort (5-year follow-up)	South Korea	49.5 ± 11.4	Both	1080				Nondiabetic Korean subjects	T2D (Hb A1c ≥ 6.5%, American Diabetes Association's diagnosis criteria)	Multivitamin intake, BMI, HOMA-IR, IgI
11 Buisse 2013	Case-cohort (follow-up of 6.6 years)	Germany	35–65	Women	2121	<25 nmol/l 25–50 ≥50	1.00 (Ref) 0.77 (0.57, 1.06) 0.86 (0.61, 1.22)	LC–MS/MS	Adults	T2D (ICD-10, diagnosed by physician)	Sex, study center, and month of blood draw, education, smoking, alcohol intake, WC activity, BMI, FHD, physical activity during leisure time, BP and sex
12 Delekskog 2012	Nested case-control (followed 8–10 years)	Sweden	35–56	Both Women Men	2378	Q1 Q2 Q3 Q4 Continuous, per 10 nmol/l Q1 Q2 Q3 Q4 Continuous, per 10 nmol/l <25 nmol/l ≥25–50 50–75 75≤	1.00 (Ref) 0.89 (0.59, 1.35) 0.72 (0.47, 1.11) 0.82 (0.53, 1.28) 0.95 (0.87, 1.04) 1.00 (Ref) 0.75 (0.53, 1.07) 0.81 (0.57, 1.15) 0.80 (0.56, 1.14) 0.98 (0.92, 1.05) 1.65 (0.75–3.63) 1.43 (0.73–2.80) 1.25 (0.62–2.52) 1.00 (Ref)	CLIA	Adults	T2D and Prediabetes	Age, BMI, FHD, physical activity during leisure time, BP and sex
13 Husenmoen 2012	Cohort follow-up 5 years	Denmark	30–65	Both	6405					Diabetes was diagnosed based on OGTT results as fasting plasma glucose ≥7.0 or 2-h plasma glucose ≥11.1 mmol/L	Season of blood collection, sex, age, family history of diabetes, BMI, and change in weight during follow-up, leisure time physical activity, dietary habits, alcohol consumption, smoking status, total energy intake, and social class,
14 González-Molero 2012	Spain	50.3 ± 14.4	Both	1226	<18.5 ng/mL ≥ 18.5 ng/mL		1.00 (Ref) 0.17 (0.05–0.61)	ECLIA	Adults	T2D (FBG >126 mg/dL, 2 h OGTT)	randomization group and self-reported changes in dietary habits, physical activity, smoking status, and alcohol consumption during follow-up

15	Phz 2012	Cohort (7.5 years follow-up)	Finland	50–75 (51% Female)	Both	351	<50nmol \geq 50 < 75 \geq 75 Per SD increase	1.69 (0.51–5.62) 1.40 (0.42–4.63) 1.00 (Ref) 0.85 (0.59–1.22)	RIA Diabetes was diagnosed based on OGTT results as fasting plasma glucose \geq 7.0 or 2-h plasma glucose \geq 7.0 or \geq 11.1 mmol/L RIA	Elderly	Fasting glucose 7.0 mmol/L, 2-h post load glucose 11.1 mmol/L or HbA1c 6.5%
16	Forouhi 2012	Nested case-cohort (EPIC-Norfolk cohort)	UK	40–75 58 ± 9.4	Both	1447	Q1 < 48.8 nmol/l Q2 49.0–63.5 Q3 63.6–80.0 Q4 > 80	1.00 (Ref) 0.66 (0.45–0.97) 0.53 (0.34–0.82) 0.50 (0.32–0.76)	CLIA	Adults	T2D (record linkage with general practice, family history of diabetes, hospital and death registries)
17	Gagnon 2012	Cohort 5-yr follow-up	Australia	\geq 25	Both	4164	Per 10-nmol/ml Per 10-nmol/ml Q1 (13.93–33.56) nmol/l Q2 (33.57–40.11) Q3 (40.12–46.38) Q4 (46.39–80.30)	1.14 (1.03–1.25) 1.08 (0.93–1.25) 3.01 (1.50–6.06) 1.68 (0.81–3.46) 1.64 (0.80–3.38) 1.00 (Ref)	CLIA	Adults	FBG \geq 100.9 mg/dl 2-h PG \geq 140.4 mg/dl Prediabetes (IFG or T1) or (GT)
18	Husemoen 2012	Cohort (follow-up 10 years)	Denmark	41–71	Both	2571	<25 nmol/l \geq 25–50 \geq 50–75 \leq 75 1.00 (Ref)	1.42 (0.66–3.11) 1.48 (1.04–2.12) 1.30 (0.93–1.82)	CLIA	Adults	T2D (ICD-8 diabetes registry)
19	Liu 2011	Cohort (follow-up 7 year)	US	>50	Both	2956 987 983 986	T1 42.3 (18.8–45.6 nmol/l) T2 47.9 (45.7–50.4) T3 54.3 (50.5–68.8)	1.00 (Ref) 0.71 (0.46–1.11) 0.60 (0.37–0.97)	RIA	Adults	T2D (FBG \geq 7.0 mmol/L or use of insulin or oral hypoglycemic drug)
20	Kavanyil 2011	Cohort (3 years of follow-up)	Canada	50 ± 10	Women	489	Per SD increase in baseline serum 25(OH)D	0.78 (0.59–1.02)	RIA	Adults	Dysglycemia (IFG, IGT, T2D)
21	Thorand 2011	Prospective case-cohort study	Germany	35–74	Both Men women	416 Case/ 1267 Non case	27.7 (5.08–36 nmol/L) 43.9 (36.13–54) 68.0 (54.71–153.92) 27.0 (9.87–33.13) 39.9 (33.14–48.24) 58.0 (48.25–127.69)	1.00 (Ref) 0.85 (0.61–1.17) 0.73 (0.50–1.05) 1.00 (Ref) 1.04 (0.66–1.64) 0.78 (0.48–1.27)	E/A	Adults	Type 2 diabetes (questionnaires or interviews, the treating physician or medical chart review)

(continued)



Table 1. Continued.

