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Biological Factors Associated with Covid-19 Disease Spread: A Systematic Literature Review and Meta-Analysis

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Abstract

The COVID-19 pandemic, which began in China in late 2019, has led to global efforts to identify risk factors and severity. This study aims to provide the association between biological factors (age, sex, comorbidities, BMI, ethnicity, and vitamin D) and COVID-19 disease severity. For the meta-analysis odds ratio and confidence interval of these factors were collected from the peer-reviewed journal articles through PubMed and Scopus database search with defined inclusion and exclusion criteria and followed PRISMA guideline in the period of 25 Aug, 2024 to 5 Feb, 2025. A meta-analysis using the inverse variance method and a random-effects model was performed. Forest plots were generated to visualize the effect sizes, confidence intervals, and overall pooled estimates, while a funnel plot was used to assess publication bias and small-study effects. Results suggest that vulnerable groups, including older adults, males, individuals from Black/African, Hispanic, and those with pre-existing conditions, face higher risks. Vitamin D, which plays a crucial role in immune function, affecting both innate and adaptive immunity, appeared to have close connection with COVID-19 disease severity. COVID-19 primarily impacts on lungs through the ACE2 receptor, leading to severe respiratory distress.

Keywords

Biological factors, Chronic respiratory Disease, Co-morbidities, Coronavirus, COVID-19, Genetic factors, immune response, Obesity, Pandemic, SARS-CoV-2

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Introduction

The COVID-19 outbreak, which began in China in late 2019 and then rapidly spread worldwide, has spurred a global effort to tackle the disease and establish risk factors and prognostic markers; one such is serum vitamin D deficiency (García-Zendejas et al., 2024). Vitamin D is a secosteroid with varied immunomodulatory, anti-inflammatory, antifibrotic, and antioxidant actions. There is growing evidence that it may play a role in the pathophysiological processes of COVID-19 (Wu et al., 2021) research by Alipio and colleagues, in a retrospective study, provides evidence of an association between vitamin D deficiency and adverse outcomes in patients with COVID-19 (Baktash et al., 2021). Vitamin D is one of the factors that may be linked to the severity of COVID-19 (Pizzamiglio et al., 2023). The serum concentration of 25-hydroxyvitamin D [25(OH) vitamin D] (D'avolio et al., 2020). Vitamin D plays a role in both innate and adaptive immunity (Didier Payen et al., 2020) The innate immune system is the defence against invading pathogens, such as the SARS-CoV-2 virus (Ünsal et al., 2021).

People older than 60 years, (De Rubeis et al., 2024) males, Black, Hispanic, and South Asian, and with pre-existing comorbidities (Santos et al., 2021) such as cardiovascular disease, diabetes mellitus, hypertension, chronic lung disease, cancer (Sun et al., 2021), chronic kidney disease, and obesity are more vulnerable to severe forms of the disease (Zhu et al., 2023).

Population subgroups with higher vulnerability and comorbidities have been identified (Guerra Veloz et al., 2021). Some studies have already highlighted that advanced age and pre-existing cardiovascular and metabolic conditions are associated with poor outcomes (Jindal et al., 2022) Moreover, some potential sex differences (Samer A Khaeeoubi & Marwa Dib-El-Harake, 2024) in the COVID-19 outcomes have been discussed (Luo et al., 2020).

Italy is one of the countries showing the highest rate of mortality in the world, mainly in the northern regions. While pre-existing pulmonary (Jiao et al., 2024a) and cardiovascular diseases as well as diabetes mellitus are known risk factors (Yin et al., 2021) for the worst outcome for COVID-19, the impact of chronic rheumatic diseases, and, in particular, if the risk of COVID-19 while using a biologic agent biological disease-modifying ant rheumatic drugs (b-DMARD). Biological agents (Doğan et al., 2024) increase the risk of infections, although the advantages largely overcome that risk (Quartuccio et al., 2020).

ACE2 is vastly present in the lungs and heart. SARS-CoV-2 mostly attacks alveolar epithelial cells, bringing about respiratory side effects. (ACE2) protein is expressed in many different types of cells, and the virus can invade multiple organs (Kolin et al., 2020). The invasion of the lungs (Jiao et al., 2024b) leads to the most critical pathology of pneumonia with severe respiratory distress and hypoxemia that accounts for the significant mortality in this disorder. Enhanced production of pro-inflammatory cytokines and chemokines by immune effector cells (Matthew Lee et al., 2022) leading to a cytokine storm is thought to be the cause of multiple systemic and respiratory symptoms (Chakrabarti et al., 2020).

Such exposures may result in the development of cross-immunity because of possible antigenic similarities among human and animal coronaviruses (Chakrabarti et al., 2020). This systematic literature review and meta-analysis seeks to fill the research gap by synthesizing findings from multiple studies to provide a comprehensive overview of how biological factors associated with COVID-19 influence the pandemic's dynamics and the severity of the disease. By examining these interconnections, this study aims to identify effective strategies and lessons learned that can inform future public health responses.

Materials and Methods

The systematic review was conducted following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines, which also applied to the study's resources, inclusion and exclusion criteria review process (identification, screening, eligibility), and data abstraction and analysis.

Population

This systematic review included studies involving participants aged 15 years and older. However, if a study also included participants under 15 years of age, only relevant data from eligible age groups (15+) were extracted. The study was excluded if it was not possible to extract this data.

Exposure

Studies reporting biological factors, vitamin D deficiency, Variation in disease severity by age and sex, Racial differences like black, Hispanic, and south Asian in disease severity, the impact of pre-existing diseases on COVID-19 transmission and disease severity, Odds ratio, and CI were included in this systematic review.

Outcome

This systematic review included studies that examined COVID-19 as a primary outcome. The analysis considered how the disease is associated with biological factors. The objective was to explore how these factors contribute to the transmission and severity of COVID-19 disease.

