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## Vitamin D Supplementation in Early Childhood and Risk of Type 1 Diabetes: a Systematic Review and Meta-analysis

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## **ABSTRACT**

**Objectives:** To assess whether vitamin D supplementation in infancy reduces risk of type 1 diabetes in later life.

**Design:** Systematic review and meta-analysis.

**Data sources:** Medline, Embase, Cinahl, Cochrane Central Register of Controlled Trials and reference lists of retrieved articles.

**Main outcome measure:** Development of type 1 diabetes.

**Inclusion criteria:** Controlled trials and observational studies which had assessed the effect of vitamin D supplementation on risk of developing type 1 diabetes.

**Results:** Five observational studies met the inclusion criteria; no randomised controlled trials were found. 4 of the 5 included studies were case control studies and the fifth study was a cohort study. Meta-analysis of data from the case control studies showed that the risk of type 1 diabetes was significantly reduced in infants who were supplemented with vitamin D compared to those who were not supplemented (pooled odds ratio 0.71, 95% CI 0.60 to 0.84). The result of the cohort study was in agreement with that of the meta-analysis. There was also some evidence of a dose-response effect, with those using higher amounts of vitamin D being at lower risk of developing type 1 diabetes. Finally, there was a suggestion that the timing of supplementation might also be important for the subsequent development of type 1 diabetes.

**Conclusion:** Vitamin D supplementation in early childhood may offer protection against the development of type 1 diabetes. The evidence for this is based on observational studies. Adequately powered, randomised controlled trials with long periods of follow-up are needed to establish causality and the best formulation, dose, duration and period of supplementation.

**Keywords:** vitamin D supplementation, type 1 diabetes mellitus, systematic review, meta-analysis

### **What is already known on this subject?**

- Observational studies have suggested that vitamin D supplementation may reduce the risk of type 1 diabetes, but the results of the studies have been inconsistent.

### **What does this study add?**

- Meta-analysis of the results of observational studies suggest that the risk of type 1 diabetes is significantly reduced in those who were supplemented in childhood with vitamin D compared to those who were not supplemented (odds ratio 0.71, 95% CI 0.60 to 0.84).
- Randomised controlled trials with long periods of follow-up are needed to establish causality and the best formulation, dose, duration and period of supplementation.

## INTRODUCTION

Type 1 diabetes is characterized by autoimmune destruction of insulin-producing  $\beta$  cells in the pancreas. The specific factors that initiate the autoimmune process are not yet well understood, but  $\beta$  cell destruction often begins during infancy and continues over many months or years<sup>1</sup>. By the time type 1 diabetes is diagnosed, about 80% of the  $\beta$  cells have been destroyed<sup>2</sup>. Peak incidence occurs around puberty, and the disease is usually diagnosed before age 30<sup>3</sup>. It is commonest in people of European descent and affects 2 million people in Europe and North America. There is a marked geographic variation in incidence, with a child in Finland being about 400 times more likely than a child in Venezuela to acquire the disease<sup>4</sup>. It is estimated that currently the incidence is increasing by 3% per year<sup>5</sup>. Furthermore, it is predicted that by 2010 the incidence of type I diabetes will be 40% higher than what it was a decade earlier<sup>6</sup>.

The fact that people with affected first-degree relatives are a lot more likely to develop type 1 diabetes than the general population points to an important genetic influence<sup>7</sup>. However, low concordance among identical twins and the fact that many children with a genetic predisposition to the disease do not develop it suggest that environmental factors are also important<sup>8</sup>. One of the environmental factors thought to be protective for development of type I diabetes, is early supplementation with vitamin D.

Vitamin D is either produced endogenously, through skin exposure to sunlight, or exogenously from ingestion of foods and supplements. Breast milk contains little vitamin D, although this is influenced by the vitamin D status of the mother<sup>9</sup> and this is the reason behind the recommendation for an administered supplement for breastfed infants<sup>10</sup>. Furthermore, in northern areas, including the northern United States, Canada, and most of Europe, little or no vitamin D is produced in the skin during winter months<sup>11</sup>. Even in the summer and at lower latitudes, many infants are so thoroughly protected from sun exposure that they produce little endogenous vitamin D. In addition, there is evidence that over the last few decades the uptake<sup>12</sup> as well as the dosage<sup>13</sup> of vitamin D supplementation have been declining leading to a resurgence of rickets and hypocalcaemia<sup>14</sup>, as well as speculation about the possible role of vitamin D in the increasing incidence of type 1 diabetes and other autoimmune conditions like rheumatoid arthritis<sup>15</sup> and multiple sclerosis<sup>16</sup>.

