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Vitamin D, type 2 diabetes and other metabolic outcomes: a systematic review and meta-analysis of prospective studies

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Vitamin D status may influence the risk of developing metabolic diseases such as Type 2 diabetes (T2D), metabolic syndrome (MetS) and insulin resistance (IR). Several studies have assessed vitamin D in relationship with metabolic outcomes; however, results remain inconsistent. A systematic review and meta-analysis using multiple databases (MEDLINE, Web of Science and EMBASE), was performed up to 10 August 2012. Prospective studies reporting association of circulating or dietary vitamin D with incident T2D, MetS and IR outcomes were included. Relative risks (RR) were pooled using random effects and subgroup analysis by pertinent study-level characteristics was performed. A total of seventeen articles based on eighteen unique prospective studies, and comprising 210 107 participants with 15 899 metabolic events, collected during a median follow up of 10 years (range 3–22 years), were included. RR for individuals in top *v*. bottom thirds of baseline vitamin D were 0·81 (95% CI 0·71, 0·92); 0·86 (95% CI 0·80, 0·92); and 0·84 (95% CI 0·64, 1·12) for T2D, MetS and IR outcomes, respectively. Moderate heterogeneity was found between fourteen studies ($I^2 = 67\%$, $P<0·001$) reporting on T2D. Findings were generally consistent across various study-level characteristics. In conclusion, vitamin D status at baseline in apparently healthy adults is inversely associated with future risks of T2D and MetS. Interventions aimed at maintaining adequate levels of vitamin D in addition to preventing deficiency may be a useful preventive measure for metabolic diseases. However, reliable evidence from carefully designed intervention studies, particularly those based on healthy populations, is needed to confirm observational findings.

Vitamin D: Type 2 diabetes: Insulin resistance: Metabolic syndrome: Prospective epidemiological studies

Vitamin D plays a critical role in the regulation of plasma Ca concentration via effects on intestinal absorption and bone metabolism[(1)]. In addition, it has also been reported to influence glucose regulation via effects on insulin secretion and action[(2)]. Vitamin D insufficiency, typically assessed by circulating blood levels of 25-hydroxy vitamin D (25(OH)D), has long been suspected as a risk factor for Type 1 diabetes[(3)]. Ecological evidence has shown higher rates of metabolic disorders including diabetes and hypertension[(4,5)] with increasing distance from the equator, suggesting possible associations of vitamin D insufficiency in areas with less sunlight. More recently, there is accumulating evidence to suggest that altered vitamin D and Ca homoeostasis may play a role in the development of Type 2 diabetes (T2D)[(6–8)]. Although several studies have reported a protective association of vitamin D and T2D, the current findings are not consistent. A previous meta-analysis of eight observational studies showed that vitamin D intake (as measured by self-reported dietary intake) or status (as measured by blood 25(OH)D

Abbreviations: IR, insulin resistance; MetS, metabolic syndrome; 25(OH)D, 25-hydroxy vitamin D; RR, relative risk; T2D, Type 2 diabetes.

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concentration) was associated with decreased risk of T2D, while pooled analysis of seven clinical trials of vitamin D supplementation did not show an effect on incident diabetes or measures of glycaemia[9].

To further clarify the inconsistencies around the associations of vitamin D with T2D, we conducted an updated literature-based meta-analysis. The present analyses differ from the previous reviews in several important ways. First, it exclusively includes studies where vitamin D status was assessed at baseline (measured as circulating blood 25(OH)D concentrations and/or dietary consumption) in apparently healthy adult participants, as opposed to vitamin D supplementations involving adults with wide-range of pre-existing clinical conditions including metabolic diseases. Second, it systematically combines the most up-to-date published data thus far to further clarify the contradictory evidence accumulated. Third, it records several clinically relevant study-level sub-groups to perform detailed exploration of potential sources of heterogeneity than previously reported. Additionally, for a comprehensive assessment, we have reviewed and quantified, where appropriate, the associations for related metabolic outcomes including metabolic syndrome (MetS) and measures of insulin resistance (IR).

