MEDICAL SCIENCE MONITOR

META-ANALYSIS

e-ISSN 1643-3750
© Med Sci Monit, 2022; 28: e935823
DOI: 10.12659/MSM.935823

Received: 2021.12.14
Accepted: 2022.04.14
Available online: 2022.04.27
Published: 2022.05.25

Effect of the COVID-19 Pandemic on Serum Vitamin D Levels in People Under Age 18 Years: A Systematic Review and Meta-Analysis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF 1 Xian Cui*
CE 2 Yuhang Zhai*
BF 1 Shuai Wang
E 1 Ke Ding
E 1 Zhenya Yang
D 1 Yan Tian
D 1 Tingting Huo

1 Department of Ultrasound, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, PR China
2 College of Sciences and Mathematics, Auburn University, Auburn, AL, USA

* Xian Cui and Yuhang Zhai contributed equally to this work

Corresponding Author: Xian Cui, e-mail: pipettor@163.com
Financial support: None declared
Conflict of interest: None declared

Background: During the COVID-19 pandemic the implementation of a range of measures to suppress transmission, such as social distancing and home confinement resulted in limited sunlight exposure and physical inactivity in people under age 18 years, which can elevate the risk of vitamin D deficiency and insufficiency. The aim of this study was to systemically evaluate the effect of the COVID-19 pandemic on serum vitamin D levels in people under age 18 years.

Material/Methods: Following the PRISMA recommendations, we searched PubMed, Embase, and the Cochrane Database for trials from inception to November 3, 2021. All trials assessing the effects of the COVID-19 pandemic on serum vitamin D levels in people under age 18 years were included and analyzed. Mean differences (MDs) of serum 25-hydroxyvitamin D (25[OH] D) levels before and during the COVID-19 pandemic were calculated and pooled using a random-effects model. Risk differences were used to assess changes in the proportions of people under age 18 years with vitamin D deficiency.

Results: Our analysis included 5 studies comprising 4141 people under age 18 years. The combined result MD of serum 25(OH)D levels before and during the COVID-19 pandemic as 3.28 ng/mL, 95% CI=0.95-5.62 ng/mL, $P<0.01$] indicated serum 25(OH)D levels were significantly lower during the COVID-19 pandemic. The decreased serum 25(OH)D level was not observed among infants (age under 1 year) ($P=0.28$).

Conclusions: During the COVID-19 pandemic, the serum vitamin D levels of people under age 18 years were significantly lower and vitamin D supplementation for people under age 18 years might reduce the risk of COVID-19. More research is needed to validate the present findings.

Keywords: Vitamin D Deficiency • Meta-Analysis • COVID-19

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/935823

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Background

The epidemic of coronavirus disease 2019 (COVID-19) is currently having a damaging impact on almost all countries around the world. Characterized by an approximately 2% mortality rate and the absence of medical countermeasures, COVID-19 remains a major public health threat globally [1,2]. Vitamin D is a steroid hormone essential in regulating body levels of calcium and phosphorus and mineralization of bones [3,4]. Insufficient levels of serum vitamin D are strongly associated with various diseases, including total cancer incidence, diabetes, and infectious diseases [5,6].

A growing body of circumstantial evidence shows an association of COVID-19 with serum vitamin D levels [7,8]. COVID-19 incidence and mortality were found to be strongly associated with vitamin D status in various populations [9]. Similar associations were also seen in children [10]. Since late December 2019, governments from various countries have implemented a series of measures to control the COVID-19 pandemic, such as social distancing and home confinement, which potentially limit sunlight exposure or physical activity of children. A main source of acquiring vitamin D is sunlight exposure. Several studies reported an elevated risk of vitamin D deficiency among COVID-19-negative children [12,13]. Although the COVID-19 pandemic has been reported to significantly affect serum vitamin D levels in children, it has not been systemically summarized.

In this study, we aimed to systemically evaluate the effect of the COVID-19 pandemic on serum vitamin D levels in people under age 18 years.