Study design

This systematic review included analytical observational studies, such as cross-sectional studies, retrospective studies, population-based studies, correlation studies.

Search Strategy

Search formula in the field Article Title "Covid-19" "coronavirus" "SARS-CoV-2" and other keywords in the field title/Abstract/key "biological factors" Comorbidities", "cardiovascular disease", "Obesity", "genetic factors" "diabetes" "Hypertension" "Odds ratio" "confidence interval", "Vitamin D", "Cancer", "chronic kidney disease", "Race" (fig-1).

Eligibility and Exclusion Criteria

There are several established inclusion and exclusion criteria. Initially, to prevent misunderstandings and translation challenges, non-English publications were eliminated from the search efforts and only English-language content was taken into consideration. Second, only empirically supported published Articles were taken into account. This indicates that the search will not include book series, reviews, letters, editorials, or short surveys. Thirdly, papers written between 2020 and 2024 are subject to a time frame limit. (Table 1).

Data Extraction

The following details were extracted: publication details (First author and year of publication), study design, study setting,

location, study period, odds ratio and 95% confidence interval were extracted. (Table 2 and table 3)

Data synthesis

The Meta-Analysis was conducted using Stata v16. The odds ratio of the severity of the disease with 95% confidence interval were pooled using the random effect meta-analysis approach and generic inverse variance. The standard errors were used in creating the forest plots, the standard error and variance were calculated in Excel by using the following formula:

$$Standard\ error = \frac{Upper\ CI - Lower\ CI}{2 \times 1.96}$$

$$Variance = (Standard\ error)^2$$

Analysis

The meta-analysis can be performed using the inverse variance method, random-effect model with an assumption of the presence of heterogeneity among the studies. The Higgin's and Thompson's I^2 Statistics, Tau-square, and Cochran's Q test were applied to test statistical heterogeneity among the selected studies. We plotted Forest plot using the random-effect model with prediction value of 95% of CI. We plotted Funnel plot at 95 % CI to demonstrate the publication bias in this meta-analysis of Covid-19.

Systematic Review Process

After rigorous examination, 241 items were identified at this level in the SCOPUS and PubMed databases. The second phase involved, removing 61 duplicates and 116 documents for other regions after screening the title and abstract. At this step, 43 articles were eliminated from 150 papers eligible for screening. The third phase is the selection phase during which entire articles are accessed. After a thorough analysis, out of 107 Articles, 29 Articles were deemed ineligible because they were not retrieved. In the final phase total of 18 articles were included in the review.

Results

Systematic literature review

Eighteen studies were selected for the systematic literature review, and thirty-two studies were included in the meta-analysis. The characteristics of the 18 studies are presented in (Table 2), while the articles selected for the meta-analysis are detailed in (Table 3).

Association of Vitamin D Deficiency and COVID-19 Outcomes

Patients over 60 years of age with COVID-19 are more likely to be vitamin D deficient. Vitamin D deficiency is associated with elevated markers of cytokine release syndrome and an increased need for ventilatory support due to respiratory failure. However, vitamin D deficiency correlates with prolonged hospital stays, increased incidence of hypertension and cardiovascular diseases, and raised inflammatory markers like serum ferritin and troponin. Patients with prior vitamin D supplementation had a lower incidence of pneumonia and required less ventilatory support.

Immunity

Immune cells migrating from blood to the lungs and lymphocytes entering the respiratory tract may explain the lymphocytopenia and high neutrophil-lymphocyte ratio seen in 80% of COVID-19 patients. In mild cases, immune cells clear the virus, inflammation subsides, and recovery follows. However, in severe cases, a dysregulated immune response triggers a cytokine storm, causing widespread lung

inflammation. Excessive protease and reactive oxygen release damages lung tissue, along with direct viral injury.

Sex Differences and Immunity in COVID-19 Outcomes

Men are more susceptible to severe COVID-19 outcomes due to differences in ACE2 gene expression and immune responses, whereas women may have better survival rates due to cardiovascular and immune differences. Significant changes in ACE2 gene expression, immune response, and pathophysiology of cardiovascular risk factors and comorbidities help reduce susceptibility to infection and better survival in women and, conversely, make men more at risk of hospitalization and mortality.

Biology of SARS-Cov-2 and Cross-Immunity

(ACE2) protein is expressed in many different types of cells, and the virus can invade multiple organs. The invasion of the lungs leads to the most critical pathology of pneumonia with severe respiratory distress and hypoxemia that accounts for the significant mortality in this disorder.

Pre-Existing Conditions

Patients with hypertension, diabetes, chronic kidney disease, cardiovascular disease, and Cancer, were at an increased risk of severe COVID-19.

Race/Ethnicity

Higher rates of severe COVID-19 among Black/African, and Hispanic appear to be driven by increased infection rates rather than biological susceptibility. These disparities are more likely due to social determinants such as healthcare access and socioeconomic factors.

BMI/Obesity

Overweight, obesity, played a significant role in elevating severity of the disease and the risk of death among young individuals. These conditions should be thoroughly assessed to prevent and/or promptly manage SARS-CoV-2 infection in high-risk patients, thereby reducing the likelihood of severe outcomes.

Meta-Analysis

The output from a meta-analysis provides the pooled odds ratios (OR) and 95% CI for various factors associated with an outcome likely COVID-19 severity. The results are based on the inverse variance method, which weights studies by the precision of their estimates.