Methods

Data sources and search strategy

We performed a systematic review and meta-analysis of prospective studies that evaluated the associations between baseline vitamin D status and incident T2D, MetS or IR in adults, using the Meta-analysis of Observational Studies in Epidemiology guidelines[10]. We searched PubMed, EMBASE and Web of Science electronic databases for prospective (cohort or nested case–control) population studies that evaluated relevant associations between vitamin D levels and metabolic outcomes. The computer-based searches combined free and MeSH search terms and a combination of key words related to Vitamin D (e.g., '25-hydroxyvitamin D' and 'cholecalciferol') and T2D (e.g., 'diabetes mellitus'), MetS (e.g., 'IR syndrome' and 'syndrome X') and IR ('HOMA index' and 'HOMA-IR'). There were no language restrictions and publications were searched up to 10 August 2012. Additionally, reference lists of all retrieved articles were scanned to identify any other relevant studies. Data were abstracted, where available, on study, publication date, geographical location, population source, time of baseline survey, sample population, study design, sample source (plasma/serum), nature of sample (fresh or frozen and storage temperature), assay type and source, case definition, sample size, numbers of events, mean age, sex, duration of follow-up, adjustment for confounders related to sun exposure (such as season and latitude of location) and summary statistics. Studies were included if they had at least 1 year of prospective follow-up, with vitamin D measured at baseline, and recruited participants from approximately general populations (i.e., did not select participants on the basis of pre-diabetes or pre-existing T2D at baseline or participants with conditions that affect vitamin D metabolism such as chronic kidney disease). Studies in which the outcome was Type 1 diabetes were excluded because its pathophysiology is somewhat different from that of T2D[9]. In addition, the search also included studies in which vitamin D status was assessed by blood 25(OH)D concentrations, dietary intake of vitamin D, or 25(OH)D score predicted from dietary vitamin D intake. We excluded studies using vitamin D supplementation as an exposure from our main meta-analysis and studies that were not based on adult populations. Literature search and data extraction were conducted in parallel by two authors. Each article was assessed using the inclusion criteria above and any disagreement regarding eligibility of an article was discussed and agreement reached by consensus and by involving a third author.

Statistical analysis

Hazard ratios, risk ratios and OR were assumed to approximate the same measure of relative risk (RR) across studies. RR with 95 % CI were used as the common measures of association. To allow consistent comparisons across included studies, all individual risk estimates were standardised to involve comparisons between the top third *v*. bottom third of the population's baseline distribution of vitamin D values by using methods previously described[11]. Briefly, log risk estimates were transformed assuming a normal distribution, with the comparison between top and bottom thirds being equivalent to 2·18 times the log RR for a 1 SD increase (or equivalently, as 2·18/2·54 times the log risk ratio for a comparison of extreme quarters). When a study published more than one estimate of the association between vitamin D and risk of a metabolic outcome according to subgroups (e.g., by gender or smoking status), a within-study summary estimate was obtained. Summary RR were pooled using a random-effects meta-analysis[12]. Statistical heterogeneity across studies was quantified using Cochran x^2 and the I^2 statistics, respectively[13,14]. To investigate possible sources of heterogeneity, where appropriate, the analyses were stratified by geographical locations, study design, population source, sample type, type of vitamin D exposure (i.e., whether blood levels or dietary intake), duration of follow-up, number of events, levels of adjustment and adjustment for seasonal variations or latitude of study location. We assessed the potential for publication bias through formal tests, namely Begg's funnel plots[15] and Egger's regression symmetry test[16]. All statistical tests were two-sided and used a significance level of $P<0{\cdot}05$. All analyses were conducted using Stata version 12 (Stata Corp, College Station, Texas, USA).

Results

Literature search

A total of 2656 citations were retrieved from the electronic search (Fig. 1). After screening of the titles and abstracts and more detailed evaluations of full texts, we identified a total of seventeen articles (based on eighteen unique