First Author (Year)	Study design / name study	Age range / Mean age	Country	Sex	No. Participants	25 (OH)D Levels, nmol/L	RR or HR (95% CI)	Method of 25 (OH) D assessment (Exposure)	Subject	Definition (Outcome)	Adjustments
22 Robinson 2011	Nested case-control (followed 7.3 years) (WHI)	US 66±7.3	Women	5140	<50nmol/l 50-<-75 ≥75	1.00 (Ref) 0.89 (0.61–1.30) 1.14 (0.68–1.90)	CLIA	Adults	T2D (self-reported of physician diagnosis of T2D, use of an oral hypoglycemic agent or insulin)	T2D (treatment with insulin or oral hypoglycemic agents, FPG ≥7 mmol/L or 2-h PG ≥11.1 mmol/L)	Age, ethnicity, WC, family history of diabetes, smoking status and PA (plus season and latitude for serum 25OHD).
23 Gagnon 2011	Cohort (5 years follow)	Australia 51	Both	5200	Q1 (9–48 nmol/l) Q2 49–63 Q3 64–78 Q4 79–233	1.00 (Ref) 0.83 (0.56–1.22) 0.48 (0.31–0.76) 0.68 (0.43–1.07)	CLIA	Adults	T2D (treatment with insulin or oral hypoglycemic agents, FPG ≥7 mmol/L or 2-h PG ≥11.1 mmol/L)	Age, race, fasting status, month of blood draw, laboratory batch for plasma 25-OHD, latitude, history of hypercholesterolemia and hypertension, family history of DM, smoking status, physical activity, alcohol consumption, multivitamin use, intake of caffeine, trans fat, cereal fiber, iron, magnesium, fish, calcium	
24 Pittas 2010	Nested case-control	US 43–70 56.4	Women	608 Case / 569 Control	Q1(144 (6.7–17.8 ng/ml) Q2 (20.8 (17.9–23.1) Q3 (25.9 (23.2–28.9) Q4 (33.4 (29.1–37.6)	1.00 (Ref) 1.09 (0.74–1.61) 0.95 (0.63–1.45) 0.52 (0.33–0.83)	RIA	Nurses	T2D (FBG > 126mg/dl)	T2D (FBG > 126mg/dl)	Age, sex, survey, and season, BMI, smoking status, alcohol consumption
25 Anderson 2010	Cohort	US 55±21	Both	41504	≤15ng/ml 16 <-< 30 >30	1.00 (Ref) 1.27 (1.09–1.50) 1.10 (0.98–1.24)	CLIA	Adults	T2D (FBG >7.0 mmol/L or use of insulin or oral hypoglycemic drug)	T2D (FBG ≥11.1 mmol / l, FBS ≥7.0 mmol / l or 2-h PG ≥ 11.1 mmol / l), HbA1c > 7.0%, use of insulin or oral anti-diabetic drug)	Age, sex, body mass index (BMI), physical activity and, in nonsmokers, former smoking, insmoker, number of cigarettes and years of smoking
26 Grønnes 2010	Cohort (follow-up 11 year)	Norway >50	Both	1962 4157	76.0–179.5 nmol / l 64.4–91.3 52.9–79.3 5.0–67.2 57.3–192.2 nmol / l 43.4–73.5 34.8–62.3 5.0–53.1	1.00 (Ref) 1.55 (0.66–3.64) 1.76 (0.76–4.05) 1.47 (0.62–3.48) 1.00 (Ref) 0.94 (0.59–1.51) 1.27 (0.82–1.97) 1.37 (0.89–2.10)	ECU/A	Smoker Non-smoker	T2D (FBG ≥11.1 mmol / l, FBS ≥7.0 mmol / l or 2-h PG ≥ 11.1 mmol / l), HbA1c > 7.0%, use of insulin or oral anti-diabetic drug)	T2D (registry of reimbursement for costs of diabetes medication.)	Age, BMI, physical activity (inactive, occasionally, or regularly active) smoking (never, past, current smoker, and dose), and education (prestige, basic level, intermediate or high level). with the exclusion
27 Knekt 2008	2. Nested-case-control Finland Finnish Mobile Clinic Health Examination Survey 1973–1976	40–74	Both Men	7503	23.52 (11–32) 37.04 (33–41) 48.95 (42–57) 74.54 (58–148)	1.00 (Ref) 0.90 (0.31–2.63) 1.68 (0.54–2.22) 0.41 (0.10–1.65)	RIA	Adults	T2D (registry of reimbursement for costs of diabetes medication.)	Age, BMI, physical activity (inactive, occasionally, or regularly active) smoking (never, past, current smoker, and dose), and education (prestige, basic level, intermediate or high level). with the exclusion	
			Women		22.56 (11–28) 32.53 (29–36) 42.61 (37–48) 62.51 (49–109)	1.00 (Ref) 0.82 (0.32–2.11) 0.88 (0.33–2.30) 0.60 (0.21–1.71)					

Men		of diabetes cases during first, BP, TC											
23.91 (11–32)	1.00 (Ref)	38.47 (33–44)	0.44 (0.15–1.25)	53.78 (45–62)	0.51 (0.18–1.50)	75.60 (63–117)	0.07 (0.02–0.35)	20.40 (9–26)	1.00 (Ref)	31.39 (27–36)	1.97 (0.74–5.20)	42.14 (37–48)	2.22 (0.78–6.26)
38.47 (33–44)	0.44 (0.15–1.25)	53.78 (45–62)	0.51 (0.18–1.50)	75.60 (63–117)	0.07 (0.02–0.35)	20.40 (9–26)	1.00 (Ref)	31.39 (27–36)	1.97 (0.74–5.20)	42.14 (37–48)	2.22 (0.78–6.26)	62.40 (49–105)	2.17 (0.71–6.63)
53.78 (45–62)	0.51 (0.18–1.50)	75.60 (63–117)	0.07 (0.02–0.35)	20.40 (9–26)	1.00 (Ref)	<30 mmol/l	1.00 (Ref)	30–41	1.23 (0.80–1.89)	42–55	0.97 (0.59–1.58)	>55	0.58 (0.32–1.06)
75.60 (63–117)	0.07 (0.02–0.35)	20.40 (9–26)	1.00 (Ref)	<30 mmol/l	1.00 (Ref)	30–41	1.23 (0.80–1.89)	42–55	0.97 (0.59–1.58)	>55	0.58 (0.32–1.06)		
Women													
4044		Both											
40–69		Finland											
Cohort (17 years follow up)													
Mattila 2007													
Abbreviations: T2D, Type 2 diabetes; FBG, Fasting blood glucose; FPG, Fasting plasma glucose; BG, non-fasting blood glucose; MS, metabolic syndrome; IGT, Impaired glucose tolerance; HT, Hormone therapy; TG, Triglyceride; WC, Waist circumference; BP, Blood pressure; HDL, High density lipoprotein; PA, physical activity; LDL, low-density lipoprotein; LP, lipo protein lipase; MVPA, Moderate-to-vigorous physical activity; BMI, Body mass index; DM, Diabet mellitus; NOS, Newcastle–Ottawa Scale; OR, odds ratio; PBA, protein-binding assay; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; EIA, enzyme immunoassay; ELISA, enzyme-linked immune sorbent assay; CLIA, chemiluminescent immunoassay; LC-MS/MS, liquid chromatography-tandem mass spectrometry; CI, 95% confidence interval; RR, relative risk; HR, hazard ratio; OR, odds ratio; CVDS, cardiovascular diseases; CHD, Coronary heart disease; CRP, C-reactive protein; eGFR, Estimated glomerular filtration rate; TLGS, Tehran Lipid and Glucose Study.													

Abbreviations: T2D, Type 2 diabetes; FBG, Fasting blood glucose; FPG, Fasting plasma glucose; BG, non-fasting blood glucose; MS, metabolic syndrome; IGT, Impaired glucose tolerance; HT, Hormone therapy; TG, Triglyceride; WC, Waist circumference; BP, Blood pressure; HDL, High density lipoprotein; PA, physical activity; LDL, low-density lipoprotein; LP, lipo protein lipase; MVPA, Moderate-to-vigorous physical activity; BMI, Body mass index; DM, Diabet mellitus; NOS, Newcastle–Ottawa Scale; OR, odds ratio; PBA, protein-binding assay; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; EIA, enzyme immunoassay; ELISA, enzyme-linked immune sorbent assay; CLIA, chemiluminescent immunoassay; LC-MS/MS, liquid chromatography-tandem mass spectrometry; CI, 95% confidence interval; RR, relative risk; HR, hazard ratio; OR, odds ratio; CVDS, cardiovascular diseases; CHD, Coronary heart disease; CRP, C-reactive protein; eGFR, Estimated glomerular filtration rate; TLGS, Tehran Lipid and Glucose Study.

(Afzal, Bojesen, and Nordestgaard 2013; Anderson et al. 2010; Deleskog et al. 2012; Husemoen, Thuesen, et al. 2012; Knekter et al. 2008; Mattila et al. 2007; Park et al. 2018; Pilz et al. 2012; Schottker et al. 2013; Husemoen, Thuesen, et al. 2012), while five others investigated women population (Buijsse et al. 2013; Kayaniyil et al. 2011; Pittas et al. 2010; Schafer et al. 2014) and two others were conducted on men (Akter et al. 2020; Napoli et al. 2016). Most of these studies have reported the risk of outcome in different quartiles, tertiles or deficient, insufficient and sufficient categories of serum vitamin D level and provided RRs for the highest versus lowest levels of the exposure ($n=25$), while three other investigations reported RRs for serum vitamin D as a continuous variable (Gagnon et al. 2012; González-Molero et al. 2012; Kayaniyil et al. 2011). Some included studies considered sufficient serum vitamin D level as the reference category to report RRs, while some others defined vitamin D deficiency or the first level of serum vitamin D as the reference. All included prospective studies were conducted on generally healthy population. For evaluation of serum vitamin D concentration various methods were used, including radioimmunoassay (RIA) ($n=8$), chemiluminescent immunoassay (CLIA) ($n=6$), electrochemiluminescence immunoassay (ECLIA) ($n=2$), enzyme IA (EIA) ($n=3$), liquid chromatography-tandem mass spectrometry (LC-MS/MS) ($n=8$); the last study used two method for assessment of vitamin D. Twenty-two studies defined T2D according to the cutoff points that were proposed by American Diabetes Association (ADA) (Association AD 2007), including fasting blood glucose (FBG) ≥ 126 mg/dl, glycated hemoglobin (HbA1C) $\geq 6.5\%$ and 2 h glucose ≥ 200 mg/dl. Cutoff points of ADA for prediabetes, including $100 < \text{FBG} < 125$ mg/dl or $5.7 < \text{HbA1C} < 6.4\%$ or $140 < 2\text{h glucose} < 199$ mg/dl, were also used by 2 eligible investigations. Confounding factors that were mostly considered in the analysis of the comprised studies were age ($n=22$), season or sun exposure ($n=16$), body mass index ($n=17$), smoking status ($n=17$), physical activity ($n=17$) and alcohol consumption ($n=8$). The same figure was found in cross-sectional and case-control studies. Details of 83 eligible cross-sectional and case-control investigations for this review are presented in Supplemental Table 3.

