

## Investigating the Effects of Vitamin D Supplementation on Triglyceride Levels in Obese Children Candidates for Surgery: A Systematic Review and Meta-Analysis

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### Abstract:

**Background and Objective:** There is a known relationship between cardiovascular diseases and low levels of vitamin D. Previous studies on the effects of vitamin D supplementation on triglyceride levels, a key indicator of cardiovascular health, have shown conflicting results. This study aims to summarize the findings of these studies. The purpose of this systematic review and meta-analysis is to investigate the effects of vitamin D supplementation on triglyceride levels in obese children who are candidates for surgery.

**Materials & Methods:** This study was conducted following the PRISMA statement guidelines. Databases searched included Scopus, Mag Iran, SID, Web of Science, PubMed, and Embase for randomized clinical trial studies published up to the end of 2021. Both Farsi and English studies were included. Search keywords were: cholesterol, triacylglycerol, triglyceride, heart risk, metabolic syndrome, child, adolescent, student, school, school age, childhood, vitamin D, 25-hydroxy vitamin D.

**Results:** The meta-analysis revealed no significant difference in triglyceride levels at the end of the study compared to the beginning (MD = 5.23-2.92 mg/dl, 95% CI: 59%, I<sup>2</sup> = 0.21-2.92, P). However, high levels of vitamin D supplementation (more than 200,000 units during the treatment period) led to a significant decrease in triglycerides (MD = -5.08 mg/dl, 95% CI: -83.00 to -4.15, I<sup>2</sup> = 64%, P = 0.31).

**Conclusion:** High levels of vitamin D supplementation significantly decrease triglyceride levels in obese children who are candidates for surgery compared to lower levels of supplementation.

**Keywords:** Vitamin D, Obesity, Child, Triglyceride, Surgery

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Received: 12/06/2024

Accepted: 16/04/2025

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## Background and Objective

Cardiovascular diseases, which may initiate as early as childhood, are increasingly acknowledged as one of the leading causes of mortality worldwide. Vitamin D deficiency is prevalent across all age demographics globally and has been linked to a higher incidence of cardiovascular diseases in adults, as well as increased cardiac metabolic risk factors in children.<sup>1,2</sup> Despite observational studies indicating a significant association between vitamin D deficiency and cardiovascular disease risk,<sup>3,4</sup> a meta-analysis of randomized controlled trials has found no protective effect of vitamin D deficiency on cardiovascular health in adults.<sup>5</sup>

Given that elevated triglyceride levels are a well-established risk factor for cardiovascular diseases, which often persist from childhood into adulthood and are associated with the development of atherosclerosis, there is a growing interest in evaluating the effects of vitamin D supplementation on metabolic cardiac risk markers, including triglyceride levels, in children and adolescents.<sup>6,7</sup>

An increasing number of randomized controlled trials have investigated the impact of vitamin D supplementation on cardiac metabolic risk profiles, particularly triglyceride levels within these populations. However, the findings to date have been inconsistent and inconclusive.<sup>8</sup> A recent meta-analysis did not corroborate the effectiveness of vitamin D supplementation for enhancing cardiovascular metabolic health during childhood.<sup>9</sup> Notably, approximately one-third of the control groups in the studies incorporated into this meta-analysis also received vitamin D supplementation, potentially undermining the validity of its conclusions.

Given the established relationship between low vitamin D levels and cardiovascular diseases, alongside the inconclusive data concerning the impact of vitamin D supplementation on triglyceride levels—a primary indicator of cardiovascular disease risk—this study seeks to consolidate findings from prior research. The objective of

this systematic review and meta-analysis is to evaluate the effects of vitamin D supplementation on triglyceride levels in obese children who are candidates for abdominal surgery.