Overall value for odds ratio and confidence interval for age OR:1.03 (95 % CI: 1.00-1.06) (table-4), sex (male) OR: 1.47 (95 % CI: 1.23-1.70) (table-6), race (black) OR: 1.51 (95 % CI: 0.81-2.22) (table-8), comorbidities hypertension OR: 2.00 (95 % CI: 1.52-2.48) (table-10), diabetes OR: 1.85 (95 % CI: 1.47-2.24) (table-12), cardiovascular disease OR: 2.66 (95 % CI: 1.91-3.40) (table-14) chronic kidney disease OR: 2.59 (95 % CI: 2.06-3.11) (table-16), cancer OR: 1.78 (95 % CI: 1.25-2.30) (table-18), BMI/Obesity OR: 1.23 (95 % CI: 1.09-1.37) (table-20), and vitamin-D OR: 1.44 (95 % CI:1.04-1.84) (table-22) based on inverse variance method. The Higgin's and Thompson's I^2 statistics, which is the percentage of variability in effect size not caused by sampling error, greater than 75% indicates a presence of high heterogeneity among these works of literature. The high value of 99.9 percent I^2 statistics confirms that these studies did not stem for the same population, tau-square statistics, the between-study variance in meta-analysis, and the Cochran's Q statistics, the difference between the observed effect size and

random-effect model, are significant for odds ratio. The random-effects model operates on the principle that the studies are derived from a broader population of studies, each having its own true effect size that varies around a common mean.

For every one-year increase in age, the odds of the outcome (e.g., severe disease or mortality) increase by 3%. The CI includes 1.00, suggesting that the association is marginally significant (p-value likely close to 0.05). Males have 47% higher odds of the outcome compared to females. The confidence interval does not include 1, indicating a statistically significant association. Black individuals have 51% higher odds of the outcome compared to the reference group (likely non-Black individuals) (fig. 7). However, the CI includes 1, indicating that this association is not statistically significant.

Individuals with hypertension have twice the odds of the outcome compared to those without hypertension. The association is statistically significant. Individuals with diabetes have 85% higher odds of the outcome compared to those without diabetes. The association is statistically significant. Individuals with cardiovascular disease have 2.66 times higher odds of the outcome compared to those without cardiovascular disease. The association is statistically significant. Individuals with chronic kidney disease have 2.59 times higher odds of the outcome compared to those without chronic kidney disease. The association is statistically significant. Individuals with cancer have 78% higher odds of the outcome compared to those without cancer. The association is statistically significant.

Individuals with higher BMI or obesity have 23% higher odds of the outcome compared to those with normal BMI (fig-19). The association is statistically significant. Individuals with lower vitamin D levels (or deficiency) have 44% higher odds of the outcome compared to those with adequate vitamin D levels. The association is statistically significant.

The results suggest that certain demographic factors (e.g., age, sex) and comorbidities (e.g., hypertension, diabetes, and cardiovascular disease) are strong predictors of the outcome. The random-effects model (implied by the inverse variance method) accounts for heterogeneity between studies, making the results more generalizable to a broader population.

Discussion

We conducted a systematic review and meta-analysis on age, sex, race/ethnicity, pre-existing conditions, BMI/obesity, vitamin D association with COVID-19 disease (Peter Lloyd-Sherlock et al., 2020). many studies have been done to evaluate the modifiable risk factors (Yadav et al., 2020) retrospective studies have determined the correlation between vitamin D status and COVID-19 (Li et al., 2021) (Heidari et al., 2022) (Rathod et al., 2023). Vitamin D is a steroid hormone and plays an important role in bone-mineral metabolism and immunity. Many studies have emphasized a correlation between vitamin D deficiency and various diseases, (Zelzer et al., 2021) including systematic infections. Vitamin D stimulates the secretion of antiviral peptides, which improves the physical barrier to viruses. (Ahmed et al., 2024) It also stimulates cellular immunity by decreasing the cytokine storm with an influence on IFN-γ and TNF-α and regulates adaptive immunity by inhibiting Th1 responses (Ünsal et al., 2021).

Older patients with lower serum concentrations of 25(OH) D (Wang et al., 2022) Markers of cytokine release syndrome were raised in these patients and they were more likely to become hypoxic and require ventilatory support in HDU (Baktash et al., 2021). Evidence of an association between vitamin D deficiency and adverse outcomes in COVID-19 is provided by many studies. (Kaya et al., 2021) Whether low vitamin D levels are a cause or consequence of disease (reverse causality) processes remains unclear (Autier et al., 2025).

In this scenario, the SARS-CoV-2 virus pandemic has rapidly spread during winter with extreme virulence through southern European countries such as Italy and Spain. Although there was a considerable variation in the prevalence of vitamin D deficiency across countries, mainly dependent on age and the use of vitamin D supplements or food fortification. (Mirghani & Begum, 2024) The population with more severe COVID-19, such as elderly people and patients with comorbidities with the highest case fatality rates, are also those with lower serum 25OHD levels according to published data (Hernández et al., 2021).

The relationship between COVID-19 and chronic diseases such as hypertension, diabetes mellitus, and cardiovascular disease (CVD) is complex and could increase infection susceptibility or affect the prognosis (De Almeida-Pititto et al., 2020) (Mishra et al., 2021). The interactions between comorbidities and COVID-19 are sufficiently supported by angiotensin-converting enzyme 2 Angiotensin-converting enzyme 2 (ACE2) participates in the pathogenesis of many chronic diseases and its role as a SARS-CoV-2 receptor on the other hand, angiotensin-converting enzyme 2 is not restricted to the respiratory epithelium; it is also found in myocardium cells, endothelium, renal tubular and intestinal epithelium, and pancreatic islets 19. Chronic diseases such as diabetes mellitus, (De Almeida-Pititto et al., 2020) in addition to the recognized deficit in neutrophil chemotaxis and phagocytosis, generate membrane ferritin protease overexpression that favors the SARS-CoV-2 entry into the cell and interleukin 6 (IL-6) overexpression that increases the COVID-19 cytokine storm20. Finally, protease dipeptidyl peptidase IV (endopeptidase DPP4), involved in diabetes treatment, could have a role in SARS-CoV-2 infections (Balboa-Castillo et al., 2021).

