The Effect of Vitamin D Supplementation on Insulin Sensitivity: A Systematic Review and Meta-analysis

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BACKGROUND
Vitamin D has been suggested to affect peripheral insulin sensitivity. Evidence regarding the effect of vitamin D supplementation on insulin sensitivity is still conflicting.

PURPOSE
This meta-analysis aimed to assess the effect of vitamin D supplementation on insulin sensitivity in humans with or at risk for insulin resistance.

DATA SOURCES AND STUDY SELECTION
PubMed, Web of Science, Embase, CINAHL, and Cochrane Library were systematically searched for randomized controlled trials (RCTs) from 1980 until 31 December 2018 reporting treatment effects of vitamin D supplementation on insulin sensitivity.

DATA EXTRACTION
The main outcome of interest was the change in insulin sensitivity, derived from the gold standard hyperinsulinemic-euglycemic clamp or the Matsuda index derived from the oral glucose tolerance test and insulin sensitivity index from intravenous glucose tolerance test. We extracted data on the standardized mean difference between the vitamin D treatment and placebo groups in change from baseline insulin sensitivity.

DATA SYNTHESIS
Eighteen RCTs were included in this meta-analysis comparing vitamin D supplementation (n = 612) with placebo (n = 608). Vitamin D supplementation had no effect on insulin sensitivity (standardized mean difference −0.01, 95% CI −0.12, 0.10; P = 0.87, I² = 0%). Visual inspection of funnel plot symmetry did not suggest potential publication bias.

LIMITATIONS
The number of individuals who participated in the included studies was relatively small, possibly due to the invasive character of the measurement (e.g., clamp).

CONCLUSIONS
This meta-analysis provides no evidence that vitamin D supplementation has a beneficial effect on peripheral insulin sensitivity in people with or at risk for insulin resistance.
The International Diabetes Federation (1) has reported that the worldwide diabetes prevalence in the adult population reached 8.8% (424.9 million people) in 2017. The majority (87%–91%) of these diabetes cases concern type 2 diabetes. Type 2 diabetes has become a major public health concern due to its complications. It decreases quality of life and increases mortality risk (2). Additionally, ~7.3% of the adult population (352.1 million people) suffers from prediabetes (1). Prediabetes is defined by increased fasting glucose or impaired glucose tolerance (postprandial hyperglycemia), which are both strongly associated with obesity (3). Moreover, postprandial hyperglycemia is a major risk factor for developing type 2 diabetes (4).

Obesity, prediabetes, and type 2 diabetes are often characterized by low circulating levels of vitamin D (vitamin D deficiency) (5). Indeed, based on cross-sectional studies, vitamin D deficiency has been linked with impaired insulin sensitivity in humans (6). Furthermore, people with low vitamin D levels (7) may be at greater risk to develop type 2 diabetes. Of interest, the vitamin D receptor, which mediates the function of vitamin D, is also expressed in insulin-sensitive tissues (including adipose tissue, muscle, and pancreas) (8–10). Therefore, currently nonskeletal functions of vitamin D in insulin-sensitive organs are being investigated.

Several plausible mechanisms have been proposed to explain a potential role of vitamin D in improving insulin sensitivity (6,11). In adipose tissue, vitamin D may affect lipid metabolism (12) and may reduce inflammation (13). Vitamin D may affect pancreatic insulin secretion via protection of β-cells from local inflammation (14). Vitamin D may also affect insulin secretion, which is mediated by a calcium-dependent mechanism (15). In addition, it has been demonstrated that vitamin D affects skeletal muscle metabolism, insulin sensitivity, and lipid composition (16,17). Thus, increasing circulating vitamin D concentration might be expected to have beneficial effects on tissue energy and substrate metabolism, thereby contributing to an improvement of whole-body insulin sensitivity.

In recent years, several meta-analyses (18–23) have been conducted to investigate the effect of vitamin D supplementation on whole-body insulin sensitivity. However, the findings from these reports are inconsistent. From the six meta-analyses published between 2015 and 2018, four studies (18–21) indicated insufficient evidence/no effect on glycemic control and insulin resistance, whereas two studies (22,23) indicated sufficient evidence for an improvement of glycemic control and insulin sensitivity. Moreover, these meta-analyses have been focusing only on glucose homeostasis under fasting conditions by studying parameters such as HOMA of insulin resistance (HOMA-IR), fasting glucose, fasting insulin, and HbA1c as main outcome measures.

Of importance, the skeletal muscle is considered an important organ in peripheral insulin sensitivity, as it affects 70%–90% of total glucose disposal under postprandial conditions (nonfasting conditions) (24,25). Studies have shown that vitamin D may affect skeletal muscle substrate metabolism and insulin sensitivity (16,17). Thus, increasing circulating vitamin D concentration by means of supplementation might be expected to have beneficial effects during postprandial conditions by improving skeletal muscle glucose handling/insulin sensitivity. Therefore, we undertook a systematic review and meta-analysis of randomized controlled trials (RCTs) to delineate the impact of vitamin D supplementation on insulin sensitivity derived from the gold standard hyperinsulinemic-euglycemic clamp or from multisampled oral (OGTT) or intravenous (IVGTT) glucose tolerance tests as well as the postprandial glucose concentrations (OGTT) in humans with or at risk for insulin resistance.