Meta-analysis of highest vs. lowest level of serum vitamin D and risk of T2D in prospective studies

As, shown in Table 2 and Figure 2, combining 27 effect sizes from 17 cohorts and 5 nested case-control studies showed that high level of vitamin D, compared to low level, was associated with a significant 35% decrease in risk of T2D (RR: 0.65; 95% CI: 0.55, 0.76) with a moderate heterogeneity ($I^2 = 56.2\%$, $P = 0.001$). Stratified analysis by study design revealed that serum vitamin D levels were significantly associated with decreased risk of T2D in cohort studies (RR: 0.66; 95% CI: 0.56, 0.77), but not in nested case-control studies (RR: 0.63; 95% CI: 0.39, 1.01), with a moderate heterogeneity in both subgroups (Figure 2). Subgroup analyses based on other variables (including study location, sex of participants, study quality, vitamin D categories used for comparison, method of vitamin D assessment, adjustment for season and energy intake and

Table 2. Results of meta-analysis for serum vitamin D levels in relation to abnormal glucose homeostasis in adults.

	T2D						Prediabetes						Combined				
	No. of studies	No. of effect sizes	OR or RR (95% CI)	P for heterogeneity	ρ^2 (%)	No. of studies	No. of effect sizes	OR or RR (95% CI)	P for heterogeneity	ρ^2 (%)	No. of studies	No. of effect sizes	OR or RR (95% CI)	P for heterogeneity	ρ^2 (%)		
Meta-analysis on prospective studies	22	27	0.65 (0.55,0.76)	0.001	56.2	2	2	0.49 (0.26, 0.93)	0.1	62.4	7	9	0.70 (0.52, 0.95)	0.001	81.4		
Cohorts	17	19	0.66 (0.56,0.77)	0.003	54.2	2	2	0.49 (0.26, 0.93)	0.1	62.4	6	7	0.69 (0.52, 0.94)	0.001	85.2		
Nested case-controls	5	8	0.63 (0.39,1.01)	0.006	65	2	No significant linear association (RR: 0.81; 95% CI 0.60, 1.09)	Each 10 ng/ml increase in serum vitamin D levels resulted in a 12% reduced risk of T2D (RR: 0.88; 95% CI 0.83, 0.94)	0.1	62.4	1	2	0.81 (0.61, 1.07)	0.932	Each 10 ng/ml increase in serum vitamin D levels reduced the risk of glycemic disorder by 11 % (RR: 0.89; 95%CI: 0.87, 0.92)	0.001	0.0
Linear dose-response analysis on prospective studies	19																
Nonlinear dose-response analysis on prospective studies	20						2	3									
Meta-analysis on case-control and cross-sectional studies	31	42	0.64 (0.57, 0.72)	0.001	97.2	10	11	0.64 (0.17, 2.37)	0.001	99.8	55	59	0.79 (0.74, 0.85)	0.001	80.4		
Case-controls	3	4	0.37 (0.16, 0.86)	0.001	87.2	10	11	0.64 (0.17, 2.37)	0.001	99.8	1	1	0.36 (0.19, 0.70)	0.0	0.0		
Cross-sectionals	28	38	0.65 (0.58, 0.73)	0.001	97.4	8	9	0.83 (0.66, 1.05)	<0.001	85.2	54	58	0.80 (0.74, 0.85)	0.001	80.1		
Meta-analysis on representative case-control and cross-sectional studies	26	35	0.64 (0.57, 0.73)	0.001	97.7					85.2	35	39	0.79 (0.72, 0.87)	<0.001	71.9		
Case-controls	2	2	0.14 (0.00, 5.66)	0.001	95.1					85.2	1	1	0.36 (0.19, 0.70)	0.0	0.0		
Cross-sectionals	24	33	0.65 (0.57, 0.74)	0.001	97.8	8	9	0.83 (0.66, 1.05)	<0.001	85.2	34	38	0.80 (0.73, 0.88)	<0.001	71		

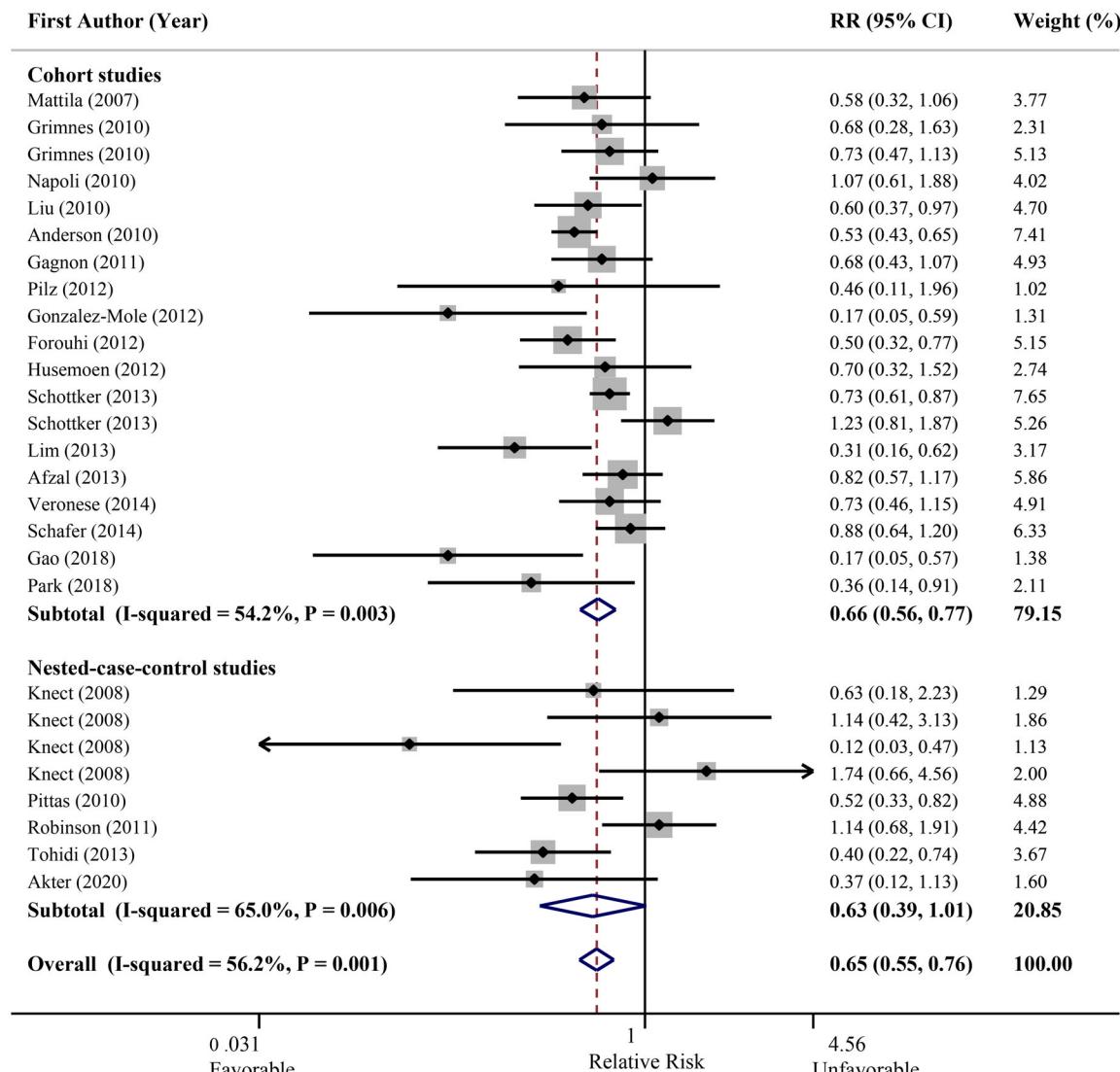


Figure 2. Forest plot of prospective studies that examined the association between highest vs. lowest level of serum vitamin D and risk of T2D.

reported estimates) were done and findings are presented in Table 3. None of these subgroup analyses could completely resolve the observed heterogeneity. Findings from sensitivity analysis revealed that the exclusion of any single study from the analysis did not alter the overall association. No significant publication bias was found using Begg's funnel plot, Begg's test ($P = 0.05$) and Egger's test ($P = 0.22$).

