Coronavirus disease 2019 (COVID-19) pandemic remains a global health challenge, claiming more than 4 million lives worldwide (1). Despite vaccine rollout at scale, it is expected to remain a problem because of inequities in resource allocation and chance of new mutants evading vaccine-mediated protection. Therefore, other treatment and prevention strategies for COVID-19 have been an area of extensive research.

Vitamin D is implicated in optimum function of the immune system. Its deficiency has been linked to susceptibility to respiratory infections (2, 3). It is postulated that vitamin D deficiency/insufficiency is also associated with COVID-19. Low cost, wider availability, and ease of administration would make it an attractive and practice-changing intervention if proven effective. These hypotheses have been tested.
in several observational and interventional studies. Despite strong scientific suspicion, these have yielded variable results. Conclusions of meta-analyses summarizing these have also been mixed (4-12). Significant but unexplained heterogeneity is common to all analyses. Since the publication of those reports, several more studies have been published.

Therefore, we aimed to systematically review the literature and determine:

1. Does vitamin D deficiency/insufficiency increase the susceptibility to COVID-19 infection, risk of developing severe COVID-19, and risk of death from COVID-19 among adults?
2. In adults with COVID-19, does treatment with vitamin D compared with standard care/placebo improve clinical outcomes?

Materials and Methods
Search Strategy and Selection Criteria
We conducted a systematic review and independent meta-analyses for 3 different outcomes of interest: susceptibility to COVID-19, risk of developing severe COVID-19, and death from COVID-19.

We searched for observational studies (prospective or retrospective cohort or case control) in adults (> 18 years) comparing the rates of our 3 outcomes in groups with and without vitamin D deficiency/insufficiency, and, for observational studies comparing 25-hydroxy vitamin D (25(OH)D) concentration in people with or without these 3 outcomes. We also searched for randomized controlled trials (RCTs) comparing vitamin D therapy against placebo/standard care in improving clinical endpoints (length of hospital stay, severe COVID-19, death, or any combination) when used to treat adults with COVID-19.

We searched CINAHL, Cochrane library, EMBASE, PubMed, Scopus, and Web of Science databases from their inception to May 30, 2021, using keywords “SARS-CoV-2” OR “COVID-19” OR “Coronavirus” OR “Coronavirus disease 2019” OR “new coronavirus infection” OR “novel coronavirus infection” OR “Coronavirus infection” OR “SARS” OR “severe acute respiratory syndrome” OR “vitamin D deficiency” OR “vitamin D insufficiency” OR “hypovitaminosis D” OR “treatment” OR “vitamin D” OR “cholecalciferol” OR “calcitriol” OR “alfalcalcidiol” OR “calcitriol” OR “calcifiediol” in all fields. The search strategy in full is available in Supplementary data file 1 section 1 (13). Articles published in the English language analyzing individual patient-level data were selected. Additional references were identified by manually screening references of the published articles. If abstracts alone were published, we contacted authors to request full texts. If reported data were inadequate to synthesize effect estimates for the meta-analysis, we contacted authors for additional information. If required data could not be obtained, those studies were excluded from the meta-analysis. The other exclusion criteria were reporting of population level data, not reporting the outcomes of interest, or analyses done in duplicate (2 reports based on the same population).

Titles/abstracts and full texts were screened by 2 authors independently (S.D.N.d.S. and C.D.). Conflicts were resolved by a third author (H.A.D.). When an abstract/research letter alone was available, the data were included in the meta-analysis. Their impact on the pooled effect estimate was assessed through sensitivity analysis.

Definition of Variables
We used the following definitions to categorize studies into subgroups for subgroup analysis and/or meta-regression.

Timing of vitamin D testing: We defined 4 categories of timing of vitamin D testing: “long ago” (> 1 year before the outcome), “before COVID-19” (within a year preceding COVID-19), “after COVID-19,” and “variable timing” (before, during, or after COVID-19).

Cutoff for vitamin D testing: We categorized the studies according to 25(OH)D cutoff used in analysis into the following categories: category 1 (studies using a cutoff 10 ± 3 ng/mL), category 2 (studies using a cutoff 20 ± 3 ng/mL), and category 3 (studies using a cutoff 30 ± 3 ng/mL). One study that used a cutoff of 15 ng/mL was included in category 1. These approximations were required because different studies used different cutoffs to dichotomize the data (eg, based on local or regional protocols or based on the distribution of the study cohorts’ 25(OH)D distribution). We use the term “vitamin D deficiency/insufficiency” to denote vitamin D insufficiency or deficiency of any severity.

Criteria for severe COVID-19: For subgroup analyses, we classified the severity criteria as follows: “hospitalization” (when hospitalization defines severe disease), “hypoxia” (when need for oxygen, noninvasive or invasive ventilation, acute respiratory distress syndrome, or a combination of these define severe COVID-19), “death” (when death defines severe disease), or “composite” (when a composite of hospitalization, hypoxia, or death defines severe COVID-19).

Data Analysis
Two authors independently extracted data from selected articles (N.L.d.S. and K.K.K.G.) under the following domains: publication details, setting, design, participant selection criteria, characteristic of participants, exposure and outcome assessment, statistical analysis, raw data relevant for meta-analysis, and adjusted and/or unadjusted effect estimates (format in Supplementary data file 1 section 2) (14). When 2 studies reported data from the same dataset, authors of both studies were asked for clarification and the most updated dataset was included in the analysis.

Statistical analysis was conducted in R (v.4.1.0) and RevMan 5.3. Inverse variance method and random-effects model was used to pool effect estimates because we anticipated significant between-study heterogeneity. We used the DerSimonian-Laird method to calculate the heterogeneity variance τ² and Knapp-Hartung adjustments (14) to calculate the CI around the pooled effect. Forest plots were used for graphical representation. Statistical assessments were 2-tailed and a P value < 0.05 was considered significant.

Susceptibility to infection/severe disease/death was reported as odds ratio (OR) in most selected studies. When it was not available, raw data were extracted from the articles to calculate the ORs. When adjusted ORs were reported (with or without unadjusted ORs), those were used for the meta-analysis. All 25(OH)D concentrations were converted to nanogram per milliliter (1 ng/mL = 2.5 nmol/L) units and mean differences were determined. When median and range or interquartile range of vitamin D were reported,
approximate mean and SDs were calculated and adopted for the meta-analysis (15-17).