Evidence for a causal relationship between vitamin D supplementation and decreased risk of type 1 diabetes comes from experiments in the non-obese diabetic mouse<sup>3</sup>. Furthermore, there is evidence of lower plasma 25-hydroxyvitamin D levels at diagnosis of type 1 diabetes compared to controls<sup>17</sup>. Moreover, epidemiological evidence suggests that type 1 diabetes is more prevalent in higher latitudes of the tropics and subtropics<sup>18</sup> and that there is a seasonal variation in type 1 diabetes with the largest proportion of cases diagnosed during fall and winter and the lowest during the summer<sup>19</sup>. In addition, epidemiological studies<sup>20</sup> suggest that supplementation with vitamin D in infants might be important in conferring protection against development of type 1 diabetes.

In this study, we sought to explore the potential association between vitamin D supplementation in early childhood and reduced risk of type 1 diabetes by conducting a systematic review and meta-analysis of human trials and observational studies.

## METHODS

### Types of studies

We searched for randomised controlled trials and observational studies. We included observational studies if they: (1) compared risk of type 1 diabetes in people who were supplemented with vitamin D with risk in those who were not supplemented, (2) had controlled for potential confounders by matching in the study design or used risk adjustment in the analysis; and (3) had provided sufficient data to allow the reconstruction of 2 by 2 table or to determine relative risks (RR) or odds ratios (OR) with 95% confidence intervals (95% CI). Subjects given cod liver oil were considered to have been supplemented with vitamin D in line with previous publications<sup>13 21 22</sup>.

### Search strategy

We systematically searched Medline (1966–June 2007), Embase (1980–June 2007), Cinahl (1982–June 2007), and the Cochrane Central Register of Controlled Trials (Issue 2, 2007) for both English and non-English language articles by entering “vitamin D”, “vitamin D2”, “vitamin D3”, “ergocalciferol”, “alfacalcidol”, “alphacalcidol”, “hydroxycholecalciferol”, “calcitriol”, “dihydroxycholecalciferol”, “colecalciferol”, “cholecalciferol”, and “diabetes”. No limits were used.

We then searched the reference lists of all relevant articles retrieved from the computerised database search to find other potentially relevant articles. The titles and/or abstracts of all identified studies were reviewed and full manuscripts obtained for those that appeared potentially relevant.

### Assessment of study eligibility

Each article was independently assessed by two reviewers for eligibility using the inclusion criteria above. Any disagreement among reviewers was discussed and agreement reached by consensus.

### Assessment of methodological quality

Two investigators independently rated the methodological quality of selected studies using the Critical Appraisal Skills Programme (Oxford, UK) tool for case-control studies<sup>23</sup>. We recorded each quality assessment criterion as being “met”, “unmet”, or “unclear”. However, as several criteria were used to assess validity, these were summarised to derive an overall assessment of how valid the results of each study were by grading them as A (low risk of bias), B (moderate risk of bias), or C (high risk of bias) according to published criteria<sup>24</sup>.

### Data extraction

A data abstraction form was developed and used to extract information on relevant features and results of included studies. Two reviewers independently extracted and recorded data using a predefined checklist. When data were missing or unclear in a paper, attempts were made to contact the authors for more information.

### Statistical methods

Statistical analyses were performed using StatsDirect statistical software (version 2.6.1). Individual OR and their 95% CI from each case-control study were calculated. Where possible, a pooled OR with 95% CI was calculated. The meta-analysis was conducted using the Mantel-Haenszel method<sup>25</sup>.

## Heterogeneity

The statistical validity of combining the results of the various trials was assessed by examining the homogeneity of the outcomes from the various trials. This was carried out by: (1) using the Cochran Q test; and (2) inspection of the graphical display.