Material and Methods

Literature Search

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [14] guidelines for the trial identification, data extraction and integrity, assessment of bias, and sensitivity analyses. We searched PubMed, Embase, and the Cochrane Database for eligible publications from inception to November 3, 2021. We used the following keywords and phrases: "COVID-19", "coronavirus disease 2019", "SARS-CoV-2", "severe acute respiratory syndrome coronavirus 2", "vitamin D", "25-Hydroxyvitamin D 2", "child", "infants", and "pediatric". Detailed search strategies for each database can be found in the **Supplementary Material**. To include more studies, we also examined the reference lists of relevant studies.

Eligibility Criteria

The inclusion criteria were: (1) studies investigating the serum vitamin D levels of participants before and during the COVID-19 pandemic; (2) study population aged <18 years and did not receive vitamin D supplementations or any other medications; (3) study population was COVID-19-negative; (4) studies published in English.

Exclusion criteria were: (1) letters, case reports, reviews, animal experiments, and expert opinions; (2) studies that included outpatients or asymptomatic COVID-19 patients; (3) studies published in languages other than English; (4) duplicate publications.

Definitions of Vitamin D deficiency and Insufficiency

Because vitamin D is converted by 25-hydroxylase to 25-hydroxyvitamin D [25(OH)D] in the liver, serum vitamin D was defined as serum 25(OH)D concentrations. Following the Endocrine Society's Clinical Practice Guideline [15], we defined vitamin D deficiency, insufficiency, and sufficiency according to serum concentrations of 25(OH)D <20 ng/mL (<50 nmol/L), 21-29 ng/mL (51-74 nmol/L), and 30-100 ng/mL (75-250 nmol/L), respectively.

Data Extraction

Two authors (XC and SW) independently screened the studies retrieved form the above-mentioned databases for eligible studies following the inclusion criteria. Necessary information was independently extracted by the 2 authors using a customized and standardized form. Any discrepancy was resolved by discussion with the third author (TTH).

For included studies, the following information was extracted: the first author, publication year, country, mean ages and proportions of males of the study population, sample size, definition of COVID-19 pandemic period, and serum vitamin D levels before and during the COVID-19 pandemic.

Quality Scoring of Studies

Two reviewers (XC and SW) independently assessed study quality using the Newcastle-Ottawa Scale (NOS) [16], a risk of bias assessment tool for observational studies. Using this tool, 3 domains were assessed: (1) selection of study population (4 items); (2) comparability of groups (2 items); and (3) ascertainment of exposure and outcomes (3 items). Studies with NOS scores 7-9 were high-quality, scores 4-6 had moderate risk of bias, and scores 0-3 had very high risk of bias.

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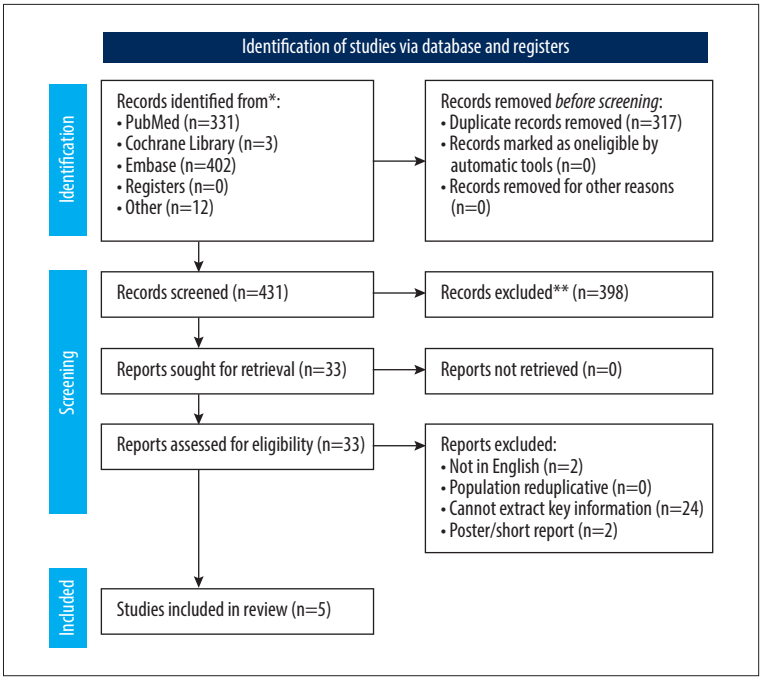