**METHODS**

**Data Sources and Searches**

We conducted our systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (26). The protocol for our systematic review was registered at the International Prospective Register of Systematic Reviews, PROSPERO (reg. no. CRD42018092961). The main outcome of interest was the change in insulin sensitivity, derived from a gold standard hyperinsulinemic-euglycemic clamp or from the form of the Matsuda index derived from OGTT and/or insulin sensitivity index derived from IVGTT, subsequent to vitamin D administration in individuals with or at risk for insulin resistance. The secondary outcome was the change in 2-h postprandial glucose concentration and/or area under the curve (AUC) for glucose during an OGTT.

A comprehensive literature search (PubMed/MEDLINE [Medical Literature Analyses and Retrieval System Online], Cochrane Library, Web of Science, Embase database [Ovid], and CINAHL [Cumulative Index to Nursing and Allied Health Literature]) was performed to identify articles from 1980 until 31 December 2018. The main keywords used were as follows: overweight, obesity, prediabetes, type 2 diabetes mellitus, vitamin D, insulin sensitivity, insulin resistance, blood glucose. These keywords were combined with Boolean operators (e.g., OR, AND, NOT), and all fields or MeSH (Medical Subject Heading) terms. This set of search terms was slightly modified when we searched in every database due to a different system and technical limitations (Supplementary Table 1).

**Study Selection**

Eligible studies met the PICOS (Patients/participants, Intervention, Comparison/control group, Outcome, and Study design) criteria: 1) study was an RCT; 2) study population consisted of individuals with elevated (risk for) insulin resistance (overweight, obesity, prediabetes, polycystic ovary syndrome [PCOS], and type 2 diabetes without complications); 3) interventions were vitamin D supplementation versus the appropriate placebo; 5) vitamin D supplementation dose was daily, weekly, or monthly; 6) trial length was ≥2 months; 7) serum 25-hydroxyvitamin D [25(OH)D] level was measured; 8) insulin sensitivity was measured by Matsuda index derived from an OGTT and/or insulin sensitivity index derived from IVGTT or by a hyperinsulinemic-euglycemic clamp at the beginning and at the end of the trial; and 9) study was published in English.

Exclusion criteria were as follows: 1) non–clinical trial studies; 2) studies without outcome of insulin sensitivity derived from multisampled OGTT or hyperinsulinemic-euglycemic clamp; 3) study populations with end-stage renal disease (kidney disease), cancers, gestational diabetes mellitus (GDM), nonalcoholic steatohepatitis, cardiovascular diseases complications, and infectious diseases; 4) intervention periods of < 2 months; 5) vitamin D supplementation provided as a single dose; and 6) study performed in children or adolescents (<18 years old).
Following the search, duplicates were removed. Titles and abstracts were screened by two authors (A.P. and M.A.v.B.). Final study selection, based on the inclusion criteria, was done by two authors (A.P. and M.A.v.B.) and approved by another author (E.E.B.). Any disagreements between the authors were resolved through discussion with the fourth author (J.W.E.J.).

Data Extraction and Quality Assessment
Data were extracted by two authors (A.P. and M.A.v.B.). Data extracted from each study included the following items: first author, reference, year of publication, country of study, study design, inclusion criteria, sample size, form of vitamin D, dose and frequency of vitamin D supplementation, any cosupplementation (e.g., diet or calcium), treatment control group, duration of supplementation, participants’ characteristics (n, sex [% male], age, BMI, ethnicities), comorbidities, baseline glucose infusion rate [GIR] or insulin-interventions (blinding of participants and generation and allocation concealment), randomization process (random sequence generation and allocation concealment), data extraction from each study data, such as converting measurement units or calculating SDs, were conducted by the first author (A.P.) and checked by another author (M.A.v.B.). Serum 25(OH)D levels were collated in nanomoles per liter; a multiplication factor of 2.456 was used to convert 25(OH)D levels from nanomoles per milliliter to nanomoles per liter. Two-h glucose tolerance test glucose concentrations (2-h glucose) were collated in millimoles per liter; we used a multiplication factor of 0.0555 to convert glucose levels from milligrams per deciliter millimoles per liter as appropriate (27).

The quality of selected RCTs was assessed independently by two authors (A.P. and M.A.v.B.) using the risk-of-bias (RoB) checklist from the Cochrane Collaboration (28). The quality assessments of the checklist included 1) bias from randomization process (random sequence generation and allocation concealment), 2) bias due to deviations from intended interventions (blinding of participants and personnel), 3) bias due to missing outcome data, 4) bias from measurements of the outcome, 5) bias from selection of reported result, and other sources of bias. Each criterion could be answered in three ways: “low risk” (adequate information), “unclear risk” (if there was unclear information), and “high risk” (if there was high concern). Study quality and the risk of bias in the eligible RCTs were systematically assessed using software Review Manager 5.3 (the Nordic Cochrane Centre, the Cochrane Collaboration, Copenhagen, Denmark, 2014).