## RESULTS

We identified 19 potentially relevant articles<sup>3 13 17 19-22 26-37</sup> on the association between vitamin D supplementation and the development of type 1 diabetes (Figure 1). Five studies were identified that satisfied the inclusion criteria and these were included in the review<sup>13 20-22 26</sup>. Four of them were case-control studies<sup>20-22 26</sup> and one a cohort study<sup>13</sup>. No randomised control trials were identified. The study by Littorin et al.<sup>17</sup> was excluded because it did not compare rates in those exposed or not supplemented with vitamin D, but rather the levels of vitamin D over time in those with type 1 diabetes. The study by Visalli et al.<sup>36</sup> was excluded because it did not provide enough data for construction of a 2 by 2 table to determine OR and despite repeated attempts to get more information from the authors this proved unsuccessful

## Methodological quality of included studies

Due to the retrospective design, all the case-control studies were prone to recall bias. All of the included case-control studies except the one by Tenconi et al.<sup>26</sup> used healthy children whose non-diabetic status was not specifically confirmed. However, as type 1 diabetes is unlikely to be asymptomatic for a long period of time, the possibility of misclassification for some controls is small. Most case-control studies used cases up to 15 years of age<sup>20-22</sup>, but Tenconi et al.<sup>26</sup> used higher cut-offs (30 years). None of the case-control studies included used an objective method to ascertain the vitamin D status of cases or controls, and none attempted to quantify the total amount of vitamin D intake from the diet or that from exposure to the sun. In addition, none of the studies looked at the ethnic backgrounds of cases vs. controls. A summary of the methodology of the included case-control studies is shown in Table 1.

Reference (Country)	Case Selection	Control Selection	Exposure Measurement	Confounding factors considered	Sample size	Age (years)
Stene et al. (2000) <sup>21</sup> (Norway, Vest-Agder)	National Childhood Diabetes Register (NCDR)	Random selection from official population register	Questionnaire	Age, sex, duration of exclusive breastfeeding, maternal education, maternal use of vitamin D supplements in pregnancy	78 cases 980 controls	Cases: mean 11.1, SD 3.6 Controls: mean 8.5, SD 4.7
EURODIAB <sup>20</sup> Austria	NCDR	Random sample from schools	Questionnaire	Combined results adjusted for age, sex, low birth weight, short duration of breast feeding, maternal age, and study centre	95 cases 346 controls	Not specified
Bulgaria	NCDR	Random sample from schools and polyclinics	Interview		126 cases 430 controls	Not specified

Latvia	NCDR	Population register	Interview		109 cases 293 controls	Not specified
Lithuania	NCDR	Random sample from polyclinics	Questionnaire		111 cases 250 controls	Not specified
Luxembourg	NCDR	Random sample from preschools and schools	Interview		55 cases 176 controls	Not specified
Romania	NCDR	Random sample from health service register	Interview		82 cases 276 controls	Not specified
Northern Ireland	NCDR	General Practitioner register	Questionnaire		168 cases 419 controls	Not specified
Stene et al. (2003) <sup>22</sup> Norway	NCDR	Random selection from population	Questionnaire	Age, sex, breastfeeding, maternal age, education, and smoking during pregnancy, time of weaning, number of siblings, family history of type 1 diabetes	545 cases 1668 controls	Cases: mean 10.9, SD 3.4 Controls: mean 9.3, SD 4.1
Tenconi et al. <sup>26</sup> (Italy, Pavia Province)	NCDR	Random selection from non-diabetic hospitalised patients	Interview	Age, sex, residency, family history of type 1 diabetes, drugs taken during pregnancy, type of delivery, early feeding, neonatal and most common childhood diseases, history of surgical operations, severe infections	159 cases 318 controls	Cases: mean 23.24, SD 9.36 Controls: mean 23.38, SD 9.64

The methodological quality of each study was summarised using the categories described above. All case-control studies included were graded “B”. The cohort study<sup>13</sup> was graded “B” because it did not use an objective method of assessing the vitamin D status of cases/controls and because no mention of blinding to the outcomes was mentioned. Furthermore, although a fair number of confounding factors were accounted for, some important ones were not e.g. duration of breastfeeding and age at weaning.