Figure 1. Flow chart of the study selection.

Statistical Analysis

Changes of the serum vitamin D levels before and during the COVID-19 pandemic were evaluated by pooling mean differences (MDs) or risk differences. MDs or risk differences from included studies were combined using a random-effects model. Stratification analysis was done according the age of the participants as infants and children (infants were defined as <1 year old and children were defined as 1-18 years old).

Heterogeneity was assessed using Cochran's Q test and Higgins's I^2, with I^2 >50% and a P value <0.10 suggested significant heterogeneity [17]. To explore the sources of significant heterogeneity, the enrolled studies were sequentially excluded to observe the overall impact of the individual study. Potential publication bias was evaluated using Begg's rank correlation [18] and Egger's weighted regression methods [19].

Review Manager Version 5.3 (Cochrane Collaboration, Oxford, United Kingdom) and STATA 15.0 (Stata Corporation, College Station, TX) were used to perform statistical analyses. A 2-side P value of <0.05 was considered significant for all analyses.

Results

Study Selection

As illustrated in **Figure 1**, a total of 748 studies were identified through the initial searches in the above-mentioned databases; 317 were excluded due duplication among various databases and 256 papers were excluded by browsing the titles or abstracts. After retrieving 33 full-length manuscripts, 5 studies [12,13,20-22] were included into the current study.

Study Characteristics

The 5 studies encompassed a total of 4141 people under age 18 years and were published between 2020 and 2021. The sample size ranged from 226 to 1800. The studies were conducted in 1 each in South Korea (21), Greece (20), Hong Kong (13), Poland (12), and China (22). Most studies (4/5) were retrospective studies. Three studies [12,20,21] focused on people age 1-18 years and 2 on infants [13,22]. Nearly half of the study population were males. All studies defined the pre-COVID-19 period as the year 2019 and the COVID-19 period as the year 2020. The demographic characteristics of the study population from the included studies are presented in **Table 1**.

Quality Assessment of Studies

NOS for included eligible studies are shown in **Supplementary Table 1**. All 5 included studies were evaluated as moderate or high quality, of which 2 each scored 6 points and 7 points, and 1 scored 8 points.

Impact of the COVID-19 Pandemic on Serum Vitamin D Levels

Of the 5 included studies, 4 [12,13,21,22] reported serum 25(OH)D levels before and during then COVID-19 pandemic. As shown in **Figure 2**, when summarizing the serum 25(OH)

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Table 1. Characteristics of the included studies.

Study included	Country	Study design	Sample size	Age (means±SD)	% of males	Definition of pre-COVID-19	Definition of COVID-19 period
Kang et al, 2020	Korea	Retrospective	226	10.5 (8.7-12.4) years*	42.5	3, 2019-3, 2021	3-9, 2020
Feketea et al, 2021	Greece	Prospective	340	8.6±4.6 years	45.6	2, 2019-12, 2019	1, 2020-1, 2021
Wong et al, 2021	Hong Kong	Retrospective	303	10.42±6.37 months	48.5	6-12, 2019	6-12, 2020
Rustecka et al, 2021	Poland	Retrospective	1472	8.0±5.0 years	52.1	1-12, 2019	1, 2020-2, 2021
Yu et al, 2020	China	Retrospective	1800	29.0±23.0 months	NA	1-12, 2019	1-12, 2020

SD – standard deviation; NA – not available. * Range of age.