Data Synthesis and Analysis
To calculate the effect size of each study, we used the mean change and SD of the outcome measures from baseline to the end of the intervention in the control and intervention groups (29). When the outcome measure was reported as mean and 95% CI or mean and SEM, values were estimated using Review Manager 5.3 software (30). If the outcome measures were reported in median, range, or 25th–75th percentiles, mean and SD values were estimated using formulas published by Wan et al. (31). If the outcome measures were only reported in figures, we used software to estimate the value. SDs of the mean difference were estimated using the following formula:

$$SD = \sqrt{\frac{SD_{pretreatment}^2 + SD_{posttreatment}^2}{2} - \frac{(2R \times SD_{pretreatment} + SD_{posttreatment})^2}{SD_{pretreatment}^2 + SD_{posttreatment}^2}}$$

Because the pretest-posttest correlation coefficients (r) were not reported in studies, an r value of 0.5 was assumed throughout this meta-analysis (30).

If a study included more than two intervention groups (e.g., two different doses of vitamin D), which were compared with one placebo (control) group, the number of subjects of the control group was divided by the number of comparisons. If the outcome measurement was performed at multiple time points after the intervention period, we only used first time point after the intervention (29).

The effect size is reported as standardized mean difference with its 95% CI (26,32). Standardized mean difference is used as a summary statistic in meta-analysis when the studies all assess the same outcome but measure it in a variety of ways (in this study, for example, all studies measured insulin sensitivity but use different methodology, i.e., clamp or Matsuda index or insulin sensitivity index). A random-effects model was used to estimate outcomes. Heterogeneity was assessed using the I² statistic, indicating what proportion of the variation in observed effects across studies is due to the variation in true effects, with values >60% indicating substantial heterogeneity. A P value < 0.05 is considered statistically significant (29). The analysis was performed and generated using Review Manager 5.3 software. The PRISMA checklist was used as a guide for checking the quality of our systematic review (Supplementary Table 2).

Publication Bias
Publication bias was analyzed by visual inspection of the funnel plots.

Meta-Regression and Sensitivity Analysis
If the heterogeneity was >60%, additional analyses were conducted. Meta-regression analysis and sensitivity analysis using the leave-one-out method (removing one study each time and repeating the analysis) were applied to gain insight into the source of the heterogeneity (29).

RESULTS
Study Characteristics
In total, 18 RCTs (33–50) published between 2011 and 2018 with 1,220 participants were included in the current meta-analysis (Fig. 1). Characteristics of the studies are summarized in Table 1. The studies were conducted in the U.S. (n = 5), Canada (n = 1), Iran (n = 1), India (n = 1), Malaysia (n = 1), Australia (n = 2), the Netherlands (n = 1), Denmark (n = 1), Norway (n = 1), Finland (n = 1), Sweden (n = 1), Austria (n = 1), and Italy (n = 1). Most studies included both men and women, except two studies that included only women (43,45) and two other studies that included only men (44,50). Among the 18 studies, 8 enrolled several ethnic populations (multiethnicity) (33,36–38,40,46–48), 2 enrolled individuals with African American ethnicity (34,44), 2 enrolled Asians (43,45), 1 enrolled participants from Middle Eastern countries (35), and 5 did not provide information about ethnicity (39,41,42,49,50). Sixteen trials were in participants with overweight, obesity, prediabetes, type 2 diabetes, or metabolic syndrome, and two...
Table 1—Characteristics of randomized controlled trial studies included in the meta-analysis