## Association between vitamin D supplementation and type 1 diabetes

### Ever supplemented versus never supplemented

Three of the included case-control studies<sup>20 21 26</sup> provided enough data on the risk of developing type 1 diabetes in infants who were supplemented with vitamin D versus those not being supplemented, to allow a meta-analysis to be performed on this variable. After contacting the authors of the final case-control study<sup>22</sup> enough information was provided to allow inclusion of this study in the meta-analysis. For the EURODIAB study<sup>20</sup> we followed the example of the authors and used each centre as a separate entry to account for the heterogeneity between centres but also to aid in the assessment of heterogeneity in the global sample. The total number of participants in included studies was 6455 (1429 cases and 5026 controls). In the main analysis using the fixed effects model (Figure 2), the risk of developing type 1 diabetes was significantly reduced in participants who were supplemented with vitamin D (OR 0.71, 95% CI 0.60 to 0.84). The results of these studies appeared to be reasonably homogeneous and the test for heterogeneity was negative ( $p=0.13$ ).

The result of the meta-analysis is in agreement with the main outcome from the cohort study<sup>13</sup>. In the latter study, the rate risk for regular vs. no supplementation was 0.12 (95% CI 0.03-0.51) and for irregular vs. no supplementation 0.16 (95% CI 0.04-0.74).

### Type of supplement used

There were not enough data in the primary studies to allow comparison of the groups based on this variable.

### Dosage of supplementation

In the majority of studies no information is given about the dosage of supplements used. Stene et al. (2003)<sup>22</sup> speculate that the cod liver oil and the different vitamin D supplements used in Norway at the time in question, would contain 10 $\mu$ g of vitamin D. They divide their patients into those that had taken cod liver oil and those that had "other" forms of vitamin D. Concentrating on the group that had the cod liver oil, one can see that as the frequency of supplementation increases from 1-4 times per week to more than 5 times per week, the OR of developing type 1 diabetes decreases (OR 0.81, 95% CI 0.55-1.19 and OR 0.74, 95% CI 0.56-0.99 respectively). There is a negligible change in OR in those that had the "other" types of vitamin D supplement (OR 0.99, 95% CI 0.69-1.42 and OR 0.97, 95% CI 0.73-1.29 respectively).

There is evidence from the Hypponen study<sup>13</sup> that those who used the recommended dose of 2000 IU regularly had a RR of 0.22 (95% CI 0.05-0.89) compared with those who regularly used less than the recommended dose. Furthermore, the authors showed that with an increase in regularity of supplementation as well as dose used, the incidence of type 1 diabetes tended to decrease<sup>13</sup>. Finally, they report that those with suspected rickets had an increased risk of developing type 1 diabetes, although the result is not statistically significant (RR 3.0, 95% CI 1.0-9.0).

### Duration of supplementation

Only the EURODIAB study<sup>20</sup> considered duration of supplementation as a factor. Although there was some improvement in the OR they did not find any significant difference between those that were supplemented for less than a year (OR 0.69, 95%

CI 0.52-0.93) and those that were supplemented for more than a year (OR 0.64, 95% CI 0.47-0.89).

#### Timing of supplementation

Stene et al.(2003)<sup>22</sup> is the only one of the identified studies that looked at the effect of the time of starting the supplementation with vitamin D. It appears that those who had the cod liver oil between 7-12 months had lower chances of developing type 1 diabetes in later life compared to those who were supplemented between 0-6 months (OR 0.55, 95% CI 0.31-0.96 and OR 0.80, 95% CI 0.61-1.06 respectively). A similar, albeit less impressive result was obtained for the “other” vitamin D supplements (OR 0.98, 95% CI 0.65-1.49 and OR 1.02, 95% CI 0.77-1.35 respectively).