Robustness of findings were assessed by sensitivity analysis. Heterogeneity across studies was estimated with $I^2$ statistic. Source of heterogeneity was explored using subgroup analyses and meta-regression.

Elements for sensitivity analyses defined a priori were extreme effect estimates (ORs < 0.2 or > 5.0; mean differences greater than the 95% CI limits), extreme sample sizes (<100 or >10 000), type of publication (with and without abstract-only publications), risk of bias (with and without publications with high risk of bias), and type of effect estimate (adjusted vs unadjusted).

Subgroup analyses were conducted to determine the impact of risk of bias, type of effect estimate (adjusted vs unadjusted), geographical territory (Africa, Asia, Europe, Middle East, North America, South America), definition of COVID-19 severity, definition of vitamin D deficiency/insufficiency, and timing of vitamin D testing. We used inverse variance random effects model for subgroup analysis. Tau squared and its CIs were estimated by the DerSimonian-Laird and Jackson methods, respectively.

Cutoff for definition of vitamin D deficiency/insufficiency, criteria to define severe COVID-19, and geographical territory of the study were the predictor variables defined a priori for meta-regression. The model fit was assessed by weighted least-squares method. Multiple meta-regression models were assessed by forward selection stepwise approach. The predictor sequence was determined by single variable meta-regression analyses. The models were compared using ANOVA likelihood-ratio test and corrected Akaike’s information criterion (AIC). Robustness of the models was ascertained by permutation testing.

Risk of Bias Analysis
The risk of bias was assessed using Newcastle and Ottawa scales for cohort and case-control studies and AUB KQ1 Cochrane tool for RCTs. Two authors independently assessed each publication (N.L.D.S., K.K.K.G.). Conflicts were resolved by a third author (H.A.D.). Abstracts and research letters were not subjected to risk of bias analysis because of limited availability of data. Impact of publications with high risk of bias was assessed by conducting sensitivity analyses. Publication bias was assessed by Funnel plots and by the Egger test.

Results
The literature search yielded 1877 records. After excluding duplicates, 1166 titles/abstracts were screened and 100 were selected for full-text review. Twenty-nine articles were excluded at full-text review (Supplementary data file 1, section 3) (13). Five additional publications were identified through manual screening of references. Seventy-six publications that matched the selection criteria were included in this review. This included 62 full papers on observational studies (18-79), 10 publications of abstracts/research letters on observational studies (80-89), and 4 full papers on RCTs (90-93) (Fig. 1). The 72 observational studies selected for the meta-analysis included 1 976 099 participants (sample sizes range: 20-987 849, range of mean age 32.0-81.0 years), from 6 geographic territories (Africa 2, Asia 10, Europe 24, Middle East 18, North America 12, South America 2, not reported 4). Characteristics of included studies are summarized in Table 1. Summary of risk of bias of included studies is shown in Fig. 2.

Susceptibility to Infection
Nineteen studies (1 967 068 participants) reported ORs for the association between vitamin D deficiency/insufficiency and risk of developing COVID-19. This included 1 abstract. Six were retrospective cohort studies and 13 were case controls. Eight studies reported adjusted ORs. Risk of bias was high in 15/18 and unclear in the remaining. Egger test indicated significant asymmetry of the funnel plot (intercept 2.842; 95% CI, 1.70-3.98; $t = 4.88; P = 0.0001$).

Vitamin D deficiency/insufficiency was associated with increased odds of developing COVID-19 (OR 1.46; 95% CI, 1.28-1.65; $P = 0.0001$) (Fig. 3). However, there was significant statistical heterogeneity ($F = 92%$, $P < 0.0001$). The association remained significant in all sensitivity analyses (Supplementary data file 1, section 5) (13).

Subgroup analyses by geographic territory ($Q = 14.02$, degrees of freedom $[df] = 4, P = 0.0072$), timing of vitamin D testing ($Q = 9.39, df = 3, P = 0.025$), and risk of bias ($Q = 5.75, df = 1, P = 0.0165$) revealed significant between-group heterogeneity. Higher ORs were reported in studies from Asia (4 studies: OR 2.60; 95% CI, 1.52-4.44; $tau^2 = 0.11; Q = 4.84; F = 38.0%$), studies reporting 25(OH)D concentration tested after the diagnosis of COVID-19 (5 studies: OR 2.83; 95% CI, 1.35-5.96; $tau^2 = 0.62; Q = 45.74; F = 91.3%$), and in studies with high risk of bias (OR 1.55; 95% CI, 1.33-1.82; $P < 0.0001; tau^2 = 0.06; Q = 202.79; F = 93.1%$). Other subgroup analyses did not contribute to heterogeneity (Supplementary data file 1, section 5) (13).

Meta-regressions with single predictor variables indicated that timing of vitamin D testing had a significant impact on effect estimate ($F(df = 1, df = 2 = 14) = 3.68, P = 0.038$), accounting for 49.82% of the observed heterogeneity. The model remained robust in permutation testing ($F(df = 1, df = 2 = 14) = 3.6818, P = 0.050$). Yet, the residual heterogeneity remained significant (94.69%, $P < 0.0001$). The other 2 prespecified predictors did not have a significant impact in single-variable meta-regression. On stepwise forward selection multivariable meta-regression, the model combining timing of vitamin D testing and cutoffs used to define vitamin D deficiency/insufficiency had a significant impact on effect estimate ($F(df = 1, df = 2 = 10) = 3.68, P = 0.03$), and was superior to the previous single variable model in the ANOVA test for model comparison ($df = 6$, AIC = 29.56 for full model vs $df = 3$, AIC 31.00 for single variable, $P = 0.0013$).

Eighteen studies (616 261 participants) compared the difference in 25(OH)D concentration between people with COVID-19 infection and those without. Two were abstract-only publications. Fourteen of the 18 studies had high risk of bias; the remainder had unclear risks. Funnel plot inspection and Egger test (intercept -1.675; 95% CI, -5.12 to -1.77; $t = -0.952; P = 0.355$) indicated a low risk of publication bias. The mean 25(OH)D concentration in people with COVID-19 infection was lower compared with those without (mean difference -3.85 ng/mL; 95% CI, -5.44 to -2.26; $P = 0.0001$) (Fig. 4). Heterogeneity across studies was high ($F = 97.7%$, $P = 0.0001$). Difference remained significant in all sensitivity analyses (Supplementary data file 1, section 6) (13).
In summary, vitamin D deficiency/insufficiency increased the odds of developing COVID-19. Patients with COVID-19 had lower 25(OH)D concentration that those without. Wide heterogeneity across studies is partly explained by differences in timing of vitamin D testing, geographical territory of the study, cutoff used to define vitamin D deficiency/insufficiency, and risk of bias. Most case-control studies assessing the association between vitamin D status and risk of developing COVID-19 had a high risk of bias because exposure status was determined after the onset of outcome.