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Study location</th>
<th>N subjects</th>
<th>Sex</th>
<th>Ethnicity</th>
<th>BMI (kg/m²)</th>
<th>Health status</th>
<th>Vitamin D levels at baseline (nmol/L)</th>
<th>Vitamin D levels after intervention (nmol/L)</th>
<th>Type of vitamin D; mode of delivery; dose (IU/day)</th>
<th>Vitamin D analytical measures</th>
<th>Duration (months)</th>
<th>Outcome measured</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitri et al. (2011)</td>
<td>U.S.</td>
<td>23/24</td>
<td>M/F</td>
<td>Multiethnic</td>
<td>25 (≥23 if Asian)</td>
<td>Prediabetes (IGT, IFG, HbA1c ≥5.8%)</td>
<td>T 59.9 ± 2.7§ P 60.4 ± 2.7§</td>
<td>T 15.7 ± 3.7§ (change from baseline), P = 20.5 ± 3.5§</td>
<td>Vitamin D₃; oral; 2,000</td>
<td>LC-MS</td>
<td>4</td>
<td>Insulin sensitivity index (FIVGTT), 2-h glucose (OGTT)</td>
</tr>
<tr>
<td>Harris et al. (2012)</td>
<td>U.S.</td>
<td>43/46</td>
<td>M/F</td>
<td>African American</td>
<td>25–39.9</td>
<td>Prediabetes or early T2D (HbA1c 6.7–7%), baseline 25(OH)D &lt; 50 nmol/L</td>
<td>T 39.6 ± 12.9, P 38.2 ± 15.5</td>
<td>T 41.6 ± 3.1§ (change from baseline), P = 0.9 ± 2.9§</td>
<td>Vitamin D₃; oral; 4,000</td>
<td>RIA</td>
<td>3</td>
<td>Matsuda index, 2-h glucose (OGTT)</td>
</tr>
<tr>
<td>Iraj et al. (2012)</td>
<td>Iran</td>
<td>20/20</td>
<td>M/F</td>
<td>Middle Eastern</td>
<td>≥25</td>
<td>First-degree relatives with T2D, 25(OH)D &lt; 75 nmol/L, prediabetes</td>
<td>T 27.5 ± 15.0, P 28.2 ± 15.0</td>
<td>T 87.4 ± 49.9, P 38.7 ± 54.9</td>
<td>Vitamin D₃; injection; 10,000</td>
<td>CLIA</td>
<td>2</td>
<td>Matsuda index, AUCglucose (OGTT)</td>
</tr>
<tr>
<td>Davidson et al. (2013)</td>
<td>U.S.</td>
<td>56/53</td>
<td>M/F</td>
<td>Multiethnic (Hispanic and African American)</td>
<td>≥25</td>
<td>Prediabetes, 25(OH)D &lt; 75 nmol/L</td>
<td>T 54.9 ± 12.5, P 54.9 ± 12.5</td>
<td>T 169.6 ± 49.9, P 54.9 ± 17.4</td>
<td>Vitamin D₃; oral; 12,695</td>
<td>LC-MS</td>
<td>3</td>
<td>Matsuda index, 2-h glucose</td>
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<tr>
<td>Oosterwerff et al. (2014)</td>
<td>Netherlands</td>
<td>53/57</td>
<td>M/F</td>
<td>Multiethnic (Morocco, Suriname, Turkey)</td>
<td>≥25</td>
<td>IFG or IGT, 25(OH)D &lt; 50 nmol/L</td>
<td>T 25.0 ± 10.8, P 22.0 ± 11.0</td>
<td>T 60.0 ± 16.0, P 23.0 ± 15.0</td>
<td>Vitamin D₃; oral; 1,200</td>
<td>LC-MS</td>
<td>4</td>
<td>Insulin sensitivity index, 2-h glucose</td>
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<tr>
<td>Gagnon et al. (2014)</td>
<td>Australia</td>
<td>35/45</td>
<td>M/F</td>
<td>Multiethnic</td>
<td>25–40</td>
<td>25(OH)D &lt; 50 nmol/L, prediabetes</td>
<td>T 47.0 ± 13.0, P 43.2 ± 13.0</td>
<td>T 89.1 ± 16.5, P 41.4 ± 16.3</td>
<td>Vitamin D₃; oral; 2,000</td>
<td>CLIA</td>
<td>6</td>
<td>Matsuda index</td>
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<td>Kampmann et al. (2014)</td>
<td>Denmark</td>
<td>7/8</td>
<td>M/F</td>
<td>NR</td>
<td>≥25</td>
<td>T2D, 25(OH)D &lt; 50 nmol/L</td>
<td>T 31.0 ± 49.5, P 34.8 ± 3.8§</td>
<td>T 104.9 ± 19.0§, P 32.1 ± 3.8§</td>
<td>Vitamin D₃; oral; 6,400</td>
<td>ELISA</td>
<td>3</td>
<td>M value derived from clamp</td>
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<tr>
<td>Mitchell et al. (2015)</td>
<td>U.S.</td>
<td>40/50</td>
<td>M/F</td>
<td>Multiethnic</td>
<td>Median 25</td>
<td>25(OH)D &lt; 50 nmol/L</td>
<td>T 44.9 ± 17.5, P 44.9 ± 17.5</td>
<td>T 107.3 ± 29.9, P 49.9 ± 24.9</td>
<td>Vitamin D₃; oral; 7,142</td>
<td>LC-MS</td>
<td>3</td>
<td>Insulin sensitivity index (FIVGTT)</td>
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<tr>
<td>Tuomainen et al. (2015)</td>
<td>Finland</td>
<td>T1/T2/ (24/21/21)</td>
<td>M/F</td>
<td>NR</td>
<td>≥25</td>
<td>Prediabetes, 25(OH)D &lt; 75 nmol/L</td>
<td>Mean baseline T + P 57.0 ± 11.0</td>
<td>Mean (change from baseline) T2 45.0 ± 23.4, P 4.1 ± 17.3</td>
<td>(T1) Vitamin D₃; oral; 1,600</td>
<td>HPLC-CEAD</td>
<td>5</td>
<td>Matsuda index</td>
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</table>