## DISCUSSION

The results of this study suggest that vitamin D supplementation in infancy may offer protection against the development of type 1 diabetes. Meta-analysis of data from four studies, which included children from many different European countries, indicated that children being supplemented had a 29% reduction in risk of developing type 1 diabetes compared with their peers who were not. The reduction in risk was also demonstrated in a cohort study<sup>13</sup>. The study by Stene et al. (2003)<sup>22</sup> reported no association between vitamin D supplementation and subsequent diabetes development. Although it was not clear in the paper how many of these patients used both vitamin D and cod liver oil and how many used none of the two, we managed to obtain this information by contacting the authors, something that allowed inclusion of the study in the meta-analysis. Some studies were not able to show an association with a reduction in risk of type 1 diabetes<sup>21 36</sup>, but none of them were associated with an increased risk.

Furthermore, there is evidence of a dose-response effect. The cohort study<sup>13</sup> showed that those that had rickets diagnosed earlier in life (and were thus more likely to be the ones with the lowest amounts of vitamin D) were more likely to develop type 1 diabetes. In addition, those that were supplemented more regularly or had higher doses of vitamin D supplements, displayed a reduced risk of developing type 1 diabetes. The positive findings with increasing frequency of use were also confirmed in one of the case-control studies<sup>22</sup> that looked at this variable.

One of the included studies<sup>22</sup> suggests that supplementation from 7-12 months of age is more beneficial than supplementation from birth to 6 months. However, the former could be a marker of longer supplementation. At the same time, infants of mothers who are themselves vitamin D deficient would be at an increased risk of hypocalcaemic complications in the first few months of life<sup>14</sup>, something that would necessitate earlier supplementation. Finally, there are many unexplored variables including an overall lack of accurate, reliable feeding information which could explain this observation.

The exact mechanism by which vitamin D supplementation protects against type 1 diabetes is unclear but it has been suggested that this is likely to be through the prevention of hypovitaminosis D<sup>27</sup>. The identification of receptors for the active form of vitamin D in both  $\beta$  cells and immune cells<sup>27</sup> has led to a number of studies for the delineation of these pathways. There is evidence for a physiological role for vitamin

D in the immune system, and also for a protective effect of the vitamin from cytokine-induced beta cell dysfunction<sup>27</sup>.

#### Strengths and weaknesses of the study

Our review included studies from many European countries and included 4 case-control studies and a cohort study. We searched multiple databases and reference lists to minimise the chance of missing relevant studies. We minimised subjectivity by carrying out study selection, data extraction, and quality assessment in duplicate. However, the validity of the results of a systematic review depends on the validity of the included studies. Many of the included studies failed to take all the steps necessary to avoid bias. Our conclusions were, therefore, limited by the quality of included studies and the information provided.

The included case-control studies are subject to recall bias. If, for instance, parents of children with type 1 diabetes could recall more accurately that their children were not supplemented with vitamin D in infancy, bias could result which would tend to inflate the association in favour of supplementation. Furthermore, none of the case-control studies included used an objective method to ascertain the vitamin D status of cases or controls, and none attempted to quantify the total amount of vitamin D intake from the diet or that from exposure to the sun. In addition, use of healthy controls without prior checking of non-diabetic status could lead to some misclassification. Case-control studies are also susceptible to bias because other risk factors of type 1 diabetes could be unbalanced across children who were supplemented and those who were not with breastfeeding being an obvious example. Some of the included studies<sup>20-22, 26</sup> made an attempt to control for breastfeeding (<3 months) but no information is given about volumes of formula milk consumed and amount of vitamin D in the formula milk. While the individual studies tried to control for a number of potential confounding factors it is possible that a number of other confounding factors could have been unbalanced across children who were supplemented and those who were not. Finally, we considered those that used cod liver oil as a supplement to be similar to those receiving other forms of vitamin D. This could lead to erroneous conclusions as cod liver oil contains other components that could be protective against type 1 diabetes.

#### CONCLUSION

In conclusion, there is evidence from observational studies that vitamin D supplementation in infancy might be protective against the development of type 1 diabetes. Despite limitations, the Hill criteria for causality<sup>38</sup> seem to be fulfilled. However, for concrete conclusions to be reached, adequately powered, randomised controlled trials with long periods of follow-up would be required to establish causality and the best formulation, dose, duration and period of supplementation.

**Contributors:** CSZ (guarantor) and AKA were both responsible for study selection, data extraction, validity assessment, data interpretation, and writing the paper.

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**Competing interests:** None

**Ethical approval:** Not required.

### **Figure Legends**

Figure 1. Flow chart of studies through the review process.