Dose-response meta-analysis of serum vitamin D and risk of T2D in prospective studies

Combining effect sizes of 19 studies involving a total of 171,784 individuals and 9,136 cases of T2D showed that each 10 ng/ml increase in serum vitamin D levels resulted in a 12% reduced risk of T2D (RR: 0.88; 95% CI: 0.83, 0.94) (Figure 3). Although a U-shape trend was observed, there was no significant nonlinear association between serum vitamin D levels and T2D ($P_{\text{nonlinearity}}=0.68$) (Figure 4).

Meta-analysis of highest vs. lowest level of serum vitamin D and risk of combined T2D and prediabetes in prospective studies

As depicted in Table 2 and Figure 5, combining 9 effect sizes from 6 cohorts and 1 nested case-control study showed that highest level of vitamin D in comparison to lowest level was associated with a significant 30% reduced risk of combined T2D and pre-diabetes (RR: 0.70; 95% CI: 0.52, 0.95), while heterogeneity was high ($I^2 = 79.2\%$, $P = 0.001$) (Figure 5). To find the source of heterogeneity, subgroup analysis based on different covariates was done. Subgroup analyses by study design (Figure 5) and other confounders (Table 3) did not provide more explanations for observed heterogeneity. Sensitivity analysis indicated that no particular study significantly affected the overall estimate. There was no evidence of significant publication bias using Begg's funnel plot and Begg's test ($P = 0.30$).

Table 3. Results of subgroup-analysis for serum vitamin D levels in relation to abnormal glucose homeostasis in prospective studies.

	No. of effect sizes	RR (95% CI)	P within ¹	I2 (%)	P between ²
Sub-group analysis cohort and nested case-control and T2D					
<i>Overall</i>	27	0.65 (0.55, 0.76)	<0.001	56.2	
<i>Adjustment for Asian vs. Non-Asian countries</i>					<0.001
Asian	5	0.34 (0.23, 0.49)	0.806	0.00	
Non-Asian	22	0.71 (0.61, 0.83)	0.003	51.5	
<i>Adjustment for sex</i>					<0.001
Both	18	0.58 (0.49, 0.68)	0.074	34.7	
Male	3	0.51 (0.13, 1.94)	0.005	81.3	
Female	6	0.83 (0.65, 1.06)	0.096	46.5	
<i>Quality score³</i>					<0.055
Low quality (Scores ≤ median of 6)	20	0.61 (0.50, 0.75)	<0.001	59.6	
High quality (Scores > median of 6)	7	0.75 (0.60, 0.93)	0.198	30.2	
<i>Adjustment for Season</i>					0.004
Yes	15	0.54 (0.42, 0.68)	<0.001	49.0	
No	12	0.76 (0.62, 0.92)	<0.001	53.1	
<i>Adjustment for energy</i>					0.953
Yes	1	0.68 (0.43, 1.07)	<0.001	0.00	
No	26	0.65 (0.55, 0.76)	<0.001	57.8	
<i>Methods of vitamin D measurement</i>					0.016
CLIA	4	0.70 (0.49, 1.00)	0.050	61.6	
RIA	10	0.61 (0.47, 0.79)	0.142	33.2	
LC/MS/MS	6	0.77 (0.57, 1.06)	0.009	67.4	
EIA	2	0.53 (0.26, 1.07)	0.096	53.7	
ECLIA	3	0.31 (0.14, 0.67)	0.218	34.0	
Other assays	2	0.78 (0.55, 1.12)	0.095	52.9	
<i>Vitamin D categories used for comparison</i>					0.015
Q ₄ vs. Q ₁	16	0.65 (0.53, 0.80)	0.052	39.6	
T ₃ vs. T ₁	7	0.59 (0.41, 0.87)	0.014	62.4	
Q5 vs Q1	2	0.91 (0.55, 1.52)	0.025	80.0	
Vitamin D sufficiency vs. deficiency	2	0.67 (0.47, 0.96)	0.164	48.5	
<i>Reported Estimates</i>					<0.001
RR	15	0.53 (0.40, 0.69)	0.004	56.6	
HR	12	0.76 (0.66, 0.88)	0.191	25.7	
Sub-group analysis cohort and nested case-control and combined T2D and prediabetes					
<i>Overall</i>	9	0.70 (0.52, 0.95)	<0.001	79.2	
<i>Adjustment for Asian vs. Non-Asian countries</i>					<0.001
Asian	2	0.43 (0.21, 0.88)	0.039	76.5	
Non-Asian	7	0.83 (0.63, 1.07)	0.007	66.0	
<i>Adjustment for sex</i>					0.350
Both	5	0.62 (0.35, 1.09)	<0.001	89.0	
Male	2	0.77 (0.57, 0.99)	0.727	0.00	
Female	2	0.80 (0.58, 1.11)	0.881	0.00	
<i>Quality score³</i>					<0.001
Low quality (Scores ≤ median of 6)	4	0.69 (0.42, 1.12)	<0.001	86.6	
High quality (Scores > median of 6)	5	0.70 (0.57, 0.87)	0.543	0.00	
<i>Adjustment for Season</i>					<0.001
Yes	5	0.81 (0.56, 1.18)	0.004	73.7	
No	4	0.61 (0.41, 0.89)	0.021	69.2	
<i>Adjustment for energy</i>					0.345
Yes	1	0.60 (0.27, 1.33)	<0.001	0.00	
No	8	0.71 (0.52, 0.97)	<0.001	81.4	
<i>Methods of vitamin D measurement</i>					<0.001
CLIA	3	0.98 (0.69, 1.40)	0.024	73.0	
RIA	1	0.58 (0.32, 1.06)	0.001	0.00	
LC/MS/MS	1	0.60 (0.27, 1.33)	0.001	0.00	
EIA	3	0.57 (0.32, 0.99)	0.019	74.6	
Other assays	1	0.59 (0.42, 0.83)	0.001	0.00	
<i>Vitamin D categories used for comparison</i>					<0.001
Q ₄ vs. Q ₁	5	0.61 (0.44, 0.85)	0.045	59.0	
T ₃ vs. T ₁	4	0.85 (0.57, 1.26)	0.004	77.5	
<i>Reported Estimates</i>					0.006
RR	6	0.70 (0.45, 1.07)	<0.001	83.3	
HR	3	0.68 (0.54, 0.84)	0.574	0.00	

Abbreviations: CLIA: Chemiluminescent immunoassay; ECLIA: Electrochemiluminescence immunoassay; RIA: Radio immunoassay; ELISA: Enzyme-linked immunosorbent assay; EIA: Enzyme-immunosorbent assay.

¹P for heterogeneity, within subgroup;

²P for heterogeneity, between subgroups;

³Quality Scores were according to Newcastle-Ottawa Scale.