## Materials and Methods

### Study Design

This investigation is structured as a systematic review and meta-analysis, conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

### Search Strategy

A comprehensive search strategy was implemented across several databases, including Scopus, Magiran, SID, Web of Science, PubMed, and Embase, to identify published randomized clinical trials up to the conclusion of 2021, without imposing any date restrictions. The search was executed in both Persian and English. The keywords employed in the search included: cholesterol, triglyceride, cardiovascular risk, metabolic syndrome, child, adolescent, student, school-age, childhood, vitamin D, 25-hydroxy vitamin D, surgery, elective surgery, surgery candidate, laparotomy, abdominal surgery, and non-emergency abdominal surgery. These keywords were utilized within the specified databases, employing Boolean operators to refine the search. In order to maximize the yield of relevant articles, the reference lists of each identified paper were meticulously reviewed to ensure that no pertinent studies were overlooked. It is important to highlight that the specified keywords were searched using Boolean operators (AND, OR, NOT). Two researchers independently conducted the search to minimize potential misunderstandings regarding the identified studies, with the name of one researcher documented as agreed upon for this study.

### Study Selection Criteria and Eligibility

Studies included in this analysis were selected according to specific criteria:

Participants must have been children and adolescents under the age of 18 who were candidates for elective abdominal surgeries. The intervention must have involved oral vitamin D supplementation, and the control group should not have included participants receiving a placebo containing vitamin D. Furthermore, all studies needed to be randomized controlled trials (RCTs) conducted prospectively. Studies that failed to meet these RCT criteria, lacked a control group, did not adhere to a prospective design, or reported outcomes solely at conferences, seminars, or in student theses were excluded from this review.

### Data Extraction

An electronic data extraction form was devised utilizing Excel to systematically collect pertinent information from each study. The extracted data encompassed the following variables: the name of the first author, year of publication, study location, sample sizes for both the intervention and control groups, participants' ages, treatment dosage, duration of follow-up, timing of endpoints, and mean changes in triglyceride levels and body mass index from the commencement to the conclusion of the study.

### Quality Assessment of Articles

The quality of the studies included in this systematic review and meta-analysis was evaluated for publication bias utilizing the Cochrane Risk of Bias Tool.<sup>11</sup> This assessment examined factors such as random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, completeness of outcome data, selective reporting, and other potential biases. Each of these components was categorized as exhibiting a "low risk," "high risk," or "unclear risk."

### Data Analysis

Data analysis was conducted using Review Manager software. Continuous data were analyzed by calculating the mean difference (MD) along with a 95% confidence

interval. Heterogeneity among studies was assessed utilizing the  $I^2$  statistic. Mixed-effects meta-regression analyses were performed to explore potential moderators of heterogeneity, including sample size, mean age, follow-up duration, and total dosages of vitamin D supplements. A funnel plot was employed to investigate publication bias. Statistical significance for all tests was established at  $P < 0.05$ .

### Findings

This meta-analysis encompassed a total of 11 studies involving 954 participants; however, gender data was not reported in two of these studies. The research demonstrated geographical diversity, with four studies conducted in the United States, three in Iran, two in Denmark, one in Saudi Arabia, and one in Argentina. The timeframe for publication of the included articles ranged from 2013 to 2020. In the control groups, no medication was administered, whereas participants in the intervention groups received vitamin D supplementation at varying doses ranging from 400 to 1,000 units per day.

Table 1 provides a comprehensive overview of the studies analyzed in this systematic review and meta-analysis, while Figure 1 illustrates the assessment of bias across these articles. It is noteworthy that six studies lacked clear descriptions regarding random sequence generation and allocation concealment, indicating an unclear risk of selection bias. Additionally, two studies did not provide sufficient information regarding random sequence generation or allocation concealment, further suggesting an unclear risk of selection bias. One study exhibited a high risk of bias related to both random sequence generation and allocation concealment. Furthermore, three studies failed to explicitly describe the blinding process in outcome assessments, which suggests an unclear risk of detection bias. In contrast, the remaining studies exhibited a low risk of performance bias, detection bias, and attrition bias.