Epidemiologists and public health experts often believe that cultural determinants of health would be taken care of if the broader domain of social causations is addressed (Aleksanyan & Wineman, 2022). Women are more likely to be infected due to their assumed roles as caregivers within families and as front-line healthcare workers (Harman, 2016; United Nations, 2020). This study also showed that even after controlling for men's and women employment status, gender norms and access to finance still have a large effect on recorded disparities. Overall, discrimination in the family, restricted access to resources, women's empowerment, and access to finance and education are significant factors explaining reported differences in case and death rates from COVID-19 between men and women (Aleksanyan & Wineman, 2022).

Conclusion

Vitamin D Deficiency: Linked to worse COVID-19 outcomes (e.g., inflammation, prolonged hospital stays). Supplementation may protect against severe disease, especially in older adults.

Table 1 The criterion used to include and exclude papers from systematic reviews

Criteria	Eligibility	Exclusion
Language	English	Non-English
Types of literature	Journal (research articles)	Book series, chapter in book, proceeding, and letters.

Immunity: Immune dysregulation (e.g., cytokine storms) drives severe lung damage in COVID-19. Balancing immune response is key to improving outcomes. NCDs and COVID-19: Non-communicable diseases (e.g., diabetes, hypertension) increase severe COVID-19 risk. Addressing NCDs is critical, especially in low-resource settings. Sex Differences: Men face higher severe COVID-19 risk due to biological factors (e.g., ACE2 expression, immune responses), while women may have better survival rates. Pre-Existing Conditions: Hypertension, diabetes, obesity, and chronic diseases significantly increase severe COVID-19 risk. Social determinants (e.g., healthcare access) drive disparities in outcomes. Meta-Analysis: Age, male sex, Comorbidities, obesity, and vitamin D deficiency are strong predictors of severe COVID-19. High heterogeneity across studies suggests varied populations and methodologies. Publication Bias: No significant bias detected, supporting the reliability of findings.

Conflict of interest

No conflict of interest was reported by all authors.

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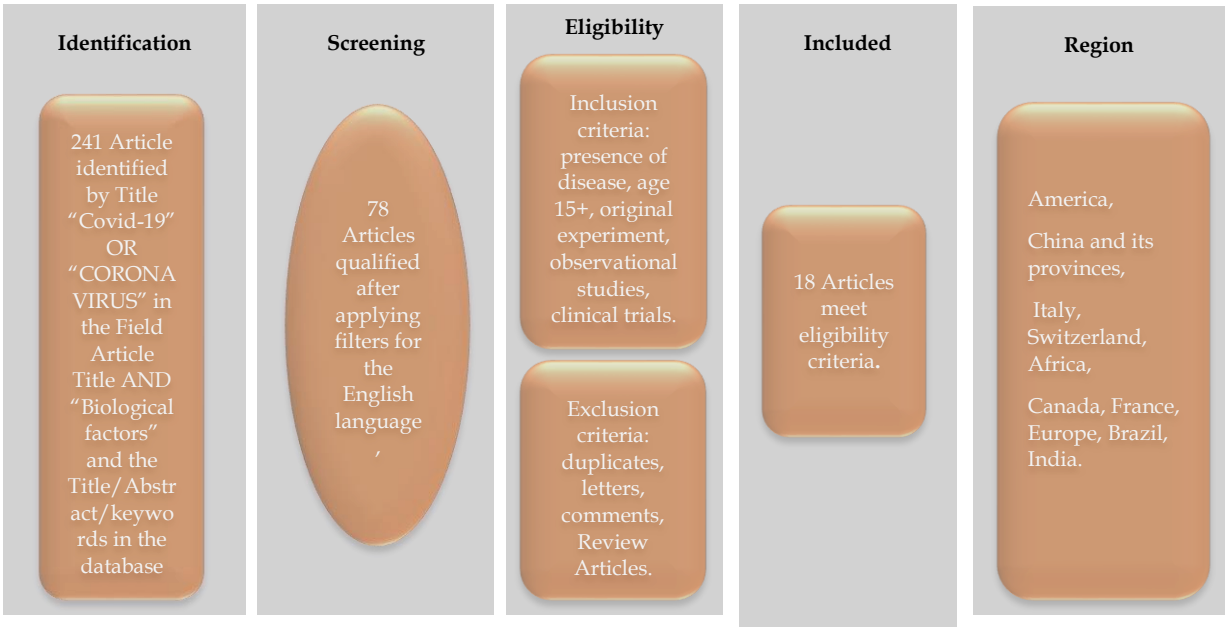