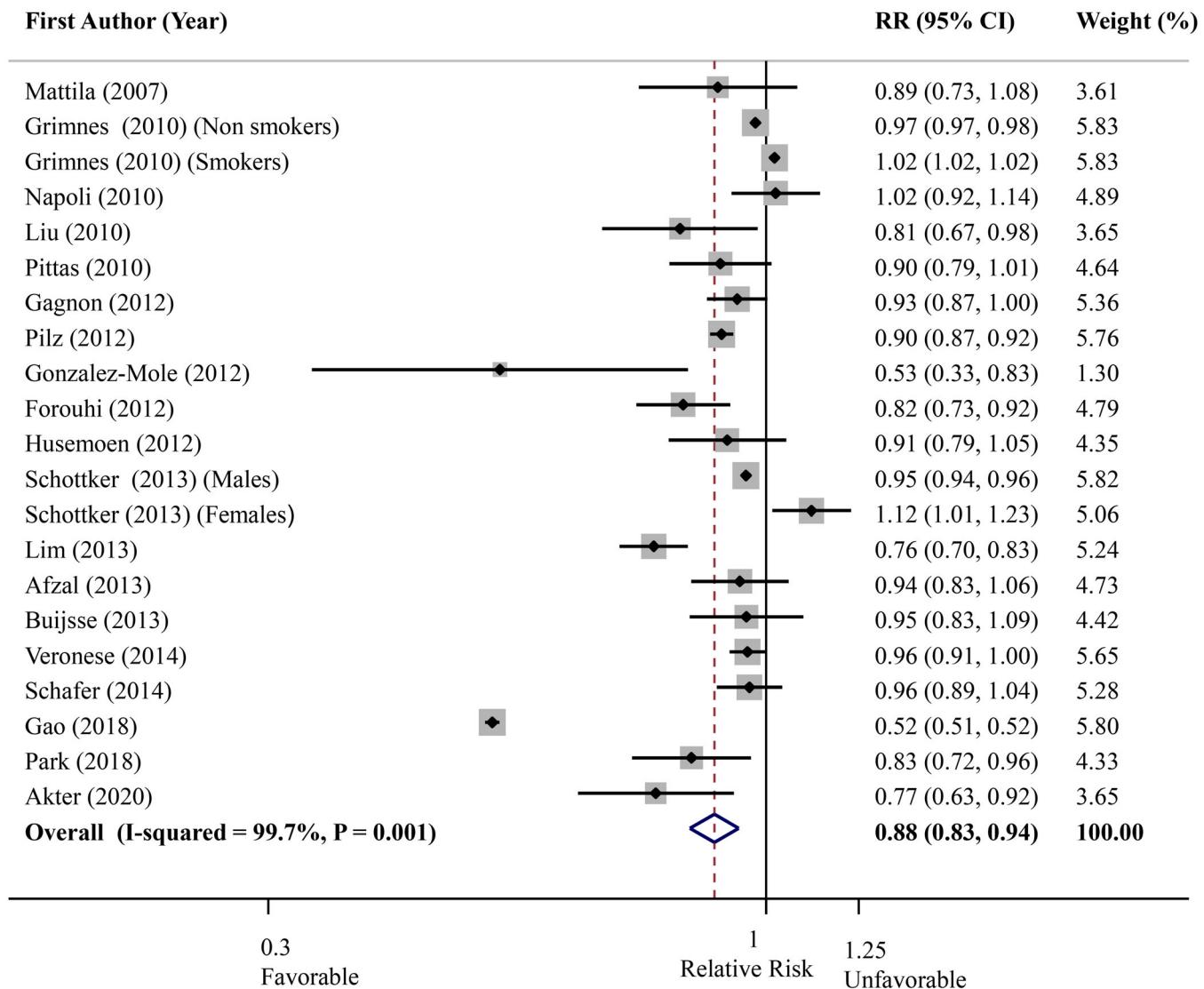


Figure 3. Linear dose-response meta-analysis of serum vitamin D and risk of T2D in prospective studies.

Dose-response meta-analysis of serum vitamin D and risk of combined T2D and prediabetes in prospective studies

Linear dose response analysis of effect sizes from 4 studies with 7,140 participants and 1,070 individuals with glycemic disorders ($FBS > 100$) manifested that each 10 ng/ml increase in serum vitamin D levels reduced the risk of glycemic disorder by 11% (RR: 0.89; 95%CI: 0.87, 0.92). A significant non-linear association was also found between serum vitamin D levels and impaired glucose levels ($P_{\text{nonlinearity}} < 0.001$) (Supplemental Figure 1).

Dose-response meta-analysis of serum vitamin D and risk of prediabetes in prospective studies

Combining effects size of 2 cohorts, which included a total of 8,254 participants and 441 subjects with prediabetes, revealed that each 10 ng/ml increase in serum vitamin D levels was linked to a 19% (RR: 0.81; 95% CI: 0.60, 1.09) reduction in risk of the disorder; however, this association was not statistically significant. There was also no significant relation in a non-linear fashion ($P_{\text{nonlinearity}} = 0.56$) (Supplemental Figure 2).

Meta-analysis of highest vs. lowest level of serum vitamin D and risk of prediabetes in prospective studies

Combing 2 effect sizes which extracted from 2 cohorts depicted that high level of vitamin D compared to low level was related to a significant 51% risk reduction for pre-diabetes (RR: 0.49; 95% CI: 0.26, 0.93) ($I^2 = 62.4\%$, $P = 0.10$).

Meta-analysis of highest vs. lowest level of serum vitamin D and risk of T2D in cross-sectional and case-control studies

Forty-two effect sizes from 28 cross-sectional and 3 case-control studies were combined and showed that highest level of serum vitamin D compared to lowest level was significantly associated with a 36% reduced odds of T2D (OR: 0.64; 95% CI: 0.57, 0.72) (Table 2 and Supplemental Figure

3); while heterogeneity was significant ($I^2 = 97.2\%$, $P = 0.001$). Subgroup analysis based on study design was performed (Supplemental Figure 3), but heterogeneity was high in both subgroups. So, studies were limited to those that included representative populations. Results showed that highest vs. lowest level of vitamin D was linked to a 36% decrease in odds of T2D (OR: 0.64; 95% CI: 0.57, 0.73)

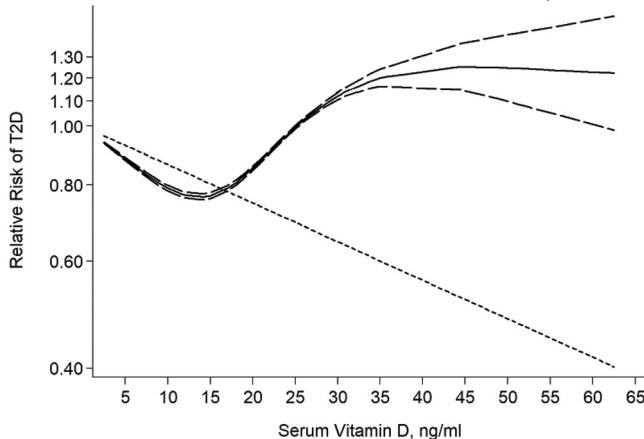


Figure 4. Non-linear dose-response meta-analysis of serum vitamin D and risk of T2D in prospective studies. The lowest level of serum vitamin D (2.5 ng/ml) was considered as the reference.

(Figure 6). Heterogeneity was still considerable among these studies ($I^2 = 97.2\%$, $P = 0.001$). Therefore, to investigate the source of heterogeneity, we performed subgroup analysis based on study location, gender, study quality, method of vitamin D measurement and other covariates and findings are presented in Supplemental Table 4. None of the subgroups could completely explain the heterogeneity. We also carried out sensitivity analysis; no particular study has significantly affected the overall estimate. Publication bias was assessed; no asymmetry was seen in funnel plot [Begg's test ($P = 0.25$) and Egger's test ($P = 0.56$)].