**Table 1 - Summary of articles included in this systematic review and meta-analysis**

<b>Author/Year/Country</b>	<b>Age</b>	<b>Gender Girl/Boy</b>	<b>Body Mass Index</b>	<b>Sample Volume</b>	<b>Intervention</b>	<b>Control</b>	<b>Total Drug Dose</b>
<i>Al-Daghri/2019/ Saudi Arabia<sup>10</sup></i>	12 to 18 years old	Boy: 150 Girl: 196	21-25	Intervention group: 180 Control group: 166	1000 units per day for six months	Placebo	Three months
<i>Hauger/2018/ Denmark (A)<sup>11</sup></i>	4 to 8 years old	Boy: 37 Girl: 42	23-26	Intervention group: 38 Control group: 41	400 units per day for 20 weeks	Placebo	Six months
<i>Hauger /2018/ Denmark (B)<sup>12</sup></i>	4 to 8 years old	Boy: 38 Girl: 43	20-25	Intervention group: 40 Control group: 41	400 units per day for 20 weeks	Placebo	Six months
<i>Hirschler /2013/ Argentina<sup>13</sup></i>	8 to 12 years old	Boy: 46 Girl: 44	21-24	Intervention group: 70 Control group: 20	5000 units per week for 8 weeks	Placebo	Four months
<i>Nader /2014/ USA<sup>14</sup></i>	12 to 18 years old	Boy: 15 Girl: 29	20-27	Intervention group: 20 Control group: 24	2000 units per day for 12 weeks	Placebo	Six months
<i>Smith/2018/ USA (A)<sup>15</sup></i>	14 to 18 years old	Boy: 31 Girl: 43	21-26	Intervention group: 35 Control group: 39	400 units per day for 20 weeks	Placebo	Six months
<i>Smith/2018/ USA (B)<sup>16</sup></i>	14 to 18 years old	Boy: 32 Girl: 43	21-25	Intervention group: 36 Control group: 39	800 units per day for 20 weeks	Placebo	Six months
<i>Kelishadi /2014/ Iran<sup>17</sup></i>	10 to 16 years old	Not mentioned	20-23	Intervention group: 21 Control group: 22	5000 units per week for 6 weeks	Placebo	Three months
<i>Kolachahi /2020/ Iran<sup>18</sup></i>	6 to 14 years old	Boy: 20 Girl: 0	22-27	Intervention group: 10 Control group: 10	5000 units per week for 10 weeks	Placebo	Six months
<i>Shah /2015/ USA<sup>19</sup></i>	11 to 18 years old	Not mentioned	20-27	Intervention group: 14 Control group: 17	150 thousand units every 12 weeks for 24 weeks	Placebo	12 months
<i>Yarparvar /2020/ Iran<sup>20</sup></i>	17 years old	Boy: 71 Girl: 0	22-26	Intervention group: 24 Control group: 37	50,000 units per month for 6 months	Placebo	Six months