Figure 1 Flow chart for selected research articles for biological factors

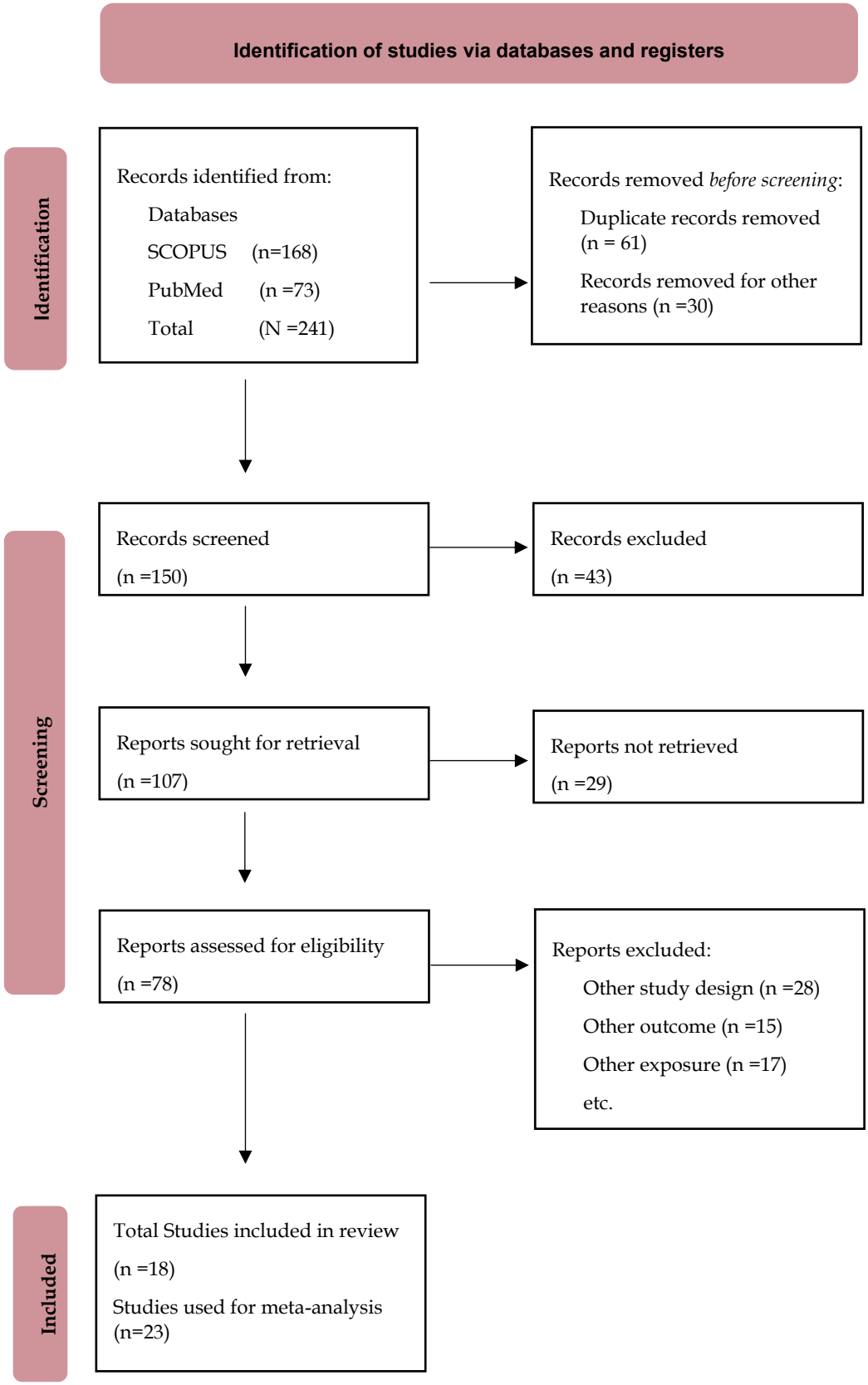

Figure 2 PRISMA 2020 flow diagram for new systematic reviews which included searches of databases

Table 2 Characteristics of included studies

Sl no.	Article title	Author	Objective	Location	Sample and study period	Types of analysis	Variables	Main result
1	Vitamin D status and outcomes for hospitalised older patients cov-19	Vadir baktash, tom hosack, nishil Patel	Whether these patients have worse outcomes with COVID-19.	China	1 March and 30 April 2020	An unpaired t-test	Covid-19 cases, vitamin level	Our study has demonstrated that patients over the age of 65 years presenting with symptoms consistent with COVID-19 are more likely to be vitamin D deficient.
2	Retrospective analysis of vitamin D status on inflammatory markers and	Y. A. Ünsal ö. Ö. Gül. Ca nder c. Ersoy e. Aydemir	Status to COVID-19 infection and parameters of immune function.	Italy	between serum 25-hydroxyvita min d status	The chi-squared test	Lower lymphocyte counts, lower haemoglobin levels, vitamin D levels	Vitamin–deficient cases can be interpreted as increased risk of mortality and morbidity in COVID-19 patients associated with lower vitamin D status.
3	25-hydroxyvitamin d concentrations are lower in patients with positive PCR	Antonio d'avolio, Valeria avataneo,	the 25 hydroxyvitamin d (25(oh)d)	Switzerl and	from 1 March to 14 April 2020	Spearman's rank correlation,	Nasopharyngeal swab PCR analysis for sars-cov-2 and a 25(oh)d	Patients who tested positive for sars-cov-2 had significantly lower 25(oh)d (vitamin d) levels compared to those who tested negative
4	Vitamin D status in hospitalized patients with sars-cov-2 infection	José hernández, Daniel nan Marta	Possible influence of vitamin D status on disease severity.	America	May 20, 2020, including, March to March, 2020	according to the distribution of data	Covid-19 patient, vitamin D	Vitamin D-deficient COVID-19 patients had a greater prevalence of hypertension and cardiovascular diseases.
5	Vitamin D metabolites and clinical outcome in hospitalized COVID-19 patients	Sieglinde Zelzer, Florian prüller, Pero	Vitamin D degradation products in a mixed cohort.		April and November 2020,148 hospitalized.	Spearman's rank correlation, median	of 25(oh)d3, 25(oh)d2, 24,25(oh)2d3 covid-19 patients	Vitamin D metabolism, as indicated by the VMR, seems to be comparable in survivors and non-survivors, and is not related to the need of ventilatory support.