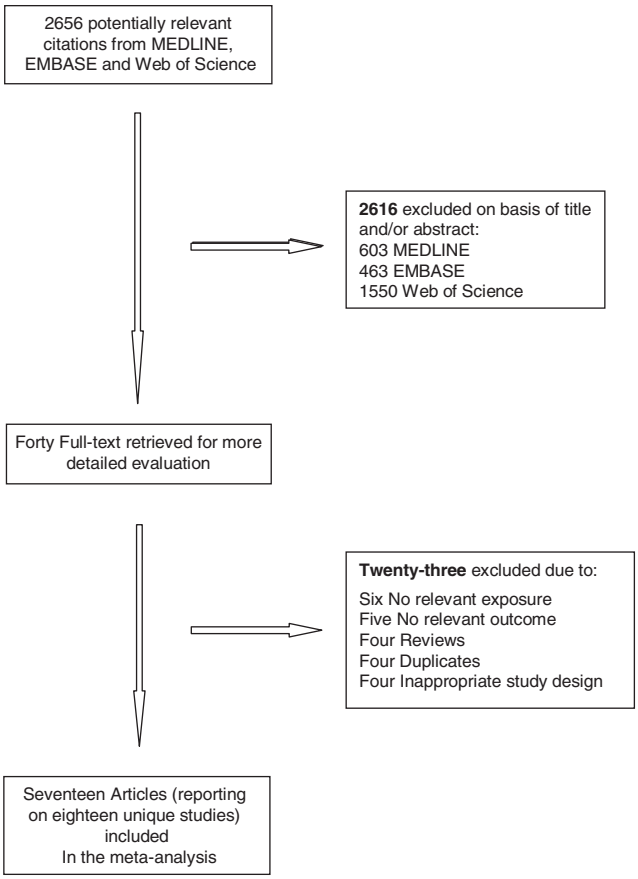

Fig. 1. Search strategy for the studies included in current review.

prospective studies in aggregate, comprising 210 107 participants and a total of 15 899 metabolic events). Table 1 summarises the general characteristics of all included studies that examined baseline vitamin D status in relationship with various metabolic outcomes. Thirteen of the included articles[6,8,17–27] consisting of fourteen prospective studies reported on vitamin D status and risk of diabetes (190 626 participants and 9399 incident diabetes outcomes). All included T2D studies were based on prospective cohort analyses carried out in Europe (Denmark, Finland, Germany, Norway and Sweden)[18,20,22,23,27]; North America (United States and Canada)[6,8,21,24–26]; Australia;[19,28] and Asia (Japan), with participants' ages ranging from 30 to 79 years. Duration of follow-up for incident T2D endpoints ranged from 3 to 22 years, with a median follow-up of 10 years. All studies assessed vitamin D status only once at baseline with ten studies measuring serum/plasma 25(OH)D concentration[6,18,20–24,27,28], three studies reporting on dietary vitamin D intake[19,25,26] and one study calculating a predicted 25(OH)D score from dietary vitamin D intake[8]. Ascertainment of diabetes outcomes were mostly by validated self-report or by medical record data. Overall seven studies adjusted for age, risk factors for diabetes and seasonality/latitude of study location[6,20–22,24,27,28], another six studies adjusted for age and diabetes risk factors[18,19,23,25,26] while one study adjusted for age only[8].

In addition, we identified four prospective cohort studies[17,25,29,30] that evaluated baseline vitamin D status and MetS outcomes. Of these, two studies measured serum 25(OH)D concentrations[17,29] and two studies reported on dietary intake of vitamin D[25,30]. One study defined MetS using a continuous MetS risk *z* score using the mean of five continuous indices of obesity[29]. In addition, we also identified two prospective studies reporting on vitamin D status and homeostasis model of assessment-insulin resistance (HOMA-IR) index[31,32].

Vitamin D status and risk of Type 2 diabetes

The pooled RR for incident T2D for individuals in the top third *v*. those in the bottom third of total baseline vitamin D levels for the fourteen available studies, typically adjusted for age, diabetes risk factors and seasonality and using a random-effects meta-analysis was 0·81 (95% CI, 0·71, 0·92; Fig. 2). Studies that measured blood 25(OH)D concentrations had a pooled RR of 0·75 (95% CI 0·62, 0·91) *v*. RR 0·90 (95% CI 0·79, 1·03) for the three studies that assessed dietary vitamin D status (Fig. 3). There was evidence of moderate heterogeneity between the findings of the fourteen studies ($I^2 = 67\%$; 95% CI, 42, 81; $P<0{\cdot}001$) with little of the difference explained by several study-level sub-groups such as geographical location, study design, population source, sample type, type of vitamin D exposure, duration of follow-up, number of T2D events and whether studies controlled for seasonality or latitude of location (Fig. 4). There was, however, evidence of publication bias as assessed by funnel plots and Egger's test ($P = 0{\cdot}006$; Supplementary Fig. 1).