Risk of Developing Severe COVID-19
Thirty-six studies (367,852 participants, 32 full texts) reported on the association between vitamin D deficiency/insufficiency and severe COVID-19; 18/32 had high risk of bias. Only 18/36 papers reported adjusted ORs. Funnel plot was asymmetric, confirmed in Egger test (intercept 2.84; 95 CI, 1.70-3.98; t = 4.88; P = 0.0001). Vitamin D deficiency/insufficiency increased the odds of developing severe COVID-19 (OR 1.90; 95% CI, 1.52-2.38; P < 0.0001). However, there was a significant statistical heterogeneity (I² = 81%, P < 0.00001) (Fig. 5). Association remained significant in all sensitivity analyses (Supplementary data file 1, section 7) (13).

A significant between-group heterogeneity was observed when studies were grouped according to the criteria used to define disease severity (Q = 9.09, df = 3, P = 0.03). Studies reporting a composite of mortality and respiratory failure reported a higher OR than the others (9 studies: OR 2.63; 95% CI, 1.60-4.36; t = 0.34; Q = 33.40; F = 76%). No significant heterogeneity was observed in other subgroup analyses (Supplementary data file 1, section 7) (13).

In single variable meta-regression models, none of the tested variables (criteria for vitamin D deficiency/insufficiency, criteria for disease severity, geographical region of the study) effectively predicted the effect size. Therefore, we conducted a post hoc multimodel analysis including the previously discussed prespecified variables and 2 additional variables: adjusted vs nonadjusted effect estimates and risk of bias. Yet, no models effectively predicted the effect size (Supplementary data file 1, section 7) (13).

Eighteen studies (2566 participants) compared the levels of vitamin D in people with complicated vs uncomplicated COVID-19. Three were abstract-only publications. Fourteen (of 15) studies had a high risk of bias. Publication bias was minimal (Egger test: Intercept 0.346; 95% CI, -2.47 to -3.16; t = 0.241; P = 0.8125) (Supplementary data file 1, section 8) (13). Patients with severe COVID-19 had a lower 25(OH)D concentration (mean difference -4.84 ng/mL; 95% CI, -7.32 to -2.35; P = 0.0001). Heterogeneity across studies was high (I² 89%, P < 0.00001) (Fig. 6). The significance in difference remained in sensitivity analyses conducted excluding abstract-only publications, studies with high risk of bias, and extreme effect size (mean difference greater than the upper limit of 95% CI [ie, 8.04 ng/mL]).