6	Development and validation of a biological risk assessment	Amir Hossein Khoshakhlagh, saeid yazdaniradid	Biological agents among hospital personnel under COVID-19.	Iran	523 nurses, the situation of 228 nurses were examined	Cross-sectional study	Covid-19 patients in two hospitals.	Based on the results, the tools developed using these items have an acceptable diagnostic accuracy for predicting the risk of biological diseases in healthcare.
7	Dysregulated leukotriene metabolism in patients	doğan1, mahir budak2	The leukotriene metabolism during COVID-19.	Europea n	180 participants,	The Shapiro-Wilk test, (ANOVA),	60 patients in the ICU with severe COVID-19.	These results indicate that 5-lo protein, its mRNA, and cysltr1 mRNA are promising biomarkers of COVID-19 severity.
8	Factors associated with resilience among children and youths with disability during the COVID-19	Afiqah Yusuf, Nicola wright, Mandy Steiman	extent to which parenting self-efficacy, support in accessing schooling,	Canada	From June to July 2020	descriptive statistics,	Developmental delays, disorders, and disabilities,	Caregivers and support access to schooling to temper the negative impact of the pandemic on vulnerable populations, such as those with ASD or ID.
9	Biological agents for rheumatic diseases in the outbreak of COVID-19:	Cristiana sieiro Santos, xenia cásas Fernandez,	To estimate covid-19 infection rate in patients treated with (bdmards)	Spain	Dec 1st 2019 and dec 1st 2020,	Retrospectiv e observationa l study	The hospital admission related to COVID-19	Patients with rheumatic disease diagnosed with COVID-19 were more likely to be receiving treatment with rituximab and a higher dose of glucocorticoids.
10	Prevalence of COVID-19 among patients with chronic inflammatory	Luca Quartuccioa, Francesca	Severe acute respiratory syndrome coronavirus 2.	Italy	Sep 2019-April 2020	Chi-square test,	All the rheumatic patients, covid-19 patients	Comorbidities were common, including hypertension (29.9%), type 2 diabetes (7.0%), and heart disease (11.8%). Among the four COVID-19-positive patients.
11	Women, men and covid-19	Yeva Aleksanyan, Jason p.	male and female COVID-19 case and death rates	133 count.		imputation method,	COVID-19 sex-disaggregated data.	Cultural factors, such as women's restricted decision-making in healthcare, may lead to underreporting of female cases and deaths.

12	Predictive Biomarkers of Covid-19 severity in SARS-CoV-2 infected	Carles Perpinan	Obesity and (MS) on covid-19.		303, 2 Feb 2020- 26 Sep 2020	Chi-square test or fisher's test	Clinical data of all patients, presence of obesity	Patients with MS presented severe pneumonia and respiratory failure more frequently, they have a higher mortality rate.
13	Clinical outcomes and immunological response to cov-2	Esimebia Adjovi Amegashie	PLHIV usually suffer with comorbidities.	America n, African	JAN 2020 - JUNE 2023	Review	HIV patients, covid-19 infection	Severity among HIV/SARS-CoV-2 CO-infected individual on combined Art.
14	COVID-19 mortality is associated with pre-existing impaired	Matthew lee	Increased hazards ratio of covid-19 mortality.	USA		Cross-cohort analysis	pre-existing conditions, covid-19 mortality	Impaired innate immunity in pre-existing health conditions is associated with increased hazard of COVID-19 mortality.
15	A longitudinal study of immune cells in severe COVID-19 Patients	Didier Payen	Subsets counts were monitored.		15 PATIENTS, 30 MAR 2020 - 30 APR 2020	Fisher's exact test,	COVID-19 patients,	a temporal variation of both innate and adaptive immunity in severe COVID-19 Patients.
16	Increased COVID-19 infection Risk Drives racial and ethnic Disparity	Susan M. shortmann	In racial and ethnic minority groups.	Colorad o,	1052774, MAR 2020 – SEP 2020	retrospectiv e cohort study	COVID-19 patients, and racial groups	Increased incidence of severe COVID-19 among Black/African American Hispanic individual is due to higher infection rate.
17	Prediction of the incubation period for COVID-19	Ayal B. Gussow	incubation periods and disease severity			Correlation analysis	incubation period, covid-19 severity	A strong positive correlation between the length of the incubation period and disease severity.
18	Sex differences in COVID-19 mortality: A large US-based cohort	Samer A Kharroubi	Analyse sex-based difference in mortality	USA, Canada	1 JAN 2020 - 31 DEC 2020	retrospectiv e cohort study	patients diagnosis of COVID-19	Mortality rates observed among males, suggesting that several factors may contribute to such differences.

Table 3 Characteristics of included studies for the meta-analysis

Sl. No.	First Author year of publication	Country	Author Country	Age in Years	Study Design	Study Period	Sample Size	Odds Ratio	CI	Document Type
1	Angulo-Aguado et.al.,2022	Colombia	Colombia,	18 - 60	bivariate analysis		145	5.73	1.2–26.5	Article
2	BADER EL DIN et al.,2024	Egypt	Egypt	53 -72	Multivariate analysis	Nov, 2021 to Jan, 2022.	200	6.86	2.83-16.6	Article
3	Santos CS, et al.,2020	Spain	Spain		observational study	Dec 2019 -Dec 2020	4464	2.25	1.18-4.27	ORIGINAL RESEARCH
4	Kolin DA, et. al.,2020	UK	UK, USA	40-69	cohort study	from March 16, 2020	397064	1.16	1.01–1.33	ARTICLE
5	Zhu et. al.,2023	UK	UK				20,320	1.55	1.36–1.78	ARTICLE
6	Caliskan, T et. al.,2020	Turkey	Turkey	(≥18	observational study	Mar 2020-May, 2020.	565	1.57	0.81-3.01	ORIGINAL
7	Bucholc M et. al.,2022	UK	UK		cohort study		6036	0.94	0.80-1.10	Scientific std
8	Pinki Mishra et al.,2021	India	UK, India		Review Article	5 Sep. 2020	6,872	2.57	2.12-3.11	REVIEW
9	Luoet et. al.,2020	China	China		pooled analysis	Dec 2019-July 2020		2.57	2.12-3.11	clinical inv.
10	Jindal, et al.,2022	India	India		Meta-Analysis	Feb 2020-20 May 2021		2.90	2.07 4.06	Metanalysis
11	deAlmeidaPititto et al.,2020	China,	Brazil		Meta-Analysis	December 2019-6 May 2020		2.98	2.37–3.75	ARTICLE
12	Wu et al.,2020	China	China		Meta-Analysis			2.67	2.08, 3.43	Article
13	Yin et al.,2021	China	China		Meta-Analysis		12,526	2.13	1.81–2.51	ARTICLE