Continued on p. 1663
Table 1—Continued

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Study location</th>
<th>N subjects (Tx/Px)</th>
<th>Sex</th>
<th>Ethnicity</th>
<th>BMI (kg/m²)</th>
<th>Health status</th>
<th>Vitamin D levels at baseline (nmol/L)</th>
<th>Vitamin D levels after intervention (nmol/L)</th>
<th>Type of vitamin D; mode of delivery; dose (IU/day)</th>
<th>Vitamin D analytical measures</th>
<th>Duration (months)</th>
<th>Outcome measured</th>
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<tr>
<td>Wagner et al. (2016)</td>
<td>Sweden</td>
<td>21/22 M/F NR</td>
<td>≤32</td>
<td>Prediabetes or drug-naive diabetes, HbA₁c ≤7.9%, FPG &lt;9 mmol/L, 25(OH)D &lt;75 nmol/L</td>
<td>T median 43.0 (IQR 36.0–50.0), P 43.0 (37.0–54.0)</td>
<td>Median change T 42.0 (IQR 32.0–50.0), P 0.0 (–7.0 to 11.0)</td>
<td>Vitamin D₃; oral; 4,285</td>
<td>CLIA</td>
<td>2</td>
<td>GIR derived from clamp</td>
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<td>Yeow et al. (2015)</td>
<td>Malaysia</td>
<td>13/13 F Asian</td>
<td>23–31</td>
<td>History of GDM during last pregnancy 6–48 months postpartum; hypovitaminosis (25(OH)D 15–50 nmol/L)</td>
<td>T median 35.6 (IQR 25.6–43.9), P 35.1 (21.6–40.7)</td>
<td>Median change T 51.1 (IQR 39.9–76.1), P 0.2 (21.0 to 11.8)</td>
<td>Vitamin D₃; oral; 4,000</td>
<td>ECLIA</td>
<td>6</td>
<td>Insulin sensitivity index, 2-h glucose</td>
<td></td>
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<tr>
<td>Barengolts et al. (2015)</td>
<td>U.S.</td>
<td>87/86 M African American</td>
<td>28–39</td>
<td>Fasting glucose 5.3–6.9 mmol/L, HbA₁c 5.7–6.4%, 25(OH)D 12.5–75 nmol/L</td>
<td>T 36.7 ± 11.7, P 34.9 ± 12.0</td>
<td>T 120.1 ± 45.9, P 49.7 ± 18.2</td>
<td>Vitamin D₃; oral; 7,142</td>
<td>CLIA</td>
<td>12</td>
<td>Matsuda index</td>
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<tr>
<td>Garg et al. (2015)</td>
<td>India</td>
<td>15/17 F Asian</td>
<td>≥23</td>
<td>PCOS, 25(OH)D &lt;50 nmol/L</td>
<td>P 16.9 ± 6.1</td>
<td>T 78.6 ± 34.6, P 16.7 ± 5.8</td>
<td>Vitamin D₃; oral; 4,000</td>
<td>CLIA</td>
<td>6</td>
<td>Matsuda index, AUCglucose</td>
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<td>Mousa et al. (2017)</td>
<td>Australia</td>
<td>28/26 M Multiethnic</td>
<td>≥25</td>
<td>25(OH)D &lt;50 nmol/L</td>
<td>T 31.4 ± 12.6, P 34.2 ± 10.0</td>
<td>T 88.4 ± 21.0, P 36.1 ± 15.3</td>
<td>Vitamin D₃; oral; 4,000</td>
<td>CLIA</td>
<td>4</td>
<td>M value derived from clamp</td>
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<tr>
<td>Gulseth et al. (2017)</td>
<td>Norway</td>
<td>33/29 M Multiethnic (Nordic and South Asian)</td>
<td>&lt;45</td>
<td>T2D, 25(OH)D &lt;50 nmol/L</td>
<td>T 38.0 ± 11.9, P 36.8 ± 12.6</td>
<td>T 53.7 ± 9.2, P 38.2 ± 12.9</td>
<td>Vitamin D₃; injection and oral; 3,333</td>
<td>RIA</td>
<td>6</td>
<td>GIR derived from clamp</td>
<td></td>
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<tr>
<td>Lerchbaum et al. (2017)</td>
<td>Austria</td>
<td>49/49 M NR</td>
<td>Median 25</td>
<td>25(OH)D &lt;75 nmol/L</td>
<td>T median 52.0 (IQR 42.0–65.0), P 51.0 (43.0–68.0)</td>
<td>Median T 107.0 (IQR 89.0–119.0), P 69.0 (46.0–79.0)</td>
<td>Vitamin D₃; oral; 2,857</td>
<td>LC-MS</td>
<td>3</td>
<td>Matsuda index, AUCglucose</td>
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<tr>
<td>Moreira-Lucas et al. (2017)</td>
<td>Canada</td>
<td>36/35 M Multiethnic</td>
<td>&lt;40</td>
<td>25(OH)D ≤65 nmol/L, HbA₁c 5.4%–6.4%</td>
<td>T 48.1 ± 14.3, P 47.6 ± 14.3</td>
<td>Mean change T 50.6 (95% CI 36.7, 64.6), P = 2.11 (–6.11, 1.89)</td>
<td>Vitamin D₃; oral; 4,000</td>
<td>LC-MS</td>
<td>6</td>
<td>Matsuda index, AUCglucose</td>
<td></td>
<td></td>
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<tr>
<td>Cefalo et al. (2018)</td>
<td>Italy</td>
<td>9/9 M/F NR</td>
<td>&gt;25</td>
<td>BMI ≥20 kg/m², 25(OH)D &lt;75 nmol/L</td>
<td>T 36.7 ± 13.2, P 34.7 ± 21.1</td>
<td>T 74.8 ± 18.7, P 41.7 ± 7.7</td>
<td>Vitamin D₃; oral; 3,571</td>
<td>NR</td>
<td>3</td>
<td>Insulin-mediated glucose uptake, AUCglucose (from OGTT)</td>
<td></td>
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</tr>
</tbody>
</table>