Vitamin D status and risk of metabolic syndrome and insulin resistance

The combined RR for MetS outcome in a comparison of individuals in the top third *v*. those in the bottom third of baseline vitamin D levels, adjusted for age, MetS risk factors and seasonality was 0·86 (95% CI 0·80, 0·92), based on a random-effects model (Fig. 2). There was no evidence of heterogeneity among the contributing studies. The corresponding pooled RR for IR (i.e., HOMA-IR) was 0·84 (95% CI 0·64, 1·12). RR for MetS outcomes remained materially unchanged when they were grouped according to several study characteristics (Supplementary Fig. 2). There was no apparent evidence of publication bias as confirmed by funnel plots and Egger's test ($P = 0{\cdot}18$; Supplementary Fig. 3). No sub-group analyses were performed for IR outcome as only two studies had relevant information.

Comment

We conducted an updated review and meta-analysis to clarify the nature and magnitude of the associations of vitamin D status with subsequent risks of developing T2D and other metabolic outcomes in apparently healthy adult populations. The pooled (albeit variably adjusted) results show that individuals within the top third of vitamin D

Table 1. General characteristics of the prospective studies included in the review

Lead author	Publication date	Study name	Location	Time period	Population source	Baseline age (year)	Male (%)	Follow up (year)	No. of participants	No. of events
(1) Type 2 diabetes						–				
Gagnon	2011	AusDiab	Australia	1999–2000	Population register	⩾25	45	5	5200	199
Liu	2010	FHS Offspring	United States	1997–1999	Population register	NR	46	7	2956	133
Knekt	2008	FMCHES	Finland	1973–1976	Population register	40–74	49	22	3327	230
Husemoen	2012	Inter99	Denmark	1999–2001	Population register	30–65	48	5	5728	141
Kirri	2009	JPHC	Japan	1990–1993	Population register	40–69	43	5	59796	1114
Knekt	2008	M-FHS	Finland	1978–1980	Population register	40–69	47	17	4176	182
Thorand	2011	MONICA/KORA Augsburg	Germany	1984–1995	Population register	35–74	53	11	1683	416
Pittas (1)	2010	Nurses Health Study	United States	1989–1990	Employee register	43–70	0	14	1167	608
Pittas (2)	2006	Nurses Health Study	United States	1980	Employee register	30–55	0	20	83 779	4843
Kayaniyil*	2011	PROMISE	Canada	2004–2006	Population register	⩾30	NR	3	489	30
Deleskog	2011	SDPP	Sweden	1992–1998	Population register	35–56	60	8–10	1000	134
Grimnes	2010	Tromso study	Norway	1994–1995	Population register	⩾25	NR	11	6119	247
Robinson	2011	WHI	United States	1993–1998	Trial register	50–79	0	7	5140	317
Liu	2005	WHS	United States	NR	Population register	45–75	0	9	10 066	805
Sub-total									*190 626*	*9399*
(2) Other metabolic outcomes										
Gagnon	2012	AusDiab	Australia	1999–2000	Population register	⩾25	42	5	4164	528
Fung	2012	CARDIA	United States	1985–1986	Healthcare register	18–30	55	20	4727	889
Forouhi*	2008	MRCEPS	United Kingdom	1990–1992	Population register	40–69	41	10	524	54†
Liu	2005	WHS	United States	NR	Population register	⩾45	0	9	10 066	5083
Sub-total									*19 481*	*6500*

AusDiab, Australian Diabetes, Obesity and Lifestyle Study; CARDIA, Coronary Artery Risk Development in Young Adults Study; CHD, FHS, Framingham Heart Study; FMCHES, Finnish Mobile Clinic Health Examination Survey; JPHC, Japan Public Health Centre-based Prospective Study; M-FHS, Mini-Finland Health Survey; MONICA/KORA Augsburg, Monitoring of Trends and Determinants in Cardiovascular Disease/ Cooperative Health Research in the Region of Augsburg; MRCEPS, Medical Research Council Ely Prospective Study; MS, Metabolic Syndrome; NR, PROMISE, PROspective Metabolism and ISlet cell Evaluation Cohort Study; SDPP, Stockholm Diabetes Prevention Program; WHI, Women's Health Initiative; WHS, Women's Health Study.

*Also assessed insulin resistance outcomes.

†This is the number of incident cases of Type 2 diabetes. MS was derived as a continuous risk *z*-score in this study.