In summary, vitamin D deficiency/insufficiency increased the odds of developing severe COVID-19. Patients with severe COVID-19 had lower 25(OH)D concentration. Heterogeneity...
| Study                  | Design          | Country  | Population characteristics | Exposure | Outcome                               |
|-----------------------|-----------------|----------|-----------------------------|----------|---------------------------------------|
| Abdollahi 2020        | Case control    | Iran     | 402 (201, 201) 48.0 46.3    | 30       | After diagnosis                       |
|                       | (20)            |          |                             |          | COVID-19 infection (by RT-PCR on NPA) |
| Abrishami 2020         | Retrospective   | Iran     | 73 (12, 61) 55.18 (14.98) 64 | 25       | On admission                          |
|                       | cohort          |          |                             |          | Mortality                             |
| Adami 2021            | Retrospective   | Italy    | 61 (44, 17) 69.4 (15.3) 69.4 | 20       | On admission                          |
|                       | cohort          |          |                             |          | hypoxia (< 60 mmHg), mortality        |
| Alsafar 2021          | Prospective     | UAE      | 464 (309, 155) 46.6 (14.9) 80.2 | 20       | On recruitment                        |
|                       | cohort          |          |                             |          | Severity of COVID, according to WHO 2020 criteria |
| Alseegai 2021         | Case control    | Egypt    | 58 (31, 27) 60.7 (14.3) 46.6 | 32       | On admission                          |
|                       | (26)            |          |                             |          | Mortality                             |
| Al-azzawy 2021         | Case control    | Iraq     | 150 (120, 30) NR            | NA       | NR                                    |
|                       | (23)            |          |                             |          | COVID-19 based on RT-PCR on NPA       |
| Al-Daghri 2021         | Case control    | Saudi Arabia | 220 (138, 82) 43 (15) cases 50 (13) controls 32 (13) | NA       | On admission                          |
|                       | (24)            |          |                             |          | Mild COVID-19 (no hypoxia/ pneumonia) |
| Angelidi 2020         | Retrospective   | USA      | 144 (79, 65) VDD 60 (48-72) VDS 68 (63.5-76.0) | 30 (and 20) | Within preceding 6 mo                  |
|                       | cohort          |          |                             |          | Death and need for mechanical ventilation |
| Anjum 2020            | Prospective     | Pakistan | 140 (82, 58) 42.46 (14.73) 59.0 | 10       | NR                                    |
|                       | cohort          |          |                             |          | Mortality                             |
| Ansari 2020           | Prospective     | India    | 125 (14, 111) 45.58 (15.66) 60.0 | 10       | NR                                    |
|                       | (28)            |          |                             |          | Mortality                             |
| Backtash 2020         | Case control    | UK       | 105 (70, 35) 81 (range: 65-102) | 54.3     | 12                                    |
|                       | (30)            |          |                             |          | On admission                          |
|                       |                |          |                             |          | COVID-19 infection (by RT-PCR on NPA) |
| Backtash 2020         | Prospective     | UK       | 70 (39, 21) VDD: 79.46 (9.52) VDS: 81.6 (7.23) | 12       | On admission                          |
|                       | cohort          |          |                             |          | Mortality                             |
| Bennouar 2020         | Prospective     | Algeria | 120 (37 deaths) 62.3 (17.6) 69.2 | <10      | On admission                          |
|                       | cohort          |          |                             |          | COVID-19 based on WHO criteria        |
| Brandao 2021          | Retrospective   | Brazil   | 13 930 (2345, 11 585) NR | 20       | 30 days before or after COVID diagnosis |
|                       | cohort          |          |                             |          | COVID-19 (RT-PCR on respiratory secretions) |
| Bychinin 2021         | Retrospective   | Russia   | 50 NR                       | 20       | Several months before pandemic        |
|                       | cohort          |          |                             |          | COVID-19                             |
| Bychinin 2021         | Case control    | Russia   | 65 (40, 25) NR | 20       | During illness                        |
|                       | (33)            |          |                             |          | Severe COVID 19 (criteria not reported) |
| Bychinin 2021         | Prospective     | Russia   | 40 (18, 22) 61 (52.5-80) 50 | 9.9 for mortality risk | On admission to ICU                   |
|                       | cohort          |          |                             |          | Mortality                             |
| Carpagnano 2020       | Retrospective   | Italy    | 42 (10, 32) VDD: 74 (11)  Nondeficient: NR | 10       | NR                                    |
|                       | (34)            |          |                             |          | Mortality                             |
| Study          | Design       | Country        | Sample size: total (vitamin D not sufficient and sufficient groups/cases and controls) | Population characteristics | Exposure | Timing of vitamin D testing | Outcome |
|----------------|--------------|----------------|-------------------------------------------------------------------------------------|-----------------------------|----------|----------------------------|----------|
| Cereda 2020    | Prospective  | Italy          | 129 (99, 30)                                                                          | Age in years mean (SD)/median (IQR) | Vitamin D cutoff for analysis (ng/mL) | Within 48 h of hospital admission | Mortality |
| Chang 2020     | Case control | USA            | 10 992 (992, 10 000)                                                                  | Age in years mean (SD)/median (IQR) | Vitamin D cutoff for analysis (ng/mL) | 1 y before COVID-19 diagnosis | COVID-19 infection (by RT-PCR on NPA) |
| Charoenngam 2021 | Retrospective | USA            | 287 (sufficient 100, insufficient 91, deficient 96)                                  | Age in years mean (SD)/median (IQR) | Vitamin D cutoff for analysis (ng/mL) | NA (continuous variable) | Within 48 h of admission Primary: in-hospital mortality |
| D Avolio 2020  | Case control | Switzerland    | 107 (27, 80)                                                                          | Age in years mean (SD)/median (IQR) | Vitamin D cutoff for analysis (ng/mL) | 3 days after RT-PCR test | COVID-19 infection (by RT-PCR on NPA) |
| Davoudi 2021   | Retrospective | Iran           | 153 (96, 57)                                                                           | Age in years mean (SD)/median (IQR) | Vitamin D cutoff for analysis (ng/mL) | At the time of hospitalization | Severe COVID-19 (WHO definition) |
| De Smet 2020   | Retrospective | Belgium        | 186 (27, 159)                                                                         | Age in years mean (SD)/median (IQR) | Vitamin D cutoff for analysis (ng/mL) | On admission with COVID-19 pneumonia, within 2 hours from chest CT staging | Mortality |
| Demir 2020     | Retrospective | Turkey         | 487 (227, 260)                                                                         | Age in years mean (SD)/median (IQR) | Vitamin D cutoff for analysis (ng/mL) | Within the preceding 6 mo | RT-PCR positive COVID-19 |
| Elham 2021     | Case control | Iran           | 283 (93, 186)                                                                         | Age in years mean (SD)/median (IQR) | Vitamin D cutoff for analysis (ng/mL) | After symptoms onset/testing for COVID-19 | 25(OH)D concentration is lower in patients with COVID-19 than those without |
| Ersoz 2021     | Retrospective | Turkey         | 310                                                                                  | Age in years mean (SD)/median (IQR) | Vitamin D cutoff for analysis (ng/mL) | Within preceding 6 mo | ICU admission, intubation, death |
| Ferrari 2020   | Case control | Italy          | 347 (128, 219)                                                                        | Age in years mean (SD)/median (IQR) | Vitamin D cutoff for analysis (ng/mL) | Before, during, or after illness (between January 1 and May 31, 2020) | COVID-19 diagnosed based on RT-PCR with a swab test |
| Gaudio 2021    | Case control | Italy          | 150 (30, 100)                                                                         | Age in years mean (SD)/median (IQR) | Vitamin D cutoff for analysis (ng/mL) | First 3 days of admission | COVID-19 (by RT-PCR) severe COVID-19 (death/need for ventilatory support—invasive/noninvasive) |
| Gavioli 2020   | Retrospective | USA            | 437 (177, 260)                                                                        | Age in years mean (SD)/median (IQR) | Vitamin D cutoff for analysis (ng/mL) | Within 3 mo preceding admission | Hospital admission, need for oxygen support, and 90-day mortality |
| Study            | Design          | Country  | Population characteristics                                                                 | Exposure | Outcome                                                                 |
|-----------------|-----------------|----------|----------------------------------------------------------------------------------------------|----------|-------------------------------------------------------------------------|
| Hernandez 2020  | Case control    | Spain    | Sample size: total (vitamin D not sufficient and sufficient groups/cases and controls)        |          | Severe COVID-19: composite of admission to ICU, requirement for mechanical ventilation, or in-hospital mortality |
| Im 2020         | Case control    | South Korea | Sample size: total (vitamin D not sufficient and sufficient groups/cases and controls)        |          | COVID-19 infection (by RT-PCR on NPA)                                   |
| Infante 2021    | Case control    | Italy     | Sample size: total (vitamin D not sufficient and sufficient groups/cases and controls)        |          | Need for oxygen                                                        |
| Israel 2020     | Case control    | Israel   | Sample size: total (vitamin D not sufficient and sufficient groups/cases and controls)        |          | Mortality                                                              |
| Jain 2020       | Retrospective cohort | India | Sample size: total (vitamin D not sufficient and sufficient groups/cases and controls)        |          | Clinical signs of pneumonia (fever, cough, breathlessness) plus 1 of the following: respiratory rate > 30 breaths/min; severe respiratory distress; or SpO2 < 90% on room air |
| Jevalikar 2021  | Retrospective cohort | India | Sample size: total (vitamin D not sufficient and sufficient groups/cases and controls)        |          | Severe COVID-19 (based on outcome severity score)                       |
| Study       | Design               | Country   | Population characteristics                                                                 | Exposure | Outcome                                                                 |
|------------|----------------------|-----------|------------------------------------------------------------------------------------------|----------|------------------------------------------------------------------------|
| Karahan 2020 | Case control         | Turkey    | **Sample size:** total (vitamin D not sufficient and sufficient groups/cases and controls) | Vitamin D cutoff for analysis (ng/mL) | Primary outcome: all-cause mortality secondary outcomes: severe—critical illness vs moderate illness |
|            | (fatal vs surviving COVID-19) |           | **Age in years mean** (SD/median (IQR))                                                 | **Timing of vitamin D testing** | Severe disease: The presence of any of the following criteria: (1) respiratory distress (≥ 30 breaths/min); (2) oxygen saturation ≤ 93% at rest; (3) PaO2/FiO2 ≤ 300 mmHg or chest imaging shows obvious lesion progression > 50% within 24-48 h |
|            |                      |           | **Males (%)**                                                                             |          | Critical disease: The presence of any of the following criteria: (1) respiratory failure and need for mechanical ventilation; (2) shock; (3) other organ failures that requires ICU care. |
| Katz 2020  | Retrospective cohort | USA       | 987,849                                                                                 | VDI: 69.7 | COVID-19 infection (based on database records) |
| Kerger 2020 | Case control         | Turkey    | 108 (88, 20)                                                                            | Cases 46.6 | COVID-19 infection (by RT-PCR or commercial kit on NPA or bronchial washings) |
|            | (COVID-9 patients Vs asymptomatic HCW) |           | Controls 40.0                                                                           |          | COVID-19 with Macrophage Activating Syndrome or ARDS data for ARDS used for meta-analysis. Data for risk of COVID-19 infection in case control design not adequate for meta-analysis |
| Lau 2020   | Case control         | USA       | 20 (13, 7)                                                                              | Cases 61.5 | ICU admission |
| Li 2021    | Retrospective cohort | UK        | 353,299                                                                                 | Cases 61.5 | COVID-19 infection (by RT-PCR on NPA) and severe COVID-19 and severe COVID-19 (need for hospitalization) |
|            |                      |           | Controls 72.0                                                                            | Controls 14.3 | COVID-19 infection (by RT-PCR or commercial kit on NPA or bronchial washings) |
| Livingston | Case control         | UK        | 104 (47, 57)                                                                            | Cases: 68.6 | COVID-19 infection (by RT-PCR or commercial kit on NPA or bronchial washings) |
|            | 2020                 |           | Controls: 68.5                                                                          | Controls: 33.3 | COVID-19 infection (by RT-PCR or commercial kit on NPA or bronchial washings) |
| Lohia 2020 | Retrospective cohort | USA       | 270                                                                                     | 63.81 (14.69) | Mortality (ICU admission, venous thrombosis, need for ventilation analyzed independently) |