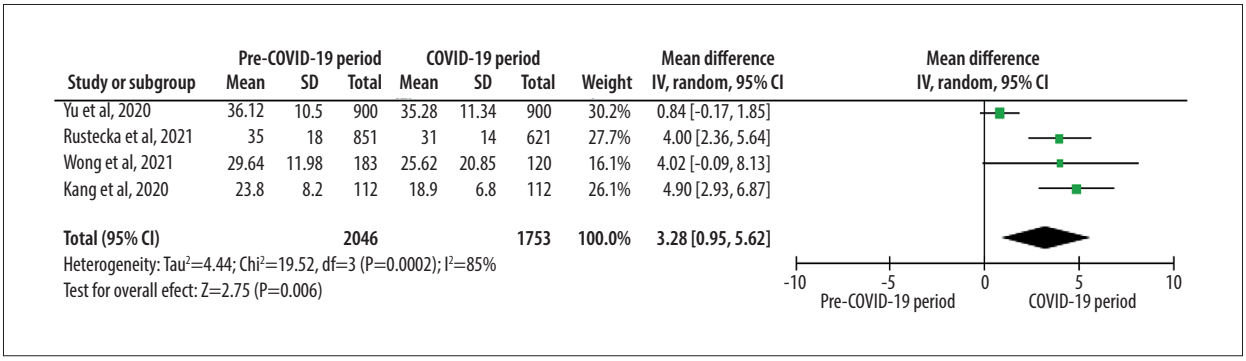

Figure 2. Summarized mean differences of serum 25(OH)D level among all participants.

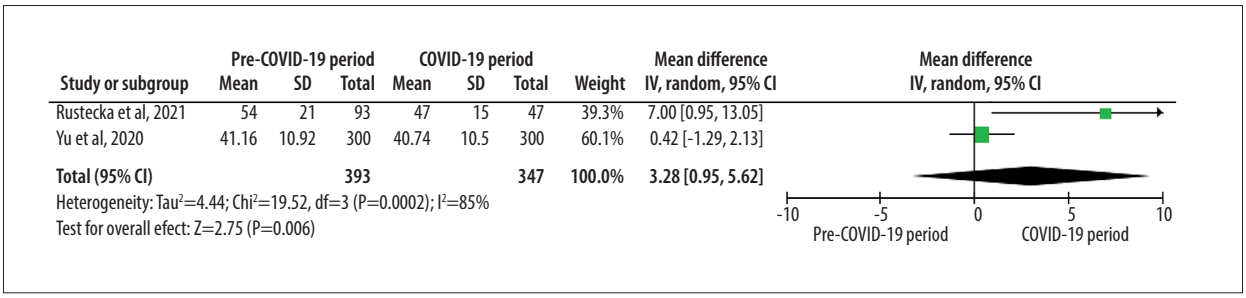

Figure 3. Summarized mean differences of serum 25(OH)D level among infants (aged <1 year).

D levels together, a statistically significant decrease was seen with pooled MD as 3.28 ng/mL (95% confidence interval (CI)=0.95-5.62 ng/mL, $P<0.01$) with a significant heterogeneity ($I^2=85\%$).

To explore the potential source of the heterogeneity, we excluded included studies sequentially. As illustrated in **Supplementary Figure 1**, when we excluded the study conducted by Yu et al [22], the heterogeneity was significantly decreased ($I^2=0\%$)

As presented in **Figure 3**, 2 studies reported serum 25(OH)D level changes among infants (<1 year old). No statistically significant serum 25(OH)D level change was seen, with *P* value 0.28.