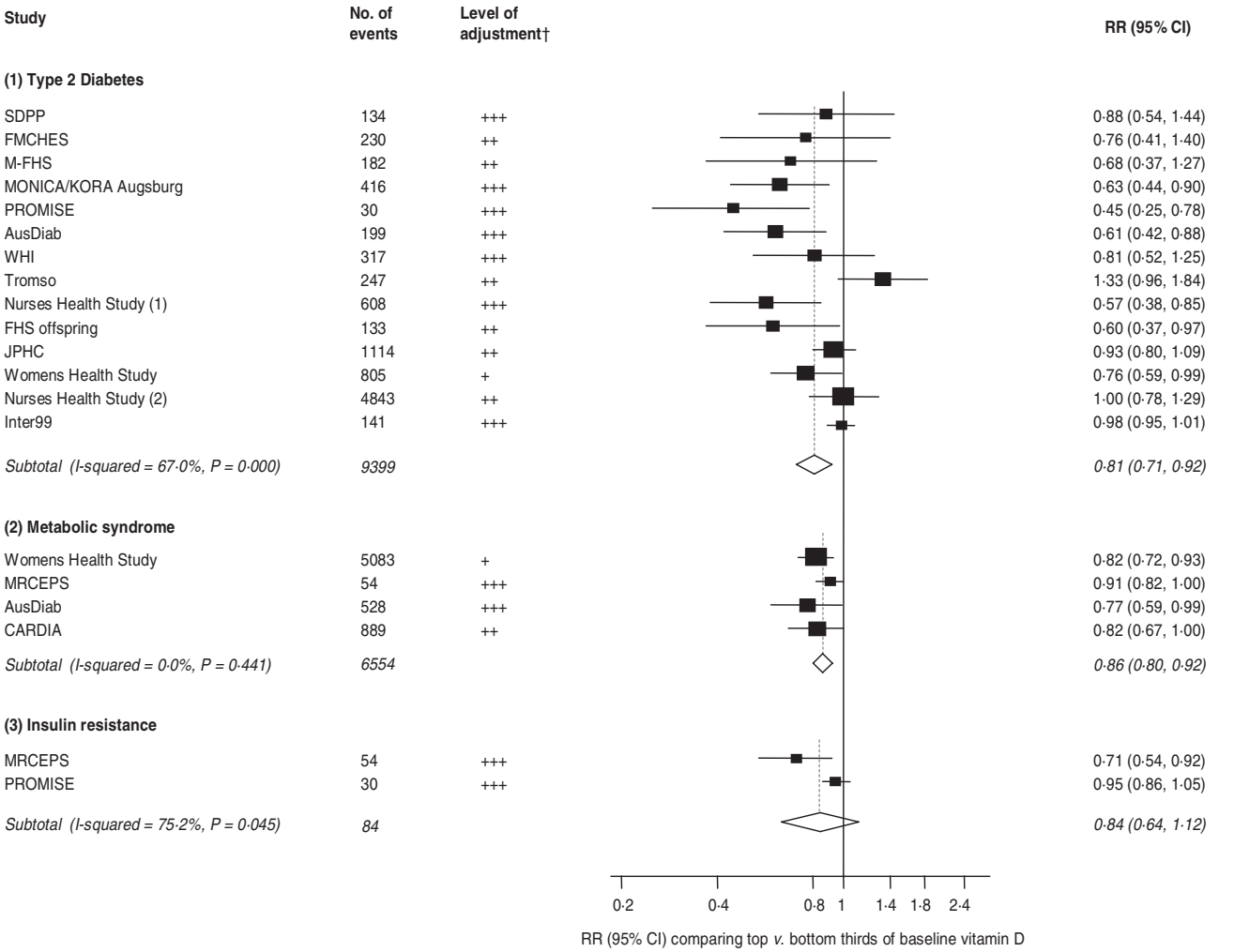

Fig. 2. Associations of vitamin D with Type 2 diabetes and other metabolic outcomes. Study acronyms and references are provided in Table 1. The summary estimate presented was calculated using a random effects model; using a fixed effects model was 0·96 (95% CI 0·94, 0·99) for diabetes, 0·86 (95% CI 0·80, 0·92) for metabolic syndrome (MS), and 0·92 (95% CI 0·83, 1·01) for insulin resistance outcomes. †Level of adjustment: +, adjusted for age and sex; ++, adjusted for diabetes/MS risk factors; +++, adjusted for diabetes/MS risk factors plus seasonality/latitude. These studies quantified insulin resistance using homeostasis model of assessment-insulin resistance, a continuous variable.

levels (measured as both 25(OH)D levels and self-reported dietary intake of vitamin D) had an approximately 19% lower risk of developing diabetes compared with those in the bottom third. We found substantial heterogeneity among contributing studies which could not be completely accounted for by the study level characteristics assessed. Additionally, individuals within the top third of vitamin D levels had about 14% lower risk of developing MetS compared with those in the lowest third. Pooled results from the two studies with available information on IR outcome also demonstrated inverse, however, non-significant, association for higher vitamin D.