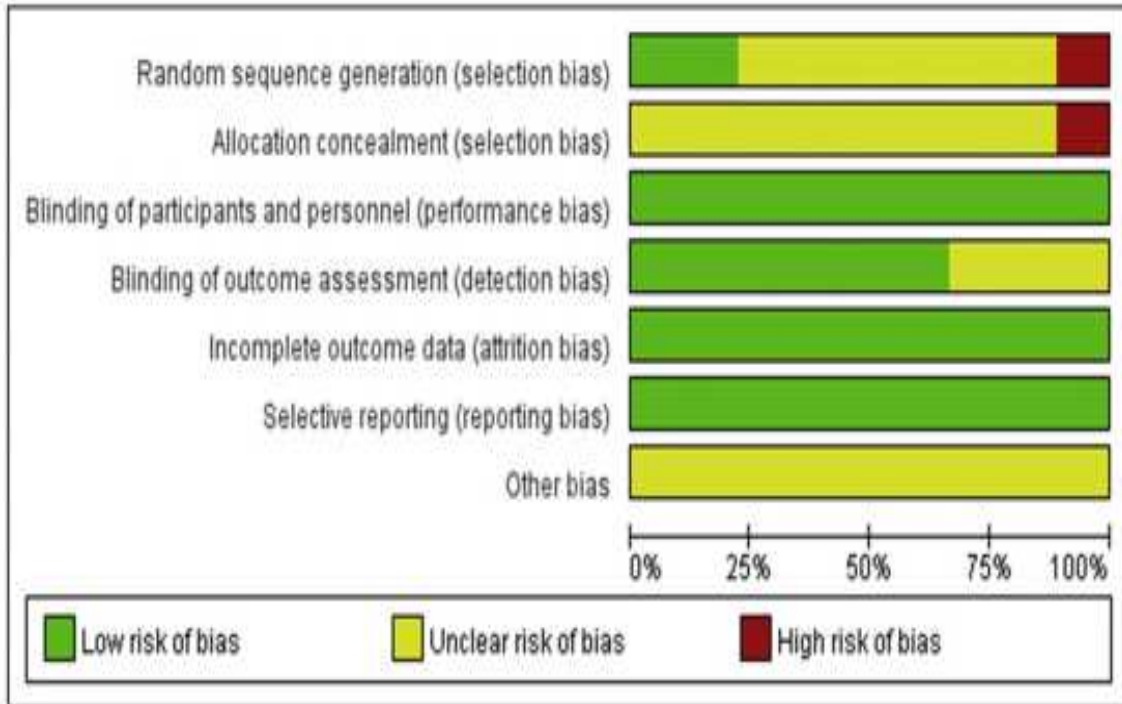


Figure 1 - Risk of bias assessment of articles included in this systematic review and meta-analysis article