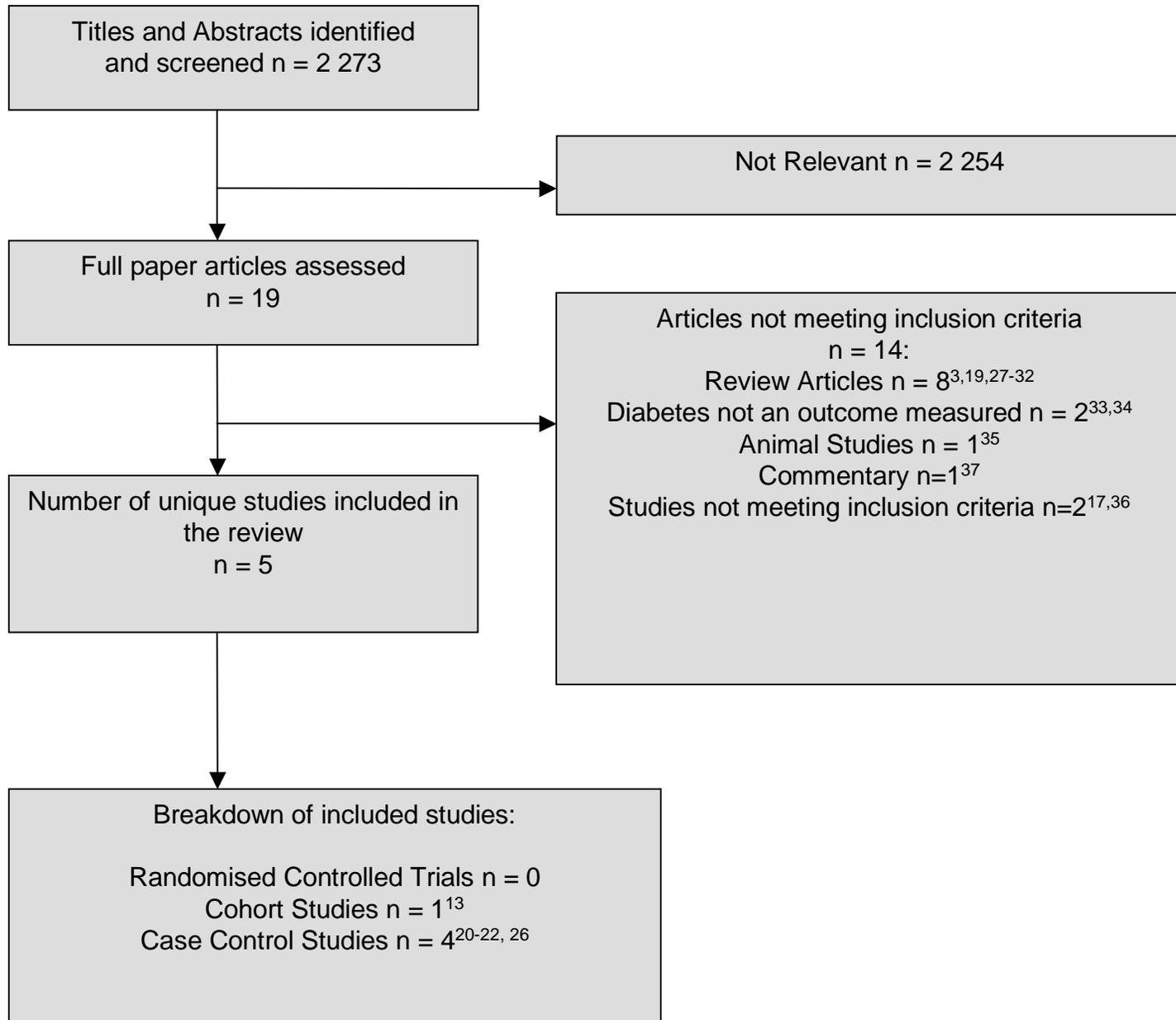
Figure 2. Odds ratios (95% CI) of effect of vitamin D supplementation in infancy on development of type 1 diabetes.

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### Odds ratio meta-analysis plot [fixed effects]