The findings of this study may have several mechanistic explanations. The role of vitamin D in metabolic disorders such as T2D is supported by the pleiotropic effects of this compound and its involvements in several important physiological pathways. For instance, vitamin D is involved in pancreatic β-cell dysfunction[33–37] and IR[7,33,34], the primary underlying defects characterising T2D. It has also been reported that direct action of 1,25-dihydroxyvitamin D, may lead to increased expression of insulin receptor and enhanced insulin responsiveness for GLUT[38,39]. Additionally, elucidation of the supposed indirect effects of vitamin D (via regulating Ca homeostasis mechanisms) will further help in understating its mechanistic links to diabetes and related metabolic disorders.

The strengths and potential limitations of this review and meta-analyses deserve careful consideration. Our updated meta-analysis of the associations between vitamin D status and T2D updated the previous literature[9,40–42] by including several recently published large-scale prospective studies. We have employed standardised RR from all individual studies to allow a consistent combination of estimates across studies. Our meta-analyses consisted of studies that had exclusively recruited participants from

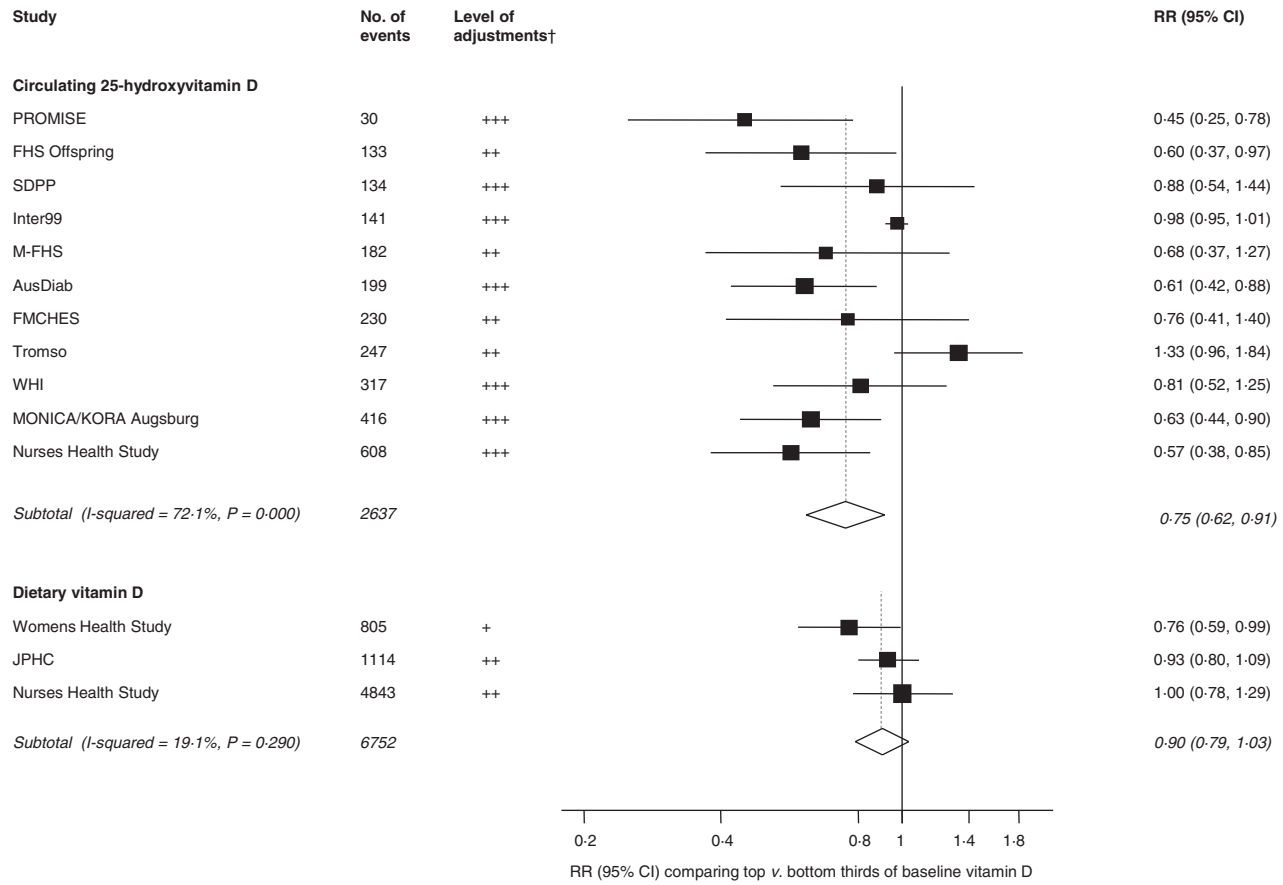

Fig. 3. Association between vitamin D and Type 2 diabetes, measured as circulating blood and dietary exposures. Study acronyms and references are provided in Table 1. The summary estimate presented was calculated using a random effects model; using a fixed effects model was 0·97 (95% CI 0·94, 1·00) for 25-hydroxyvitamin D and 0·91 (95% CI 0·81, 1·02) for dietary vitamin D intake. †Level of adjustment: +, adjusted for age and sex; ++, adjusted for diabetes/metabolic syndrome (MS) risk factors; +++, adjusted for diabetes/MS risk factors plus seasonality/latitude.

general populations, thereby potentially reducing any 'reverse-causation' effects of clinically-evident pre-existing disease on vitamin D levels. The included studies were carried out in several different geographical locations across Europe, Asia and North America, increasing the likelihood that these results can be generalised to white and mixed