According to serum 25(OH)D level, 3 studies [12,20,22] categorized serum vitamin D levels into vitamin D deficiency, insufficiency, and sufficiency (**Figure 4**). No significantly increased vitamin D deficiency and vitamin D insufficiency risk were seen, with pooled risk differences as 0.03 (95% CI=-0.11-0.18, $P=0.64$, $I^2=96\%$) and -0.01 (95% CI=-0.09-0.07, $P=0.81$, $I^2=81\%$), respectively, which indicates the proportions of vitamin D deficiency and vitamin D insufficiency among children remained unchanged.

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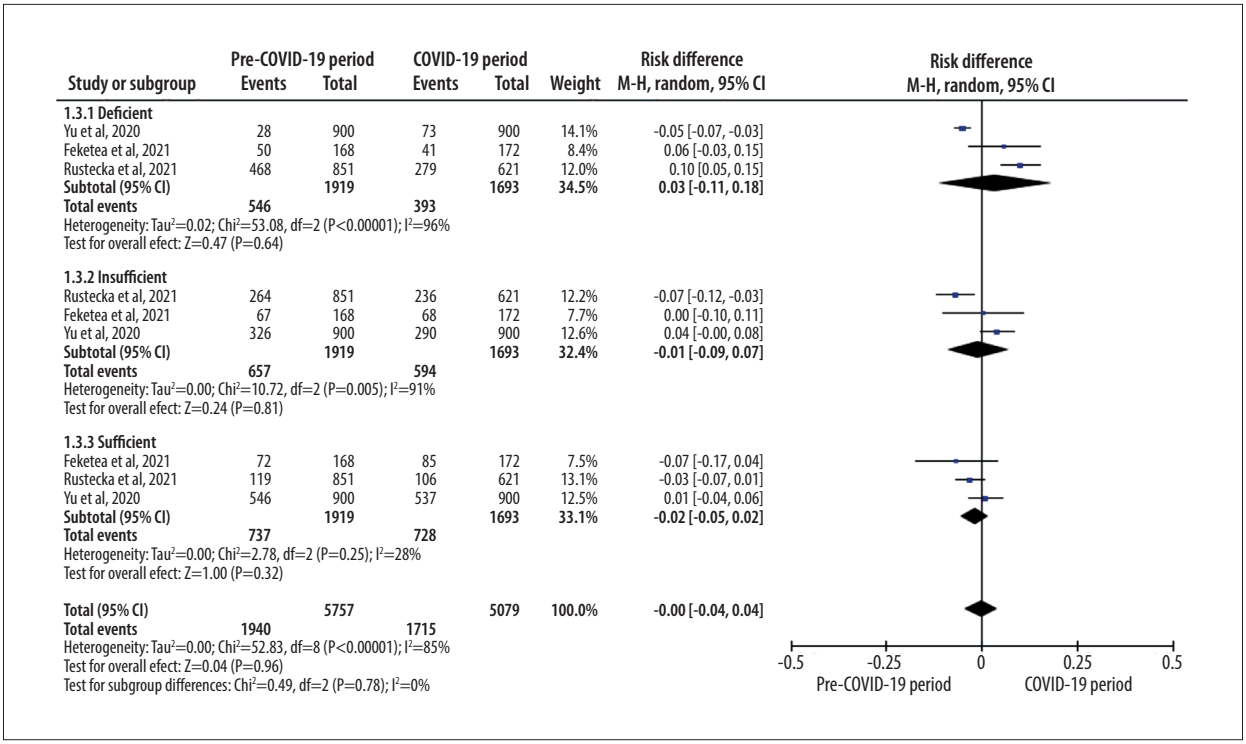

Figure 4. Summarized risk differences among participants by serum 25(OH)D level status.

Similarly, to explore the potential source of the heterogeneity, we excluded the study specifically focused on infants (**Supplementary Figure 2**). Decreased heterogeneity was then 0%, 36%, and 0% for vitamin D deficiency, vitamin D insufficiency, and vitamin D sufficiency risk, respectively. Then we assessed the association among infants (<1 year old). Similarly, no statistically significant differences were seen (**Supplementary Figure 3**).