Meta-analysis of highest vs. lowest level of serum vitamin D and risk of combined T2D and prediabetes in cross-sectional and case-control studies

As depicted in Supplementary Figure 4, combining 59 effect sizes extracted from 36 cross-sectional and 1 case-control studies showed that highest versus lowest level of vitamin D was associated with a significant 21% decrease in risk of combined T2D and pre-diabetes (OR: 0.79; 95% CI: 0.74, 0.85); remarkable heterogeneity was seen ($I^2 = 80.4\%$, $P = 0.001$). When we restricted the investigations to those

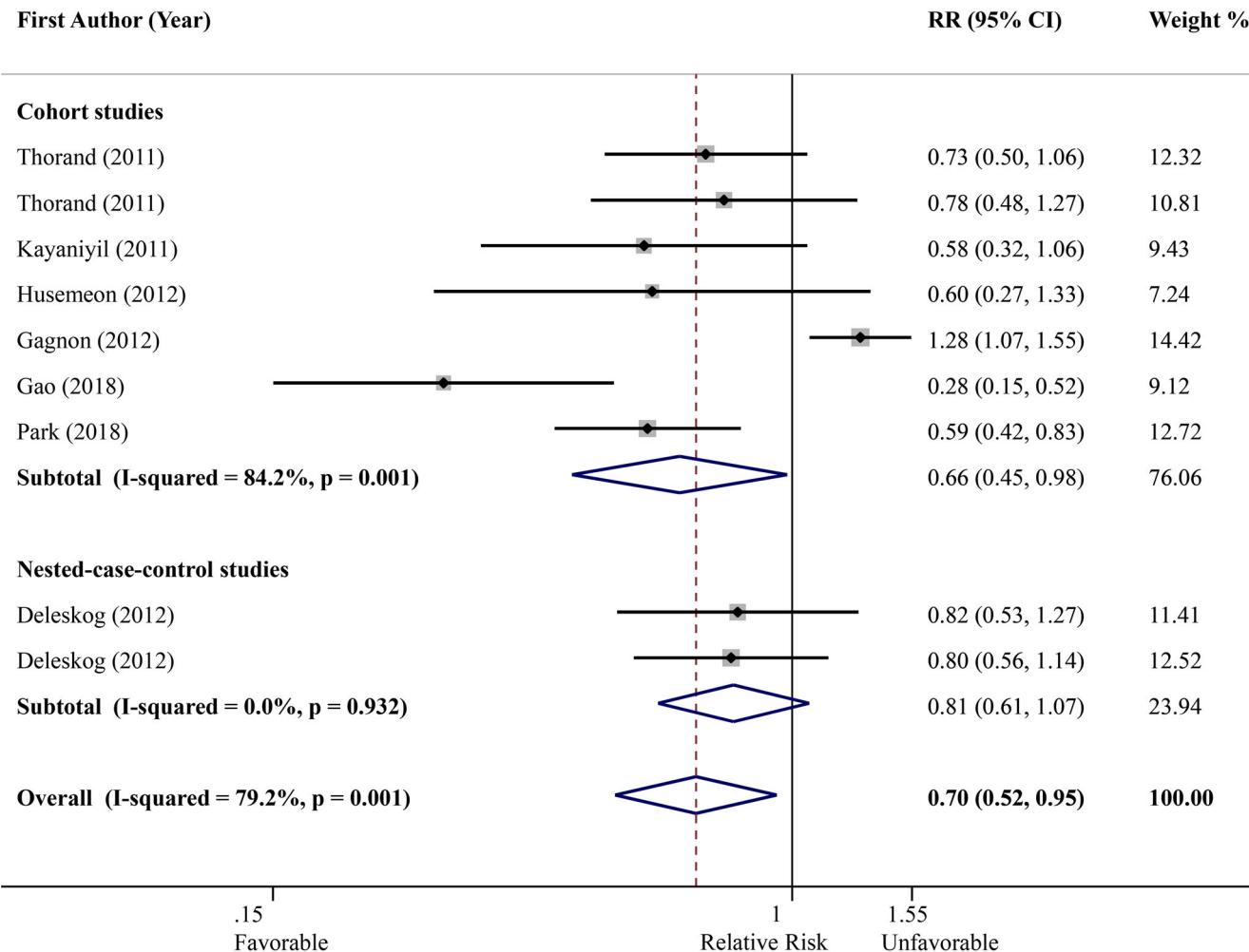


Figure 5. Forest plot of prospective studies that examined the association between highest vs. lowest level of serum vitamin D and risk of combined T2D and prediabetes.

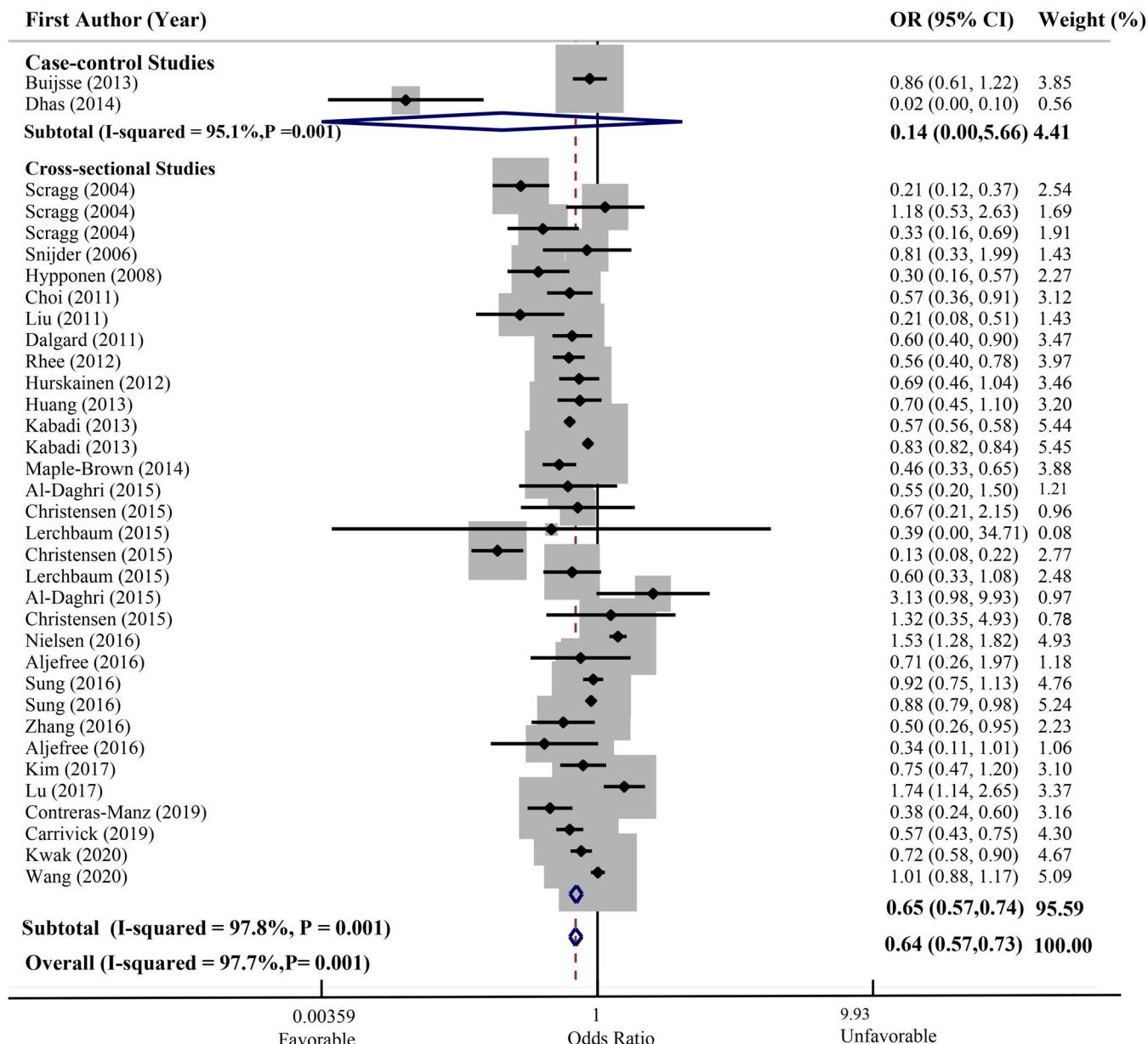


Figure 6. Forest plot of representative cross-sectional and case-control studies that examined the association between highest vs. lowest level of serum vitamin D and risk of T2D.

with representative population; we found that high level of serum vitamin D, compared to low level, was associated with a 21% risk reduction for combined T2D and pre-diabetes (OR: 0.79; 95% CI 0.72, 0.87) (Figure 7); but considerable heterogeneity was still observed. Therefore, subgroup analysis according to different covariates was done and the findings are provided in *Supplemental Table 4*. Sensitivity analysis showed that each specific study had no considerable effect on the overall estimate. No publication bias was observed based on no asymmetry in Begg's funnel plot [Begg's test ($P = 0.13$)].