CLIA, chemiluminescence immunoassay; ECLIA, electrochemiluminescence immunoassay; FPG, fasting plasma glucose; FIVGTT, frequently sampled intravenous glucose tolerance test; HPLC-CEAD, high-performance liquid chromatography-coulometric electrode array detector; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IQR, interquartile range; LC-MS, liquid chromatography–mass spectrophotometry; M, male; F, female; NR, not reported; P, placebo; RIA, radioimmunoassay; Tx/Px, treatment/placebo group; T, treatment; T2D, type 2 diabetes. §Data are means ± SE.
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of these trials also included apparently healthy participants (40,50), while participants in the two other trials had PCOS (45) or a history of GDM (43). Studies used different cutoffs for baseline vitamin D levels: nine studies (34,37–40,45–47) recruited individuals with vitamin D levels <50 nmol/L, and the others (33,35,36,41,42,44,48–50) included individuals with vitamin D levels <75 nmol/L at the beginning of trial (Table 1). Mean serum 25(OH)D concentrations at baseline varied from 19.2 nmol/L (45) to 59.9 nmol/L (33) in vitamin D–supplemented groups and 16.9 nmol/L (45) to 61.4 (33) in placebo groups. The mean oral dose of vitamin D was 4,608 IU per day (range 1,200 [37] to 12,695 [36] per day), with the majority of studies providing daily doses 4,000 IU (33,34,37–39,41,43,45,46,48–50). The duration of vitamin D supplementation ranged from 2 (42) to 12 (44) months.

The Effect of Vitamin D Supplementation on Serum Vitamin D Levels

All 18 trials (n = 1,223; 613 individuals treated with vitamin D and 610 individuals with placebo) reported the change in serum vitamin D level after the intervention. There was a significant increase in the serum vitamin D level in the vitamin D supplementation groups compared with the control groups (standardized mean difference 2.25, 95% CI 1.90–2.60, P < 0.001) (Fig. 38) with considerable heterogeneity (I² = 81%, P < 0.001).

Risk of Bias

Most included studies had a low risk of bias according to randomization process (random sequence generation and allocation concealment), blinding participants (comparability of intervention groups and placebo [control] groups), and incomplete outcome data (clear description of dropout/withdrawal/attrition rate). The blinding of outcome assessment was not clearly mentioned in some of the studies (34–36,41,44,45,48,49), which resulted in unclear risk of detection bias. The overall quality assessment of the included trials in this meta-analysis is shown in Supplementary Fig. 1.

Publication Bias

The visual inspection of funnel plots of changes in insulin sensitivity and postprandial glucose did not suggest potential publication bias. In addition, the funnel plot of serum vitamin D changes in this meta-analysis following vitamin D supplementation also did not indicate publication bias (Supplementary Fig. 2).
Regarding the change in serum vitamin D levels following supplementation, there was a considerable heterogeneity ($I^2 = 81\%$). A meta-regression analysis of dose or duration with standardized mean difference of serum vitamin D levels showed that the dose of vitamin D supplementation may partly explain the heterogeneity (Supplementary Table 3). Further sensitivity analysis by leave-one-out analysis shows that no single study is responsible for the heterogeneity of changes in serum vitamin D levels.

**DISCUSSION**

We conducted a systematic review and meta-analysis of 18 RCTs to determine the effect of vitamin D supplementation on insulin sensitivity in individuals with or at risk for insulin resistance. In this meta-analysis, vitamin D supplementation had no significant effect on insulin sensitivity derived from a hyperinsulinemic-euglycemic clamp or the Matsuda index derived from an OGTT and/or insulin sensitivity index from IVGTT. Additionally, no significant changes in 2-h glucose or AUC glucose during an OGTT were observed following vitamin D supplementation.

In our analysis, study populations were often characterized by the presence of overweight or obesity (33–39,41–44,46–49), accompanied by baseline serum concentrations of 25(OH)D, 50 nmol/L (33–44,46–50) or 75 mmol (35,36,41,42,44,49,50). Indeed, it has been described that human obesity often coincides with low circulating 25(OH)D levels (5). Several mechanisms, such as uptake/sequestration of vitamin D within adipose tissue (51) and volumetric dilution due to increased body volume (52), may explain the link between obesity and low vitamin D levels. Furthermore, a comprehensive systematic review by Autier et al. (53) suggests that the low serum vitamin D levels could also be due to the chronic low-grade inflammation, which is an important characteristic of individuals with obesity and type 2 diabetes. Thus, vitamin D supplementation in human overweight/obesity could be expected to increase serum 25(OH)D levels.

In this meta-analysis, we showed that vitamin D supplementation increased the mean 25(OH)D level of treatment groups in all studies, although with considerable heterogeneity. Additional meta-regression analysis showed that some of the heterogeneity is explained by dose but not by treatment duration. Nevertheless, in our meta-analysis, improving 25(OH)D concentrations did not translate into an improvement in insulin sensitivity and glucose metabolism. In the present meta-analysis, we included only studies using standardized methodologies (nonfasting measures of insulin sensitivity), by multisampled OGTTs or IVGTTs (33–38,40,41,43–45,48,50) or the gold standard hyperinsulinemic-euglycemic clamp (39,42,46,47,49). Our meta-analysis, which shows no effect of vitamin D supplementation on peripheral insulin sensitivity and postprandial glucose handling, supports several other findings of studies that used fasting
indices of insulin sensitivity (e.g., HOMA-IR) (18,19).