**Table 1.** Continued
| Study          | Design       | Country | Sample size: total (vitamin D not sufficient and sufficient groups/cases and controls) | Population characteristics | Exposure | Outcome                                                                 |
|---------------|--------------|---------|-----------------------------------------------------------------------------------|-----------------------------|----------|-------------------------------------------------------------------------|
| Luo 2021 (59) | Prospective cohort | China   | 74                                                                                | 62.5 (51.0-75.3)            | Cases 58.1 | Severe COVID-19: respiratory distress, respiratory rate ≥30 breaths/min,  |
|               |              |         |                                                                                   |                             | 30       | hypoxemia, SpO2 ≤93% (at rest), or lung infiltrates of >50% within 24-48 h |
|               |              |         |                                                                                   |                             |          | Critical COVID-19: meeting any of the following criteria: respiratory failure |
|               |              |         |                                                                                   |                             |          | requiring mechanical ventilation, shock, or multiple organ dysfunction requiring |
|               |              |         |                                                                                   |                             |          | intensive care unit monitoring and treatment. Nonsevere patients whose symptoms |
|               |              |         |                                                                                   |                             |          | became progressively severe during hospitalization were defined as severe cases |
| Luo 2021 (59) | Case control | China   | 8297 (1378, 6919)                                                                | 56.2 (9.2) Controls: 57.8 (8.4) | Cases 53.4 | Severe COVID defined by: death, admission to the ICU, and/or need for higher oxygen flow than that provided by a nasal cannula |
| Ma 2021 (60)  | Retrospective cohort | UK     | 80 (45, 35)                                                                        | NR                          | 10 (vs >20) | COVID-19 (RT-PCR on respiratory secretions) |
| Macaya 2020   | Retrospective cohort | Spain  | 235 (158, 77)                                                                     | NR                          | 30       | Severe disease (dyspnea, respiratory frequency >30/min, blood oxygen saturation < 93%, and/or lung infiltrates >50% of the lung field within 24-48 h) and critical (respiratory failure, septic shock, and/or multiple organ dysfunction/failure). Patients with at least 2 complications, including ARDS, acute cardiac injury, acute kidney injury, or acute liver injury considered as multiple organ damage. |
| Maghbooli 2020| Retrospective cohort | Iran    | 348                                                                                | 68                          | 64.0     | After admission (28 patients had 25(OH)D concentration before admission, within the preceding 6 mo) |
| Mazzotti 2021 | Retrospective cohort | Italy   | 489 (172, 317)                                                                    | Cases 45.9 Controls: 51.0   | Cases 23.0 | Mortality                                                                |
| Meltzer 2020  | Case control | USA     | 689 (91, 598)                                                                     | Cases 60.5 Controls: 47.2   | Cases 50.5 | COVID-19 vs no infection                                                |
| Mendy 2020    | Case control | USA     | 689 (172, 317)                                                                    | Cases 45.9 Controls: 51.0   | Cases 23.0 | Admission to ICU and/or death during hospitalization                   |
| Study         | Design            | Country       | Sample size: total (vitamin D not sufficient and sufficient groups/cases and controls) | Age in years mean (SD)/median (IQR) | Males (%) | Vitamin D cutoff for analysis (ng/mL) | Timing of vitamin D testing | Outcome |
|--------------|-------------------|---------------|----------------------------------------------------------------------------------|-------------------------------------|-----------|----------------------------------------|-----------------------------|---------|
| Merzon 2020  | Case control      | Israel        | 7807 (782, 7025)                                                                 | Cases 35.58 (34.4-36.67) Controls 47.35 (46.87-47.85) | Cases 49.2 | Controls 40.6                          | 20 Before illness; timing not specified | RT-PCR (specimen not clearly reported) |
| Nasiri 2021  | Prospective cohort | Iran          | 329 (32 deceased)                                                               | 64.7 (18.5)                        | 50.8      | NA                                     | 20 On admission                | Death (other outcomes—length of hospital stay, not included in the analysis) |
| Orchard 2021 | Retrospective cohort | UK          | 165 (116, 49)                                                                  | NR                                 | NR        | 20 On admission                         | 20 On admission                | Mortality, need for ICU care |
| Osman 2021   | Retrospective cohort | Oman        | 445 (133, 312)                                                                | 50.8                               | 62.0      | 20 NR                                  | 20 NR                         | Intubation, mortality, |
| Radučkovic 2020 | Prospective cohort | Germany      | 185                                                                            | 60 (49-70)                         | 51.0      | 12 On admission                        | 2006-2010                    | COVID-19 diagnosed based on RT-PCR |
| Raisi-Estabragh 2020 | Case control | UK          | 4510 (1326, 2184)                                                             | Cases: 68.11 (± 9.23) Controls: 68.91 (± 8.72) | Cases 52.5 | Controls 47.3                          | NA                           | 20 On admission Mortality, need for invasive mechanical ventilation |
| Susianti 2020 | Prospective cohort | Indonesia    | 50 (8, 42)                                                                     | NR                                 | 54.0      | 20 On the first day of admission       | 20 On admission                | Severe COVID (clinical DVT/ISTH DIC score 5 or more) |
| Szeto 2021   | Retrospective cohort | USA          | 93                                                                             | NR                                 | NR        | 20 Within 1 y preceding admission      | 20                          | Death |
| Tehrani 2021 | Retrospective cohort | Iran        | 205 (43, 162)                                                                 | 59.71 (14.92)                      | 33.7      | 10 NR                                  | 10 NR                         | Death |
| Tuncay 2021  | Retrospective case control | Turkey       | 655 (596 cases: 450 with nonsevere, 146 with severe COVID-19: 120 survived)     | Nonsevere: 48.1 (9,4) severe-survived: 66.6 (7,2) Severe-nonsurvival: 68.2 (9,2) | Non-severe: 75.5, severe-survived: 60.0 severe-did not survive: 69.2 | NA                        | NR | COVID-19 (clinical features/ RT-PCR/ radiology-based WHO criteria), severe COVID-19 (not defined), death |
| Unsal 2021   | Retrospective Cohort | Turkey       | 56                                                                             | Median age 56 (range 26-76)        | 32.1      | 20 Within preceding 6 mo before COVID-19 | Need for respiratory support (criteria not reported) | Mortality |
| Vanges Cedillo 2021 | Prospective cohort | Mexico       | 551                                                                            | 51.92 (13.74)                      | 64.4      | 12 At the time of presentation         | Mortality |
| Vasiliiou 2020 | Prospective cohort | Greece       | 30                                                                             | 65 (11)                           | 80.0      | 15.2 On admission to ICU               | Mortality |
| Walk 2020    | Prospective cohort | Netherlands  | 133 (58, 75)                                                                   | 68 (12)                            | 69.0      | NA After admission                       | Severe COVID-19 (need for intubation/ ventilation or death) |
was significant and may partly be explained by differences in definition of severe disease. Most studies did not report the timing of vitamin D testing in relation to the stage of illness, leading to high or unclear risk of bias in the exposure and outcome assessment domain.