populations. Further studies, however, are still needed in other ethnic populations (such as cohorts involving participants from the African continent). We were unable to examine the associations with IR as information was available on only two studies (1013 participants and eighty-four events). Neither were we able to perform consistent multivariate adjustments by combining models with the same set of potential confounders owing to our reliance on published data with variable degrees of adjustments across eligible studies. Despite attempts to provide results in a consistent manner by contacting various study authors, there remained some heterogeneity among the available studies which requires further investigation. Additionally, current evidence from prospective studies on the association between vitamin D status and risk of diabetes was limited by the use of vitamin D intake or a single measurement of 25(OH)D concentrations as a surrogate for the 'usual' levels of vitamin D[9–11]. A single baseline measure of circulating or dietary vitamin D may not be able to take into account the within-individual variations of vitamin D levels across seasons, as evident in our sub-group analysis. Studies are, therefore, needed with serial measurements of vitamin D status to adjust for its variability while quantifying the associations. Furthermore, studies where vitamin D status was solely measured by dietary intake are unlikely to capture overall vitamin D status in their participants as sunlight exposure is the principal source of this vitamin, and such intake assessments may also be affected by misclassification biases that are inherent to self-reported dietary instruments[43].

Although this updated meta-analysis involved aggregate data from >200 000 participants with >16 000 incident metabolic events, it was primarily based on summary results abstracted from the published reports, thereby precluding us from undertaking more in-depth analyses (e.g., assessments of optimum levels, shapes of association, regression dilution analyses, etc.). Such detailed analyses, under a broader range of circumstances, may require collaborative pooling of individual patient-level data from prospective studies in order to yield the most consistent