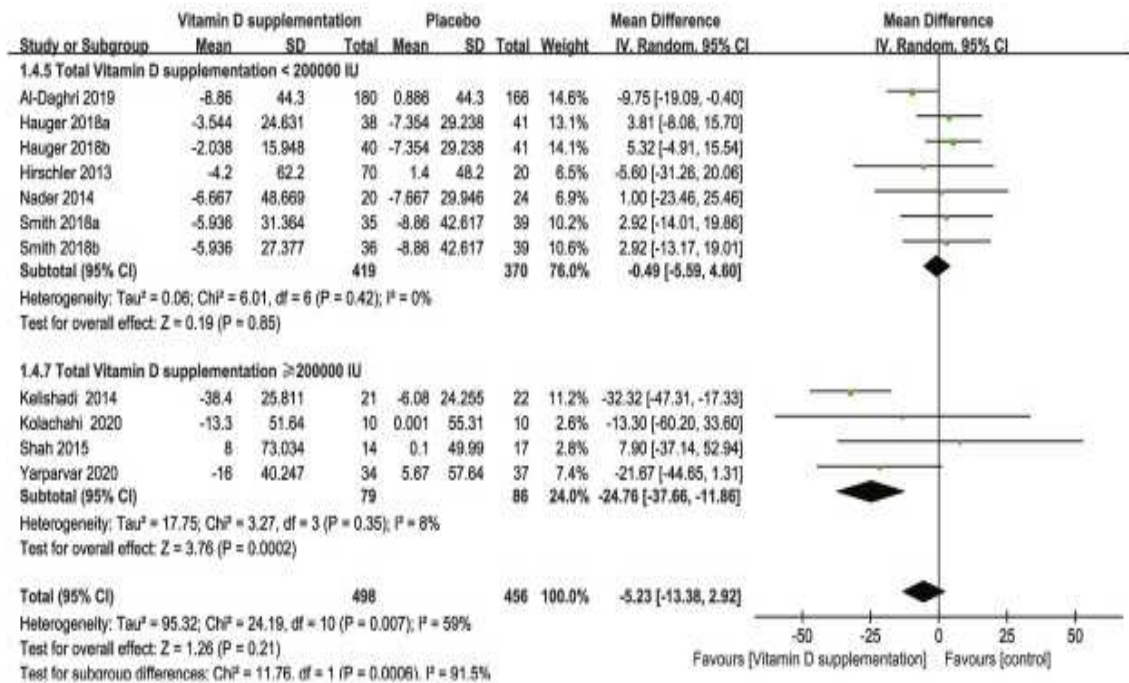
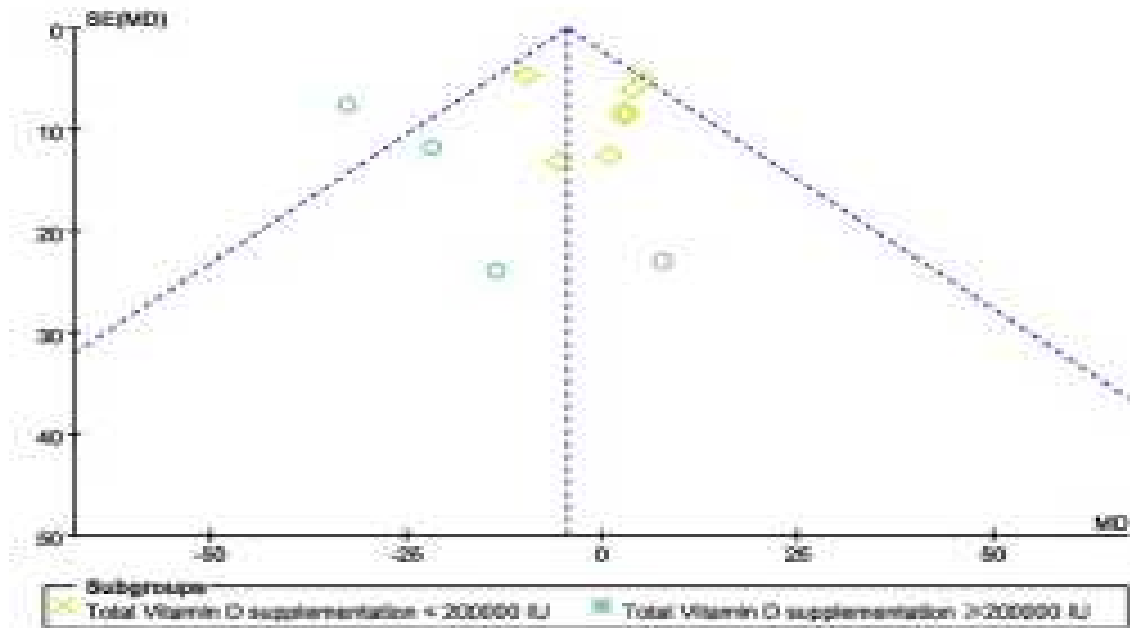


Figure 2 - Forest plot showing changes in triglycerides before and after intervention



**Figure 3 - Funnel diagram to show the publication bias of studies included in this systematic review and meta-analysis article**

The analysis revealed no significant difference in triglyceride levels from the beginning to the end of the study (mean difference (MD) = -5.233 mg/dl; 95% confidence interval (CI) = -132.921 to -2.2;  $I^2 = 59\%$ ;  $P = 0.210$ ). However, it was observed that elevated levels of vitamin D (exceeding 200,000 units during the treatment period) were associated with a reduction in triglyceride levels (MD = -5.081 mg; 95% CI = -15.830 to -4.0;  $I^2 = 64\%$ ;  $P < 0.311$ ).