Mortality

We identified 20 publications (3686 participants) reporting association between vitamin D deficiency/insufficiency and risk of death from COVID-19. All were full-article publications. Ten were prospective studies; the others were retrospective. Only 8 studies reported adjusted effect estimates. Twelve studies were judged to have high risk of bias. Asymmetry in funnel plot was minimal (Egger test intercept 1.78; 95% CI, 0.09-3.48; \( t = 2.06; P = 0.054 \)).

Vitamin D deficiency/insufficiency increased the odds of death from COVID-19 (OR 2.07; 95% CI, 1.28-3.35; \( P = 0.003 \); \( I^2 = 73\% \)) (Fig. 7). The significance of association was lost in sensitivity analyses excluding publications with high risk of bias (8 publications, 1368 participants: OR 1.93; 95% CI, 0.75-4.96; \( P = 0.17 \); \( I^2 = 80\% \)), studies reporting unadjusted ORs (8 publications, 1773 participants: OR 2.22; 95% CI, 0.88-5.59; \( P = 0.09 \); \( I^2 = 83\% \)), and studies with extreme effect estimates (13 publications, 3071 participants: OR 1.18; 95% CI, 0.78-1.78; \( P = 0.44 \); \( I^2 = 56\% \)). The significance remained in the other sensitivity analysis for sample size (Supplementary data file 1, section 9) (13).

In subgroup analysis, grouping by cutoff to define vitamin D deficiency/insufficiency showed significant-between-group heterogeneity (\( Q = 12.33, df = 2, P = 0.0021 \)). Higher ORs were observed in studies using lower cutoffs (10 ± 2 ng/mL) (OR 5.03; 95% CI, 2.72-9.30; \( P < 0.0001 \); \( I^2 = 26.3\% \)) (Supplementary data file 1, section 9) (13). Other subgroup analyses for geographic territory, risk of bias, and adjusted vs unadjusted effect estimates did not show significant between-group heterogeneity.

In stepwise multivariable meta-regression analysis, only the model comprising vitamin D cutoff as the predictor variable was significant, accounting for 59.73% of the heterogeneity (\( F(df/1 = 2, df/2 = 16) = 5.45, P = 0.0157 \)) but significant residual heterogeneity remained (\( F = 53.03\% \), \( P = 0.0033 \)) (Supplementary data file 1, section 9) (13).

Nine studies (n = 1421) compared 25(OH)D concentration in survivors and nonsurvivors of COVID-19. Eight were full-article publications. Six (of 8) had a high risk of bias. Funnel plot was asymmetric. Egger test was not applied because of the small number of studies.

Nonsurvivors had lower mean 25(OH)D concentration compared with the survivors (mean difference -4.80 ng/mL; 95% CI, -7.89 to -1.71; \( P = 0.002 \)) (Fig. 8). Studies were significantly heterogeneous (\( F = 85.1\% \), \( P < 0.0001 \)). The association lost significance when studies with extreme effect estimates (>7.89 ng/mL) were excluded (6 studies, 1147 participants: OR -2.11; 95% CI, -4.34 to 0.13; \( P = 0.06 \)). Difference remained significant in other sensitivity analyses (Supplementary data file 1, section 10) (13).