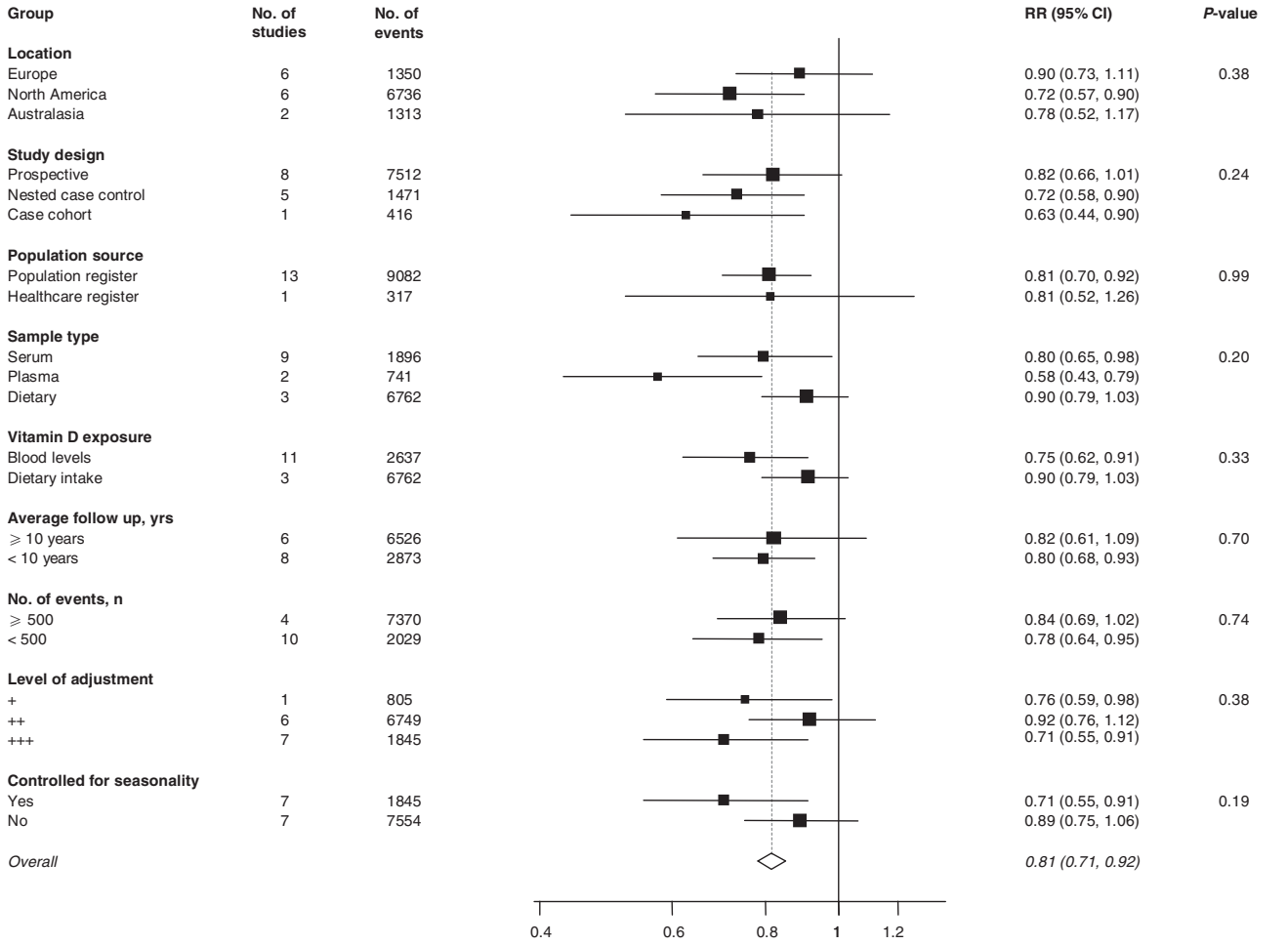

Fig. 4. Association of vitamin D with Type 2 diabetes, according to various study-level characteristics. The summary estimate presented was calculated using a random effects model; size of data markers is proportional to the inverse of the variance of the relative ratio. +, Adjusted for age and sex; ++, adjusted for diabetes risk factors; +++, adjusted for diabetes risk factors plus seasonality/latitude.

and precise estimates[44]. Finally, as our meta-analysis involves exclusively prospective studies, findings of this review are not able to establish causality, which requires robust evidence from the intervention studies. However, currently available randomised controlled trials typically involve participants with pre-existing or at high risk of metabolic disorders, are generally short-duration or under-powered and report inconsistent results[9]. Therefore, carefully designed intervention studies assessing optimum dosage, long-term safety and independent effects of vitamin D supplementations on metabolic outcomes, involving particularly healthy individuals, are warranted.

In conclusion, the results of this review, based on long-term prospective studies involving apparently healthy adults, confer significant inverse associations of baseline vitamin D status with incident T2D and MetS. Interventions aimed at maintaining adequate levels of vitamin D in addition to preventing deficiency may be a useful preventive measure for metabolic disorders. Nonetheless, reliable evidence from randomised supplementation trials with adequate power, scientific rigour and participants without pre-existing metabolic diseases, will be essential to help confirm the observational findings and inform clinical guidelines.

Supplementary material

The supplementary material for this article can be found at http://www.journals.cambridge.org/pns

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