It has been shown that postprandial glycemia is strongly associated with obesity (3) and predicts cardiovascular events among insulin resistant individuals (4,54). Wood et al. (55) and Manson et al. (56) have shown that vitamin D supplementation did not result in the prevention of cardiovascular events. The most recent work by Pittas et al. (57) showed that vitamin D supplementation (4,000 IU) did not result in a significantly lower risk of diabetes, assessed by 2-h OGTT in 2,423 individuals. The skeletal muscle is a key

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Vitamin D</th>
<th>Control</th>
<th>Std. Mean Difference</th>
<th>Std. Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>Weight</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Total</td>
<td>IV, Random, 95% CI</td>
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<td></td>
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<td>IV, Random, 95% CI</td>
</tr>
<tr>
<td>2.1.2 2OGTT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Davidson et al., 2013</td>
<td>-0.55</td>
<td>1.88</td>
<td>56 -0.89</td>
<td>1.98</td>
</tr>
<tr>
<td>Harris et al., 2012</td>
<td>-0.4</td>
<td>1.97</td>
<td>43 -0.41</td>
<td>1.97</td>
</tr>
<tr>
<td>Met et al., 2011</td>
<td>-0.25</td>
<td>2.68</td>
<td>27 0.09</td>
<td>1.9</td>
</tr>
<tr>
<td>Tsuimama et al., 2015A</td>
<td>0.5</td>
<td>1.8</td>
<td>21 -0.5</td>
<td>1.6</td>
</tr>
<tr>
<td>Tsuimama et al., 2015B</td>
<td>0.7</td>
<td>1.7</td>
<td>21 -0.5</td>
<td>1.6</td>
</tr>
<tr>
<td>Wagner et al., 2016</td>
<td>-0.3</td>
<td>1.91</td>
<td>21 0.22</td>
<td>2.62</td>
</tr>
<tr>
<td>Yeow et al., 2015</td>
<td>-0.95</td>
<td>2.12</td>
<td>13 0.05</td>
<td>1.56</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>198</td>
<td>178</td>
<td>50.8%</td>
<td>0.09 [-0.14, 0.32]</td>
</tr>
</tbody>
</table>
| Heterogeneity: $\chi^2 = 0.03$, d.f. = 6 ($P = 0.62$), $P = 15$
| Test for overall effect: $Z = 0.36$ ($P = 0.45$) |
| 2.1.2 AUC$_{\text{glucose}}$ |
| Celano et al., 2018     | -0.4      | 1.68    | 9 -1.6               | 9.63                 | 9 2.9% 0.22 [-0.71, 1.15] |
| Garg et al., 2015       | -0.10     | 3.64    | 35 -2.06             | 3.64                 | 35 12.1% 0.16 [-0.51, 0.84] |
| Raj et al., 2012        | -0.58     | 1.75    | 20 0.01              | 1.75                 | 20 7.7% 0.15 [-0.87, 1.18] |
| Larhamaa et al., 2015   | 0.03      | 3.26    | 35 -0.1              | 3.26                 | 35 9.8% 0.02 [-0.44, 0.48] |
| Moreira-Luca et al., 2017 | -0.03     | 2.03    | 23 -1.12             | 2.03                 | 23 12.1% 0.03 [-0.41, 0.14] |
| Oosterweel et al., 2016 | -0.03     | 2.03    | 23 -1.12             | 2.03                 | 23 12.1% 0.03 [-0.41, 0.14] |
| Subtotal (95% CI)       | 181       | 188     | 45.2%                | 0.08 [-0.19, 0.35]    |
| Heterogeneity: $\chi^2 = 0.04$, d.f. = 5 ($P = 0.08$), $P = 14$
| Test for overall effect: $Z = 0.46$ ($P = 0.65$) |
| Total (95% CI)          | 379       | 366     | 100.0%               | 0.09 [-0.08, 0.25]    |
| Heterogeneity: $\chi^2 = 0.02$, d.f. = 11 ($P = 0.26$), $P = 18$
| Test for overall effect: $Z = 1.06$ ($P = 0.29$) |
| Test for subgroup differences: $\chi^2 = 0.00$, d.f. = 1 ($P = 0.96$), $P = 0$

Figure 3—Forest plots of the effect of vitamin D supplementation on postprandial glucose (A) and serum vitamin D level (B). Horizontal lines span individual study 95% CIs. Diamonds represent the combined study standardized mean value and the corresponding 95% CIs. 2OGTT, 2-h oral glucose tolerance test; d.f., degrees of freedom; IV, inverse variance. †Vitamin D$_3$, 1,600 IU/day (41). ¶Vitamin D$_3$, 3,200 IU/day (41).
organ for peripheral insulin sensitivity, as it is responsible for the majority of glucose disposal during postprandial conditions (24,58). Although effects of vitamin D on glucose responsiveness, insulin receptor substrate (59) and insulin sensitivity (17), and muscle mitochondria biogenesis (16) as well as lipid metabolism (17) have been documented at the transcriptional and posttranslational level in vitro, our analysis showing no effect on postprandial glucose concentrations suggests that these beneficial effects do not translate into beneficial effects at the functional level.