Sl. No.	First Author year of publication	Country	Author Country	Age in Years	Study Design	Study Period	Sample Size	Odds Ratio	CI	Document Type
14	Pizzamiglio et al.,2023	13 con.	UK, Italy	50-64	regression analyses	till 31 December 2021	315	1.37	0.7 - 2.3	A RTICL E
15	L. Sun et al.,2020		USA		population-based study		323	2.16	1.12-4.18	
16	V. De Rubeis et. al.,2024	Canada	Canada	50-97	longitudinal study	April 2020-June 2020)	28086	1.13	1.02-1.23	Research
17	Kondili et. al.,2022	Italy	Italy	≤65	Case-Control Study	Feb2020–Dec 2020	(593	1.72	1.18–2.51	Article
18	M.F.Guerra Veloz et al.,2020	Spain	Spain		binary logistic	Mar to April, 2020		2.05	0.78-5.41	ORIGINAL
19	L. Jiao et. al.,2023	USA	USA		A case-control study	Feb2020andFeb 2021.	21,765	1.32	0.89-1.95	Original res.
20	Kolin et al.,2020	USA	USA		longitudinal cohort study		968	1.42	1.25-1.62	Article
21	Zhu et. al.,2023	China	China	40-69	Logistic regression	Feb, 2020-Mar, 2021	20,320	2.15	1.91,2.42	ARTICLE
22	Lara et al.,2020	USA	USA	≥18	cohort study	Mar, 2020-May, 2020		1.19	0.88–1.60	Article
23	Chung et. al.,2021	14 con.	Canada, China,		cross-sectional		26,539	1.25	0.78–2.0	ORIGINAL
24	Mirghani et. al.,2024	Saudi	Saudi Arabia		controlled trials	up to July 2023		1.10,	0.74–1.63	Article
25	Autier P et. al.,2025	France			randomised trials			0.92	0.86–0.99	ARTICLE
26	MMGarcía-Zendejaset al.,2023		Mexico		a cross-sectional		54	2.79	0.70-11.1	ARTICLE
27	H. Sh. Ahmed et al.,2024	USA	Iraq		Observational		464383	1.51	1.23–1.86	Article

Sl. No.	First Author year of publication	Country	Author Country	Age in Years	Study Design	Study Period	Sample Size	Odds Ratio	CI	Document Type
28	Wang et. al.,2021	USA	USA		observational studies	Jan. 2019-Dec. 2020	2756	2.18	1.48–3.21	Article
29	Kaya MO et al.,2021	Turkey	Turkey		Meta-Analysis	Jan. and Dec. 15, 2020	205869	2.42	1.13-5.18	REVIEW
30	Li S., et al.,2020	UK	China, USA		logistic regression	Mar.16, -May31, 2020	353299	2.33	2.0–2.7	Article
31	Heidari et. al.,2021	Iran	Iran		retrospective study		144	1.06	1.03–1.09	ARTICLE
32	Rathod, et al.,2023	India	India		prospective cohort study		748	1.07	1.0–1.1	Article

Age

Table 4 Meta summary for the age and COVID-19

Study	Effect Size	[95% Conf.	Interval]	% Weight
Bader El Din et al.,2024	1.020	0.965	1.075	11.09
Macedo MCF et. al.,2020	0.970	0.955	0.985	15.64
Caliskan, T et. al.,2020	1.060	1.040	1.080	15.25
Kondili et. al.,2022	1.050	1.030	1.070	15.25
M. F. Guerra Veloz et al.,2020	0.980	0.945	1.015	13.64
L. Jiao et. al.,2023	1.050	1.045	1.055	16.12
Rathod, et al.,2023	1.090	1.050	1.130	13.02
theta	1.031	0.999	1.064	

Test of theta = 0: z = 61.93 Prob > |z| = 0.0000
Test of homogeneity: Q = chi2(6) = 120.17 Prob > Q = 0.0000

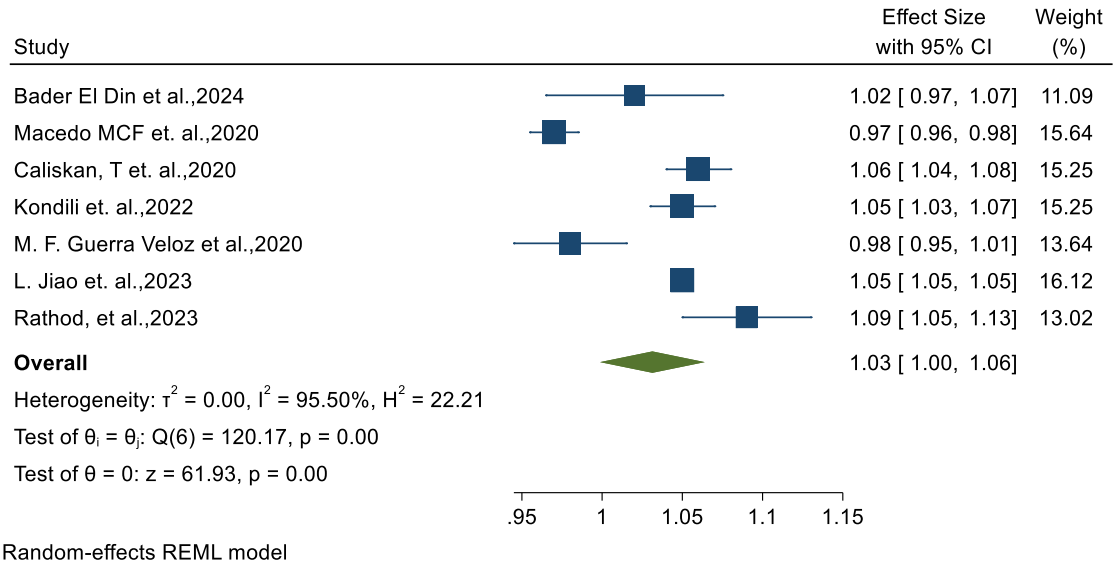

Figure 3 Forest plot of the association between age and COVID-19.