Meta-analysis of highest vs. lowest level of serum vitamin D and risk of prediabetes in cross-sectional studies

As shown in *Supplemental Figure 5*, combining 11 effect sizes from 10 cross-sectional studies showed that high vs.

low serum vitamin D levels was associated with a 36% decrease in the risk of pre-diabetes, but this association was not significant (OR: 0.64; 95% CI 0.17, 2.37) and heterogeneity was remarkable ($I^2 = 99.8\%$, $P = 0.001$). When studies were confined to those with representative population, high level of vitamin D compared to low level was related to a non-significant risk reduction for pre-diabetes (OR: 0.83; 95%CI: 0.66, 1.05) (Figure 8). Heterogeneity between studies was reduced, but was still considerable ($I^2 = 85.2\%$, $P < 0.001$). Therefore, subgroup analysis based on different confounders was performed and results are shown in *Supplemental Table 4*. The observed heterogeneity could not completely be explained by the moderators. Sensitivity analysis revealed that none of included studies significantly influenced the overall effect. There was no evidence of significant publication bias using Begg's funnel plot, Begg's test ($P = 0.30$) and Egger's test ($P = 0.40$).

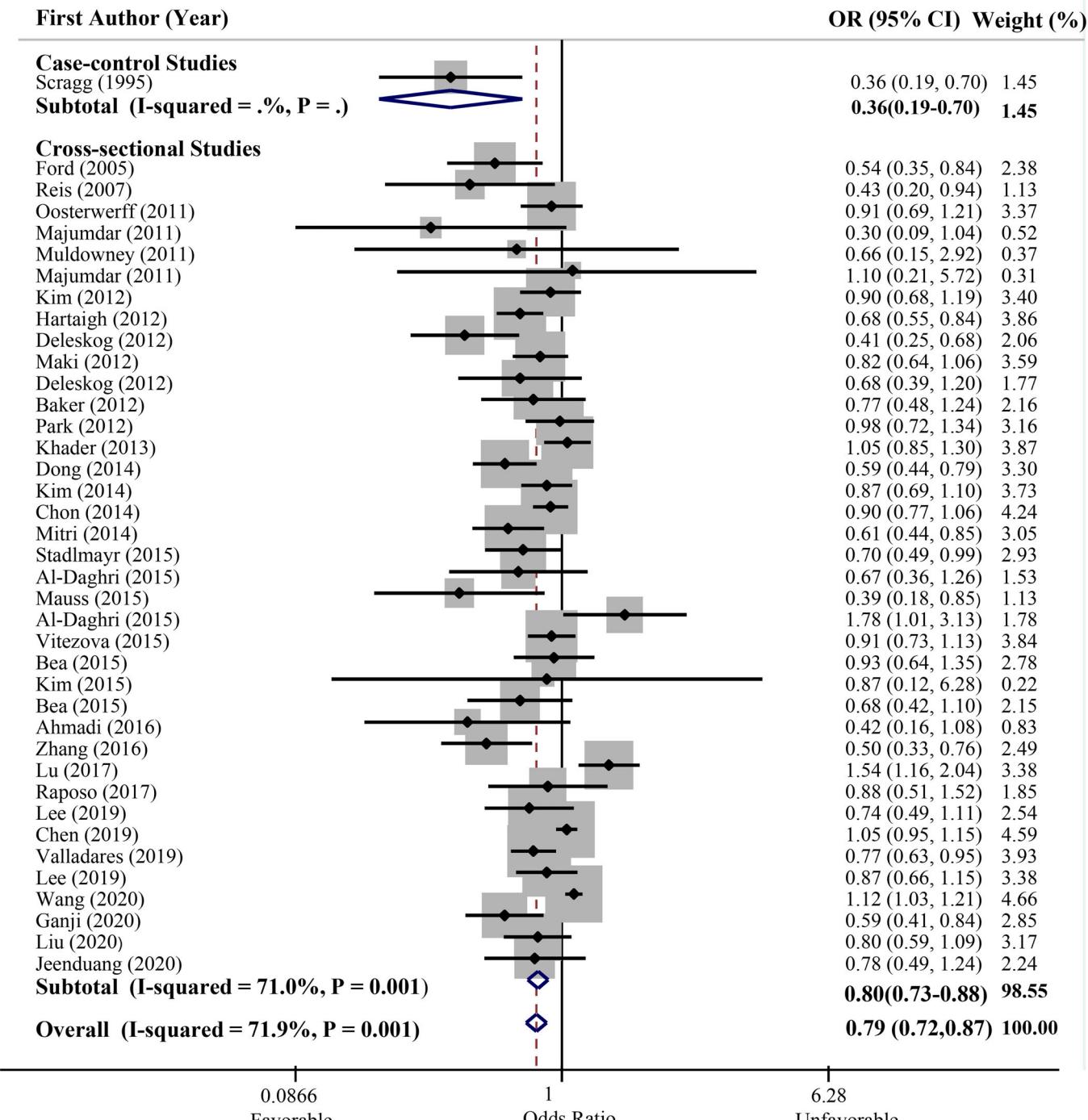


Figure 7. Forest plot of representative cross-sectional and case-control studies that examined the association between highest vs. lowest level of serum vitamin D and risk of combined T2D and prediabetes.

Discussion

This meta-analysis revealed that the highest serum levels of vitamin D in comparison to the lowest serum levels in prospective studies were significantly associated with both T2D and prediabetes in adult population. This association remained significant in case of investigations that considered the combination of T2D and prediabetes as the endpoint. Dose-response meta-analysis of prospective studies has also

revealed that each 10 ng/ml increment in circulating 25-hydroxy vitamin D was linearly associated with 12% and 11% reduction in risk of T2D and combined T2D and prediabetes, respectively. However, no linear association was observed between serum vitamin D and prediabetes. In cross-sectional and case-control studies, the highest versus the lowest level of vitamin D was associated with both T2D and combined T2D and prediabetes. However, no significant association was observed with prediabetes.

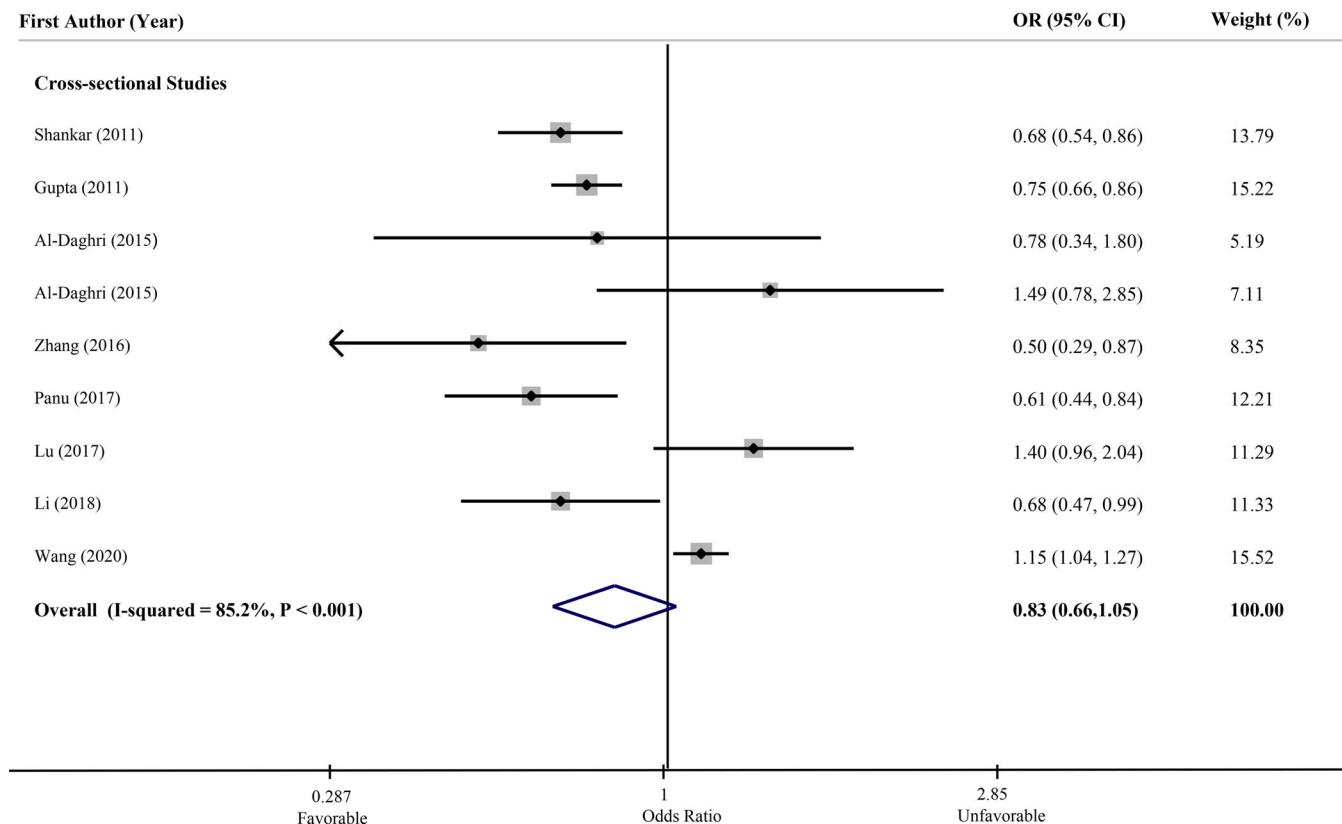


Figure 8. Forest plot of representative cross-sectional and case-control studies that examined the association between highest vs. lowest level of serum vitamin D and risk of prediabetes.