The results of the meta-analysis, as depicted by the forest plots, further corroborated that there was no significant difference in mean triglyceride levels from the beginning to the end of the study (MD = -5.233 mg/dl; 95% CI = -132.921 to -2.2;  $I^2 = 59\%$ ;  $P = 0.210$ ). A meta-regression analysis was conducted to identify potential factors (sample size, duration of follow-up, mean age, and total dose of vitamin D supplements) that might account for the observed high heterogeneity in the meta-analysis.

The findings indicated that the total dose of vitamin D supplementation served as a significant moderator ( $P < 0.01$ ), demonstrating that higher vitamin D levels (greater than 200,000 units) correlated with decreased triglyceride levels (MD = -5.081 mg; 95% CI = -15.830 to -4.0;  $I^2 = 64\%$ ;  $P < 0.311$ ). Conversely, factors such as sample size ( $P = 0.87$ ), duration of follow-up ( $P = 0.250$ ), and mean age ( $P = 0.211$ ) did not serve as significant moderators (Figure 2).

Finally, publication bias was analyzed and represented in the accompanying funnel plot, indicating no evidence of publication bias within the studies reviewed.

## Discussion

The findings of the present study elucidate that high-dose vitamin D supplementation significantly decreases triglyceride levels in obese children preparing for surgery, particularly when compared to lower doses. We categorized vitamin D supplementation as either below

or above 200,000 units over a one-month period, and our results indicate that doses exceeding 200,000 units were associated with a marked reduction in triglyceride levels.

In recent years, there has been an increasing interest in the role of vitamin D in cardiovascular health and its potential influence on the risk of cardiovascular diseases. Several systematic reviews and meta-analyses have evaluated the effects of vitamin D supplementation on cardiovascular metabolic health.<sup>21,22</sup> For instance, a meta-analysis of randomized controlled trials involving patients with type 2 diabetes reported no significant effect of vitamin D-containing supplements on reducing blood glucose or insulin levels.<sup>23</sup> Similarly, another systematic review examining patients with gestational diabetes revealed that while vitamin D supplements positively affected serum LDL cholesterol, they did not demonstrate significant benefits for triglyceride and HDL levels.<sup>24</sup>

Two primary factors may influence the efficacy of vitamin D supplementation on metabolic markers: the baseline vitamin D status of participants and the strategies employed for vitamin D supplementation. A prior meta-analysis identified an inverse relationship between serum 25-hydroxy vitamin D levels and systolic blood pressure; however, it did not establish a consistent connection between vitamin D status and lipid profiles or insulin/glucose metabolism in children.<sup>25</sup> Furthermore, another meta-analysis indicated a relatively weak inverse correlation between triglyceride levels and vitamin D in children and adolescents. These findings underscore the importance of considering baseline vitamin D status when

evaluating the impact of supplementation on cardiac metabolic risk markers.<sup>26</sup>

Vitamin D plays a pivotal role in the differentiation of mesenchymal stem cells into adipocytes, with adequate vitamin D levels during early development promoting the maturation of pre-adipocytes into myocytes. Research involving murine models has demonstrated that offspring of mothers on a vitamin D-deficient diet exhibited larger visceral fat layers and an increased susceptibility to diet-induced fat hypertrophy. Additionally, this study revealed heightened expression of peroxisome proliferator-activated receptor gamma in visceral adipose tissue— a receptor known to regulate adipogenesis and fat storage.<sup>14</sup>

While the inclusion of studies with control groups receiving no vitamin D supplementation enhances the robustness of our findings, it is important to acknowledge the limitations of our research. Variability in sample sizes, differences in the ages of the children included, and discrepancies in treatment duration may compromise the quality of the results.

## Conclusion

Numerous factors influence triglyceride levels in obese children, among which vitamin D levels are notably significant. Our study suggests that the administration of high levels of vitamin D supplementation leads to a substantial reduction in triglyceride levels within this population. However, due to the observed heterogeneity among the studies, caution is warranted in extrapolating these results to clinical practice. Further research is required to establish standardized guidelines for vitamin D supplementation in obese children at risk of cardiovascular complications.

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