Studies have shown that vitamin D may affect insulin secretion (15,33) rather than insulin sensitivity per se. Vitamin D may contribute to normalization of intracellular calcium, ensuring normal calcium flux through cell membranes, and regulate the β-cell calcium pool (15). Nevertheless, whether there is sufficient evidence that vitamin D supplementation may improve insulin secretion in the postprandial condition (e.g., disposition index) needs further investigation.

Furthermore, there is only one trial included in this meta-analysis, by Cefalo et al. (49), that reported a significant increase of insulin sensitivity derived from a clamp after vitamin D supplementation. Of note, in that study vitamin D supplementation was combined with a low-calorie diet intervention, yet the sample size of this study was relatively small. Therefore, whether combining vitamin D supplementation with diet restriction may improve insulin sensitivity in humans with or at risk for insulin resistance needs further investigation in a well-controlled study.

In interpretation of the results, several factors should be taken into consideration. The optimal time of intervention and dose that are necessary to evaluate the effects of vitamin D supplementation on parameters related to glucose metabolism and insulin sensitivity are not well established. We showed that neither dose nor treatment duration was associated with changes in insulin sensitivity and postprandial glucose. It also should be noted that the results could be affected by other factors such as variation in age, season (19), and ethnicity (23) as well as tissue-specific metabolism and insulin resistance (60). A recent meta-analysis in populations with type 2 diabetes by Li et al. (23) has suggested that vitamin D supplementation may have more beneficial effects in individuals with Middle Eastern ethnicity as compared with other ethnicities, but some of the included studies on which this suggestion was based were of questionable quality. In this meta-analysis, we could not perform subgroup analysis based on ethnicity because 8 out of 18 trials (33,36–38,40,46–48) were conducted in multiethnic populations, whereas 5 other studies (39,41,42,49,50) did not report any information about ethnicity. In addition, the heterogeneity regarding the change in serum vitamin D levels may also be partly explained by compliance that was achieved during intervention, which we were unable to ascertain in more detail. Another limitation might be that the number of individuals who participated in the included studies was relatively small, possibly due to the invasive and expensive character of the measurement (e.g., clamp).

Despite the fact that the number of studies using clamps, the gold standard for the measurement of insulin sensitivity, was relatively small (only 5 studies), the outcome on insulin sensitivity derived from clamps was similar to the outcome based on the results from OGTTs and IVGTTs (13 studies). In addition, three studies that met our inclusion criteria and used a hyperinsulinemic-euglycemic clamp (61–63) were published in 2019—after the window for being included in the meta-analysis. After repeating of the meta-analysis with in total 21 studies (3 studies in 2019 and the original 18 studies), the outcome did not change (Supplementary Fig. 3A–C). In conclusion, this systematic review provides no evidence that supplementation with vitamin D has a beneficial effect on peripheral insulin sensitivity, as determined by hyperinsulinemic-euglycemic clamp, the Matsuda or insulin sensitivity index, and postprandial glucose concentrations after an OGTT in people with or at risk for insulin resistance.

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Author Contributions. A.P., E.E.B., J.W.E.J., and M.A.v.B designed the study. A.P. and M.A.v.B. searched databases and performed the selection of studies. A.P. analyzed the data. M.A.v.B checked the data analysis. A.P. wrote the manuscript. M.A.v.B., J.W.E.J., and E.E.B. critically evaluated the review and meta-analysis, commented on it, and approved the last version. All authors reviewed and approved the final manuscript. E.E.B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. International Diabetes Federation. IDF Diabetes Atlas. 8th ed. 2017
7. Gagnon C, Lu ZX, Magliano DJ, et al. Serum 25-hydroxyvitamin D, calcium intake, and risk of type 2 diabetes after 5 years: results from a national, population-based prospective study (the Australian Diabetes, Obesity and Lifestyle study). Diabetes Care 2011;34:1133–1138
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36. Davidson MB, Duran P, Lee ML, Friedman TC. High-dose vitamin D supplementation in people with prediabetes and hypovitaminosis D. Diabete Care 2013;36:260–266


42. Wagner H, Alvarsson M, Mannheimer B, Degerblad M, Östenson CG. No effect of high-dose vitamin D treatment on β-cell function, insulin sensitivity, or glucose homeostasis in subjects with abnormal glucose tolerance: a randomized clinical trial. Diabetes Care 2016;39:345–352


47. Gulseth HL, Wiium C, Angel K, Eriksen EF, Birkeland KI. Effects of vitamin D supplementation on insulin sensitivity and insulin secretion in subjects with type 2 diabetes and vitamin D deficiency: a randomized controlled trial. Diabete Care 2017;40:872–878


52. Drincic AT, Armas LA, Van Diest EE, Heaney RP. Volumetric dilution, rather than sequestration best explains the low vitamin D status of obesity. Obesity (Silver Spring) 2012;20:1444–1448


58. DeFranzo RA, Ferramini E, Sato Y, Felig P, Wahren J. Synergistic interaction between exercise


60. Trouwborst I, Bowser SM, Goossens GH, Blaak EE. Ectopic fat accumulation in distinct insulin resistant phenotypes; targets for personalized nutritional interventions. Front Nutr 2018;5:77