The prevalence of T2D and prediabetes has been globally increasing. These chronic conditions are highly correlated with metabolic outcomes such as, dyslipidemia, hypertension, obesity and degenerative diseases such as Parkinson's (Xu et al. 2011; Moon et al. 2017). Also, T2D is shown to double the mortality rate (Group NDD et al. 1995; Tancredi et al. 2015). We found that both diabetes and prediabetes are higher in individuals with lower levels of serum vitamin D. Therefore, it is noteworthy to clinically recommend people to improve their serum level of vitamin D in the hope of reducing the risk of T2D and prediabetes.

Similar to our findings, a previous meta-analysis found that vitamin D deficiency was associated with a 17% higher risk of T2D in elders (Lucato et al. 2017). Furthermore, a recent meta-analysis found that highest levels of 25(OH)D is associated with 61% lower odds of type 1 DM (T1DM) (Hou et al. 2020). It was also shown that each 10 ng/ml increment in 25(OH)D would be in relation to 9% decrease in risk of T1DM (Hou et al. 2020). However, this association might be overestimated because most of the included studies had case-control design that did not provide a convincing or conclusive relation. Another meta-analysis revealed that highest levels of circulating vitamin D could be inversely related to gestational diabetes (Sadeghian et al. 2020). On the other hand, a meta-analysis of cohort studies did not

find a significant association between dietary intake of vitamin D and T2D (Zhao et al. 2013). Similarly, another meta-analysis found significant association between vitamin D intake and T1DM in case-control studies, but not in prospective cohort studies (Dong et al. 2013). However, the number of prospective cohort studies in the aforementioned meta-analyses was not remarkable. Also, it should be kept in mind that vitamin D does not remarkably exist in food sources. Meta-analyses on the effect of vitamin D supplementation on glycemic control have also conflicting findings. In a meta-analysis, significant lowering effect of vitamin D supplementation on HbA1c and insulin resistance in patients with T2D was documented (Hu et al. 2019). However, the results did not remain significant when long-term interventions were solely examined (Hu et al. 2019). Another meta-analysis found that vitamin D supplementation significantly reduced fasting blood sugar, HbA1c in women with gestational diabetes (Ojo et al. 2019). However, a limited number of trials was included. In contrast, some meta-analyses did not find significant effects of vitamin D supplementation on glycemic control (Swart et al. 2018; Wang et al. 2020; Wei et al. 2020).

Previous investigations have shown associations between serum vitamin D levels and risk of chronic diseases, such as cardiovascular disease (CVD), dyslipidemia, obesity,

autoimmune diseases, and particular types of cancer (Holick 2002; Kienreich et al. 2013; Wang et al. 2017). A meta-analysis showed that each 10 ng/ml increment in 25(OH)D decreased 13% risk of metabolic syndrome (Ju, Jeong, and Kim 2014). In some investigations, a reverse correlation has been found between the serum status of vitamin D and BMI (Saneei, SalehiAbargouei, and Esmaillzadeh 2013). A dose-response meta-analysis has also demonstrated that each 2 ng/ml enhancement in blood vitamin D levels was associated with 6% reduction in risk of breast cancer; while 400 IU/day increment in vitamin D intake was not remarkably associated to breast cancer (Song et al. 2019). Based on prospective investigations, highest levels of plasma 25(OH)D was also pertained to declined risk of all-cause mortality in subjects with chronic kidney disease (Pilz et al. 2011). The present meta-analysis demonstrated a significant inverse connection between serum vitamin D levels and glycemic profile disorders. With regard to pre-diabetes the findings were not remarkable, perhaps due to low number of included studies.

Impaired function of beta cells in pancreas and insulin resistance could be the primary causes of T2D. Several mechanisms have been proposed for serum 25(OH) D levels and glycemic homeostasis disorders. Vitamin D might have both direct and indirect effects on insulin synthesis and secretion (Forouhi et al. 2012). Presence of vitamin D receptors (VDRs) on pancreatic beta cells makes the assumption that vitamin D might be directly linked to insulin synthesis (Forouhi et al. 2012). VDRs are also expressed in skeletal and adipose tissue, which mostly determine peripheral insulin sensitivity (Bischoff et al. 2001; Norman 2006). Indirect effects of vitamin D could be explained by its role in improving calcium metabolism (Forouhi et al. 2012). Calcium could trigger insulin secretion via voltage-dependent calcium channels and therefore, improve glucose metabolism (Shimodaira et al. 2015). Additionally, parathyroid hormone (PTH) increases in response to vitamin D deficiency (Holick 2007). PTH may lead to elevated intracellular calcium (Reusch et al. 1991). This could in turn impair insulin action by dephosphorylating glycogen synthase, as well as insulin dependent glucose transporter 4 (GLUT-4) (Reusch et al. 1991; Draznin 1993). Another possible indirect effect of vitamin D might be defined through osteocalcin. This osteoblast-derivative bone output marker could amend beta-cell propagation, insulin secretion, and insulin sensitivity (Bouillon et al. 2008; Dirks-Naylor and Lennon-Edwards 2011; Harinarayan 2014).

Current meta-analysis has several strengths. This is the first meta-analysis that evaluates the relationship between 25(OH) D and glycemic disorders, including diabetes and pre-diabetes and considering both diabetes and pre-diabetes together in the analysis. It contained both prospective and cross-sectional investigations and studied a large population of adults. Dose-response analysis was also performed and an inverse linear relevance between blood vitamin D and glycemic disorder was found. However, several limitations should be taken into account while interpreting the findings. First, total energy intake, sun exposure and season of blood

sample were not considered as confounding factors in some included studies. Second, not all included investigations had separately reported the linkage between serum 25(OH)D and diabetes or prediabetes in men and women; so, we could not totally provide different estimates for males and females. Furthermore, although the included prospective studies could define a causal relationship, cross-sectional studies could not determine causality.

In conclusion, this meta-analysis of epidemiologic studies disclosed that serum vitamin D level was reversely associated with the risk of abnormal glucose homeostasis (including T2D and combined T2D and pre-diabetes) in adults, in a dose-response manner. However, the association was not remarkable for pre-diabetes. Further prospective studies are demanded to confirm these findings.

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Authors' contribution

SM, ZH and PS contributed in conception, design, statistical analyses, data interpretation and manuscript drafting. All authors approved the final manuscript for submission.

Abbreviations

DM	Diabetes mellitus
T2D	Type-2 diabetes
CVDs	cardiovascular disease
BP	Blood pressure
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
FBS	Fasting blood glucose
FBG	Fasting blood glucose
FPG	Fasting plasma glucose
OR	Odds ratio
RR	Relative risks
CI	95% Confidence intervals
HR	Hazard ratio
NOS	Newcastle-Ottawa scale
CLIA	Chemiluminescent immunoassay
RIA	Radioimmunoassay
IA	Immunoassay
ECLIA	Electrochemiluminescence immunoassay
ELISA	Enzyme-linked immune sorbent assay
EIA	Enzyme immunoassay
LC-MS/MS	liquid chromatography-tandem mass spectrometry
ADA	American diabetes association
HbA1C	Glycosylated Hemoglobin Type A1C
BMI	Body mass index
T1DM	Type 1 diabetes mellitus
VDRs	vitamin D receptors
PTH	parathyroid hormone
GLUT	Glucose transporter

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