Publication Bias

No potential publication bias was observed ($P>0.05$), and the detailed results of potential publication bias can be found in **Supplementary Table 2**.

Discussion

To the best of our knowledge, the current study is the first systematic review and meta-analysis study to summarize the impact of the COVID-19 pandemic on serum vitamin D levels in people under age 18 years. Five studies with a total 4141 pediatric participants were included and analyzed. For the pediatric population, the serum vitamin D levels were significantly decreased during the COVID-19 pandemic.

The general metabolism and actions of vitamin D are well-established [23]. Vitamin D has 2 forms (D_2 and D_3), which differ chemically in their side chains. Vitamin D_2 is obtained from daily diet such as oil-rich fish [24]. Vitamin D_3 is produced in the skin from 7-dehydrocholesterol by UV irradiation. Due to the COVID-19 pandemic, many negative effects on lifestyle choices were reported [25]. A study conducted by Xiang et al [26] in 2426 children and adolescents from China reported a substantial decrease in physical activity and increase in screen time during the COVID-19 pandemic. Another study, conducted in Italy, also reported significantly less time spent in sports activities [27]. The home confinement and decreased physical activity during the COVID-19 pandemic thus resulted in inadequate exposure to sunlight, which can lead to decreased serum vitamin D levels. Moreover, studies also reported that red meat, high-sugar and high-fat diets, and sugary drink intakes increased significantly during the lockdown and school closure [25,26,28]. The daily diet changes might also promote decreased serum vitamin D levels.

The findings of our study that the serum vitamin D level was significantly decreased during COVID-19 pandemic highlight the importance of vitamin D supplementation people under age 18 years. A recent meta-analysis reported that low serum 25 (OH) vitamin D level was strongly associated with an increased risk of COVID-19 infection [29]. Another meta-analysis reported that there was about 3 times higher chance of getting infected with COVID-19 among vitamin D-deficient individuals and about 5 times increased probability of developing severe COVID-19 disease in vitamin D-deficient patients

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[30]. Improving serum vitamin D levels in people under age 18 years therefore has a potential benefit in reducing the risk of acquiring COVID-19. Grant et al [7] recommended that people at risk of influenza and/or COVID-19 consider taking 10 000 IU/d of vitamin D3 for a few weeks to rapidly raise 25(OH)D concentrations, followed by 5000 IU/d.

While interpreting the findings in the current study, limitations need to be considered. First, most of the studies did not compare the prior and current COVID-19 period serum vitamin D levels in the same population. Even if the sensitivity analyses and subgroup analyses were performed carefully, the heterogeneities of some comparisons remained substantial. Second, the mean ages of the participants among the 5 included studies varied greatly. Because age has an important effect on living habits, the impact of the COVID-19 pandemic on serum vitamin D levels may be significantly different, such between infants versus kindergarten or elementary school students. However, as described above, 2 studies provided data on infants <1 year and we observed they differed from the entire pediatric population. Third, the serum vitamin D levels might be affected by various factors, such as the season. However, due to the limited number of included studies and the information provided by each study, we could not perform more subgroup analyses. Fourth, potential language bias might exist because we only included articles published in English. Fifth, possible publication bias could not be assessed for all analyses, as a small number of studies were included.

Conclusions

Our meta-analysis provides pooled results based on 5 studies and reported the quantized changes in serum vitamin D levels during the COVID-19 pandemic. Vitamin D supplementation may be needed for people under age 18 years. The measures aimed to reduce the transmission of SARS-CoV-2 need to take into account the detrimental effects on people under age 18 years. Further research should focus the long-term impact of the COVID-19 pandemic on serum vitamin D levels and health outcomes.

Data Sharing Statement

Data are available on request from the authors.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.

Supplementary Material. Search strategies

Supplementary Table 1. Quality assessment of included studies by Newcastle-Ottawa Scale.