In summary, vitamin D deficiency/insufficiency increased the odds of death from COVID-19. Nonsurvivors had lower 25(OH)D concentration compared with survivors. However, this finding is likely influenced by studies with high risk of bias, studies reporting unadjusted effect estimates, and studies with extreme effect estimates.

| Study      | Country | Design                | Population characteristics | Sample size: (Mean vitamin D deficient/insufficient and sufficient groups/cohort) | Age in years mean (SD)/median (IQR) | Males (%) | Vitamin D cutoff Timing of vitamin D testing for analysis (ng/mL) | SARS-CoV2 PCR in throat swab | Outcome |
|------------|---------|-----------------------|----------------------------|---------------------------------|------------------------------------|-----------|---------------------------------------------------------------|-------------------------------|----------|
| Ye 2020    | China   | Case control          | 142 (62.80)                | Cases 43 (39-52) and controls 42 (31-52) | 37.0-40.0                          | 37.0      | After admission after admission                               | SARS-CoV2 PCR in throat swab | SARS-CoV2 PCR in throat swab |
| Ye 2020    | China   | Prospective cohort    | 60 (10.50)                 | 43                               |                                    |           | 20                                                            | After admission after admission | SARS-CoV2 PCR in throat swab |

| Abbreviations: ARDS, adult respiratory distress syndrome; BP, blood pressure; COVID-19, coronavirus disease 2019; CT, computed tomography; DIC, dissemination intravascular coagulation; DVT, deep vein thrombosis; DPHC, Department of Public Health, China; DMAC, Department of Medicine, Austin Hospital; DYG, Department of Infectious Diseases; EME, European Medical Association; VDD, vitamin D deficient; VDI, vitamin D insufficiency; VDS, vitamin D sufficient; WHO, World Health Organization |

Table 1. Continued
Vitamin D in the treatment of COVID-19

Four RCTs assessed vitamin D therapy in treatment of COVID-19 (Table 2). Of the 3 studies reporting hard clinical endpoints, 2 showed no benefit of vitamin D therapy. All studies had a small number of participants. There were significant variations in participant selection criteria, vitamin D regimen, and outcomes assessed. Considering this heterogeneity, their methodological limitations and risks of bias, a meta-analysis was not performed (Supplementary data file 1, section 4) (13).

Discussion

Our findings indicate increased odds of developing COVID-19, progression to severe COVID-19, and death in people with vitamin D deficiency/insufficiency. People who developed COVID-19, severe COVID-19, and fatal disease had lower 25(OH)D concentration compared with people without COVID-19 or nonsevere COVID-19 or nonfatal COVID-19, respectively. Association with fatal COVID-19 was less robust. Overall, the studies are largely heterogeneous, with significant risk of bias. Discrepancies in timing of vitamin D testing in relation to the illness, definition of severe COVID-19, and cutoff used to define vitamin D deficiency/insufficiency were the key contributors to heterogeneity in association between vitamin D deficiency/insufficiency and susceptibility to COVID-19, severe COVID-19, and death, respectively. Our findings add evidence to the hypothesized association between vitamin D deficiency/insufficiency and COVID-19. However, observational nature and heterogeneity of the studies precludes deriving definite conclusions.

Previous meta-analyses explored the association between vitamin D deficiency/insufficiency and risk of developing COVID-19 (11, 12), or developing complications of the disease (5), or both (8, 10) whereas another reported prevalence of vitamin D deficiency/insufficiency among patients with COVID-19 without a comparison group (94). All included < 40 studies in meta-analysis. A significant association was shown in some (10, 11) but not others (8). Significant heterogeneity was a common feature, but the sources remained inadequately explained. Three meta-analysis reported therapeutic benefit of vitamin D in patients with COVID-19 (6, 9, 95).

This meta-analysis is the most updated and largest in terms of number of studies and participants on the topic to the best of our knowledge. We explored clinically relevant endpoints: susceptibility to COVID-19, severe disease, and death. Association with each outcome was analyzed in 2 dimensions: risk estimate as OR and the mean difference of 25(OH)D concentration. We tested the robustness of association through multiple sensitivity analyses and recognized contributors to heterogeneity through subgroup analyses and meta-regressions.

The main source of bias in the studies stemmed from exposure and outcome assessment (ie, the timing of vitamin D testing in relation to the illness). Evaluating the risk of developing COVID-19 requires a large cohort of individuals with a premorbid 25(OH)D concentration determined and followed over time for development of COVID-19: a less pragmatic strategy. Evaluating the role of vitamin D in severity of the illness is methodologically less challenging. However, 25(OH)D concentration is known to decrease with...
### Figure 4

Forest plot of studies reporting comparison of 25(OH)D concentration in patients with and without COVID-19.

### Figure 5

Forest plot of studies reporting association between vitamin D deficiency/insufficiency and severe COVID-19.
Figure 6. Forest plot of studies reporting comparison of 25(OH)D concentration in patients with severe and nonsevere COVID-19.

Figure 7. Forest plot of studies reporting association between vitamin D deficiency/insufficiency and death from COVID-19.