NOS case-control Study	Is the case definition adequate?	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of intervention	Same method of ascertainment for cases and controls	Non-response rate	Total quality scores
Kang et al, 2020	☆	☆	☆	☆	☆☆	–	☆	☆	8
Feketea et al, 2021	☆	☆	☆	☆	☆	–	☆	☆	7
Wong et al, 2021	☆	☆	☆	☆	☆	–	☆	☆	7
Rustecka et al, 2021	☆	☆	–	☆	☆	–	☆	☆	6
Yu et al, 2020	☆	☆	–	☆	☆	–	☆	☆	6

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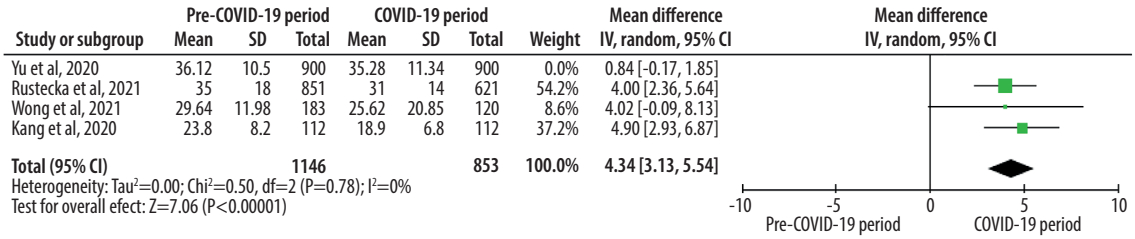
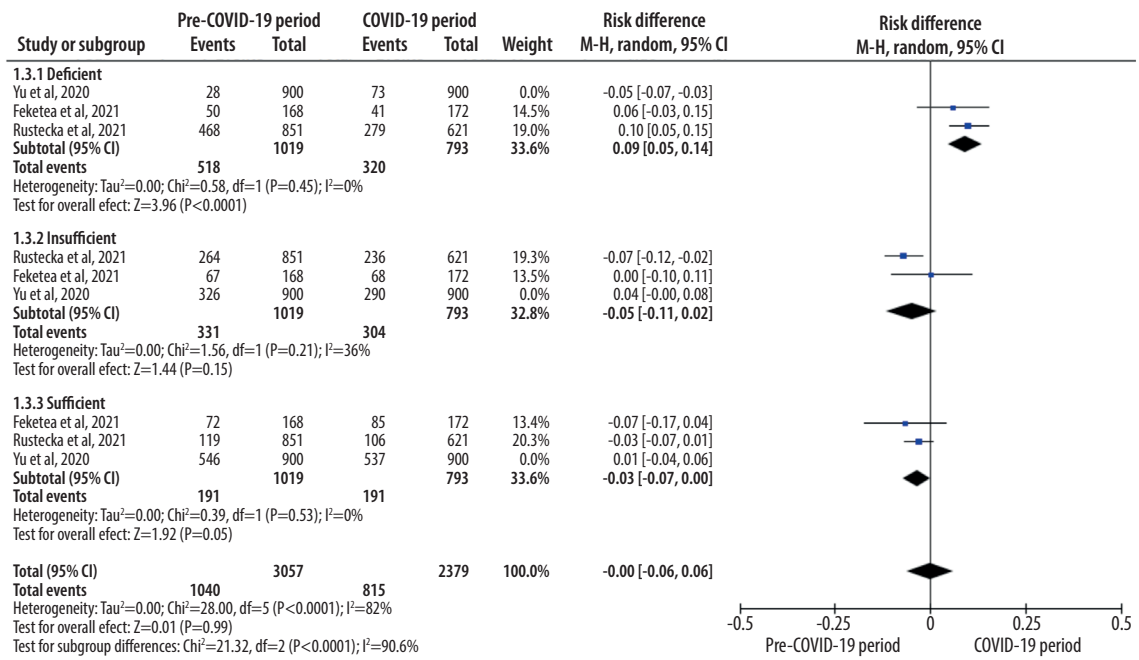


Supplementary Figure 1. Sensitivity analysis on summarized mean differences of serum 25(OH)D level.



Supplementary Figure 2. Sensitivity analysis on summarized risk differences among participants by serum 25(OH)D level.

Supplementary Table 2. Publication bias of summarized outcomes.

Outcomes	Publication bias	
	Begg (*P* value)	Egger (*P* value)
Summarized mean differences of serum 25(OH)D level	0.74	0.51
Summarized risk differences among participants with deficient serum 25(OH)D level	0.66	0.32
Summarized risk differences among participants with insufficient serum 25(OH)D level	0.19	0.21
Summarized risk differences among participants with sufficient serum 25(OH)D level	0.84	0.60

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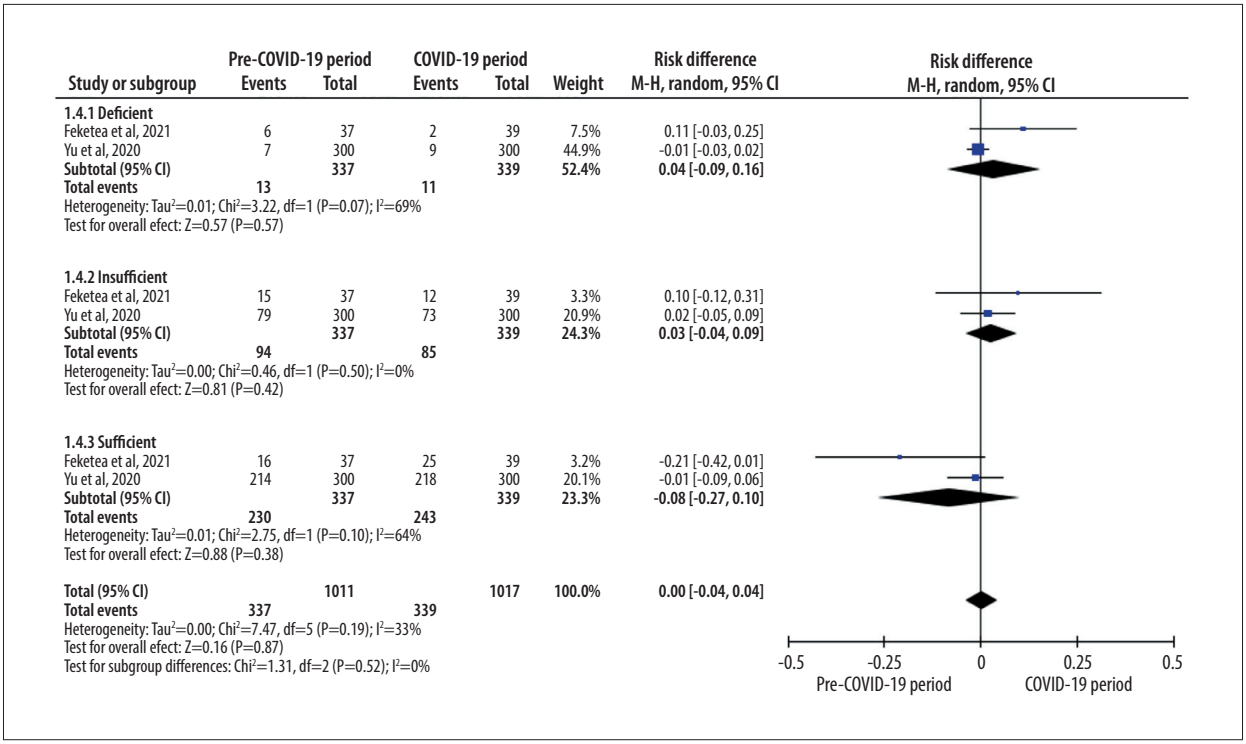

Supplementary Figure 3. Summarized risk differences among participants by serum 25(OH)D level status among infants (aged <1 year).

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