Figure 8. Forest plot of studies reporting comparison of 25(OH)D concentration in nonsurvivors and survivors of COVID-19.
| Study (Country), method | Participants | Intervention | Control | Outcome | Results |
|------------------------|--------------|-------------|---------|---------|---------|
| Rastogi, 2020 (93) (India) | Asymptomatic or mildly symptomatic individuals with SARS-CoV-2 infection, vitamin D < 20 ng/mL and without comorbidities or ventilation. (Intervention = 16, placebo = 24) | Oral cholecalciferol 60 000 IU daily for 7 days (if target 25(OH)D concentration > 50 ng/mL not achieved on day 7, same dose continued, if target achieved weekly 60 000 IU supplemented) | Placebo | Proportion of patients with negative SARS-CoV-2 virus RNA by day 21. | Significant difference in SARS-CoV-2 RNA |
| Randomized, placebo controlled (placebo not identical) | | | | Change in the inflammatory markers. | |
| Entrenas Castillo, 2020 (90) (Spain) | Patients older than 18 y with positive SARS-CoV-2 PCR, clinical and radiographic pattern of viral pneumonia and CURB-65 > 1 (Intervention = 50, placebo = 26) | Oral calcifediol 0.532 mg on day of admission and 0.266 on days 3 and 7 and weekly until discharge | Standard care | Rate of ICU admission and death | Need for ICU admission was lower in the group receiving intervention (2% vs 50%, P < 0.001). Two patients in control group died, none in the intervention group died. |
| Randomized open label, double-masked study | | | | Change in level of inflammatory markers before and after intervention, between 2 groups and subgroup analysis on patients who have not received any specific additional treatment. | Significant reduction of inflammatory markers (CRP, LDH, Ferritin, IL-6, N/L ratio) in intervention group compared with control group. No difference in hospital stay or mortality. |
| Lakkireddy, 2021 (91) (India) | Confirmed COVID-19 with 25(OH)D concentration < 30 ng/mL, having mild-moderate illness, > 18 y (intervention: recruited = 65, completed = 44; control: recruited = 65, completed = 43) | Cholecalciferol aqueous nano solution 60 000 IU daily for 8 days in participants with BMI 18-25 kg/m² and 10 days for participants with BMI > 25 kg/m² | Standard care | | |
| Randomized open label trial (intervention group had higher inflammatory markers on enrollment) | | | | | |
| Murai 2021 (92) (Brazil) | COVID-19 confirmed by SARS-CoV-2 PCR or ELISA for IgG, Moderate-severe disease (respiratory rate > 24/min or SpO2 < 94% or presence of comorbidities), age >18 y (intervention: recruited = 120, analyzed 119, control: recruited = 120, analyzed = 118) | Single dose of oral cholecalciferol 200 000 IU | Identical placebo | Length of hospital stay, mortality, ICU admissions, need for ventilation | No significant difference between groups in median length of hospital stay (7 vs 7, P = 0.94), mortality (7.6% vs 5.1%, P = 0.43). No significant difference in need for ventilation or length of ventilation. No significant difference in post hoc analysis on patients with vitamin D deficiency. |

Abbreviations: 25(OH)D, 25-hydroxy vitamin D; BMI, body mass index; CRP, C-reactive protein; CURB-65, CURB-65 score for pneumonia severity; ICU, intensive care unit; LDH, lactate dehydrogenase; N/L ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SpO2, oxygen saturation.
acute illness or inflammation (95, 96). The change may have a bidirectional effect: it may be causal, driving the worsening of illness, or it may be an effect of the severe illness (i.e., reverse causality). Most reported studies indicate the timing of vitamin D testing in relation to the day of admission rather than the stage of illness, thus obscuring the interpretation of findings.

The other source of bias arose from the challenge in having comparable groups and/or in adjusting for appropriate confounding variables. Vitamin D deficiency/insufficiency has been linked to myriad diseases, some of which are recognized risk factors for severe COVID-19. For example, a recent study reported vitamin D deficiency to be associated with hyperglycemia, high body mass index, and worse severe COVID-19, implying complex interplay between risk factors (97). Therefore, a comprehensive adjustment for such confounding variables is likely to be overly exhaustive and meaningless. But, it is important to consider the comparability of clinical profiles of studied subjects and adapt methods to adjust for variations in the common and strong risk factors for severe COVID-19 like atherosclerotic cardiovascular disease, hypertension, and metabolic syndrome.

The 4 interventional studies reported some benefit in vitamin D in the treatment of COVID-19. Improvement in inflammatory markers was consistent but only 1 study showed clinical benefit, whereas the others were neutral. However, there is marked heterogeneity in study population characteristics and type of intervention (dose, duration, and timing). Furthermore, it is questionable whether administration of vitamin D after the onset of illness raises the body’s active 25(OH)D concentration fast enough to have a significant impact. Therefore, more RCTs with early administration of adequately high doses of vitamin D are needed.

There are several limitations in our analysis. First, most studies had a high risk of bias, hence the need for cautious interpretation of the findings. Second, we could not establish a model to fully explain the wide heterogeneity in observed results across studies, with the prespecified predictors as well as with other post hoc analyses. This probably the result of wide clinical and methodological heterogeneity and bias. Third, we could not analyze several important predictors of heterogeneity like sex, ethnicity, body mass index, and comorbidities because of a lack of disaggregated data. Fourth, we could not determine outcomes like length of hospital stay, thromboembolic complications, cost-effectiveness of treatment, and impact on patient-perceived outcomes (well-being and quality of life during and after COVID-19). Another problem in pooling data from different 25(OH)D studies is the differences in 25(OH)D testing methods. Although some assays measure cholecalciferol and ergocalciferol in combination, others measure cholecalciferol only. The specific method is not reported in most studies. In the absence of a standardized method for vitamin D testing, the measured 25(OH)D concentrations may not reflect the true circulating 25(OH)D concentration. Finally, although we identified 4 RCTs evaluating the therapeutic role of vitamin D, meta-analysis of those findings was precluded by significant heterogeneity.

Nevertheless, the finding of possible increased susceptibility to COVID-19 and severe COVID-19 with vitamin D deficiency/insufficiency calls for future research. Therapeutic role of vitamin D needs urgent evaluation in well-designed randomized trials. Interventional studies should examine clinically relevant endpoints and adopt standardized definitions of vitamin D status and outcomes, thus ensuring relevance and comparability across studies. Vitamin D is a relatively inexpensive treatment. If proven effective, it has the potential to change the course of COVID-19 pandemic.

Conclusions
Vitamin D deficiency/insufficiency may increase the risk of developing COVID-19 infection and susceptibility to more severe disease. Its association with mortality is less robust. The data arise from a heterogeneous group of studies with substantial risk of bias; hence, the reduced certainty of evidence and need for cautious interpretation. RCTs investigating the therapeutic role of vitamin D were largely heterogeneous in design, precluding a meta-analysis.

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Author Contributions
P.K. and M.S. conceived the research question and provided leadership. M.S., H.A.D., P.K., S.P., and N.L.d.S. defined the research questions. D.C.K. planned and conducted the literature search. S.D.N.d.S. and C.D. screened abstracts and full texts. N.L.d.S., K.K.K.G., and H.A.D. conducted data extraction and risk of bias analysis. H.A.D. planned and conducted the statistical analysis. P.R. critically reviewed the statistical methods and results. H.A.D. drafted the manuscript and compiled supplementary data files. H.A.D. and S.D.N.d.S. developed the figures. P.K., S.P., and M.S. critically reviewed the manuscript. H.A.D., N.L.d.S., and K.K.K.G. vouch for fidelity of the data. All authors read and approved the final manuscript for submission.

Disclosures
The authors declare no conflicts of interest relevant to this manuscript.

Data Availability
Additional data (protocol, data extractions of individual studies, summary of extracted data of all studies and for studies in different meta-analyses, analytical codes, and detailed results) are available through H.A.D. and can be provided upon request.

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