Table 5 Meta regress with odds ratio

_meta_es	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
OR	1	.091232	10.96	0.000	.8211885	1.178811
_cons	0	.095156	0.00	1.000	-.1865024	.1865024

Test of residual homogeneity: Q_res = chi2(5) = 0.00 Prob > Q_res = 1.0000

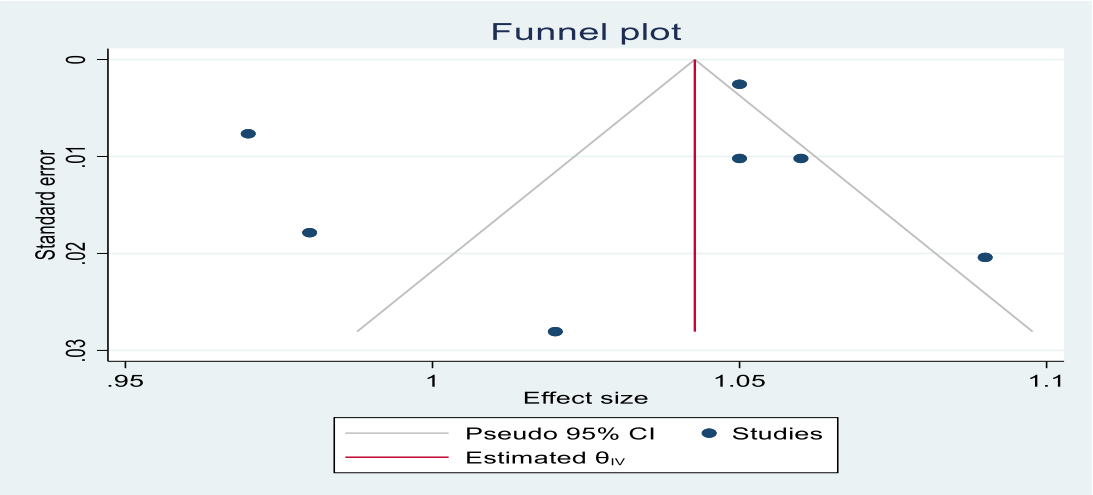

Figure 4 Funnel plot to access publication bias for age

Sex (male)

Table 6 Meta summary for sex (male)

Study	Effect Size	[95% Conf.	Interval]	% Weight
Angulo-Aguado et al.,2022	2.510	0.361	4.659	1.12
Baqui et. al.,2021	1.100	1.084	1.116	15.39
Bucholc M et. al.,2022	1.410	1.193	1.627	13.63
Wu et al.,2020	1.660	1.313	2.007	11.55
Pizzamiglio et al.,2023	1.360	0.613	2.107	6.05
L. Jiao et. al.,2023	1.370	1.256	1.484	14.87
Kolin et al.,2020	1.420	1.220	1.620	13.86
Zhu et. al.,2023	2.150	1.874	2.426	12.71
Lara et al.,2020	1.190	0.800	1.580	10.84
theta	1.466	1.230	1.702	

Test of theta = 0: z = 12.19 Prob > |z| = 0.0000
Test of homogeneity: Q = chi2(8) = 104.26 Prob > Q = 0.0000

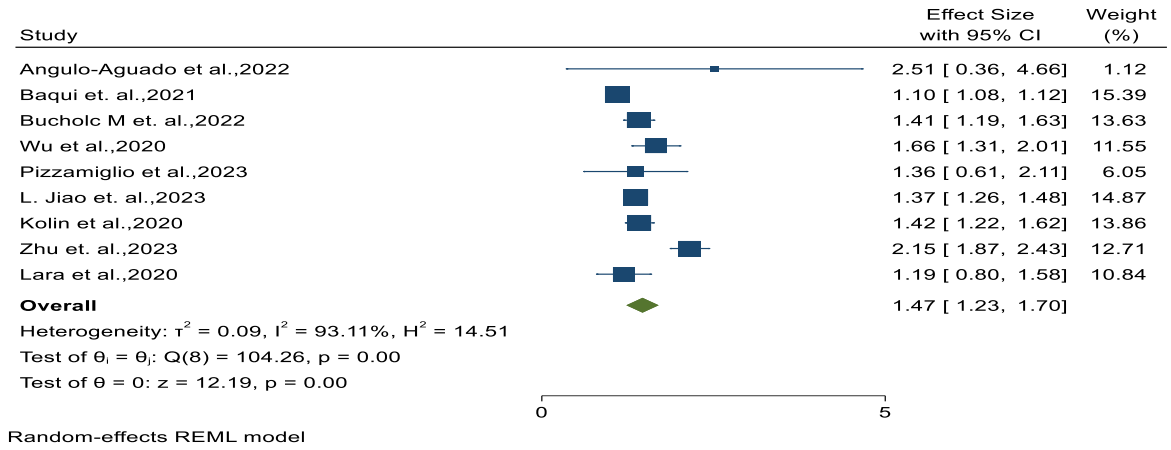

Figure 5 Forest plot of the association between sex (male) and COVID-19

Table 7 Meta regress Odds ratio for sex (male)

_meta_es	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
OR	1	.0979351	10.21	0.000	.8080508	1.191949
_cons	-2.22e-16	.1094035	-0.00	1.000	-.214427	.214427

Test of residual homogeneity: Q_res = chi2(7) = 0.00 Prob > Q_res = 1.0000

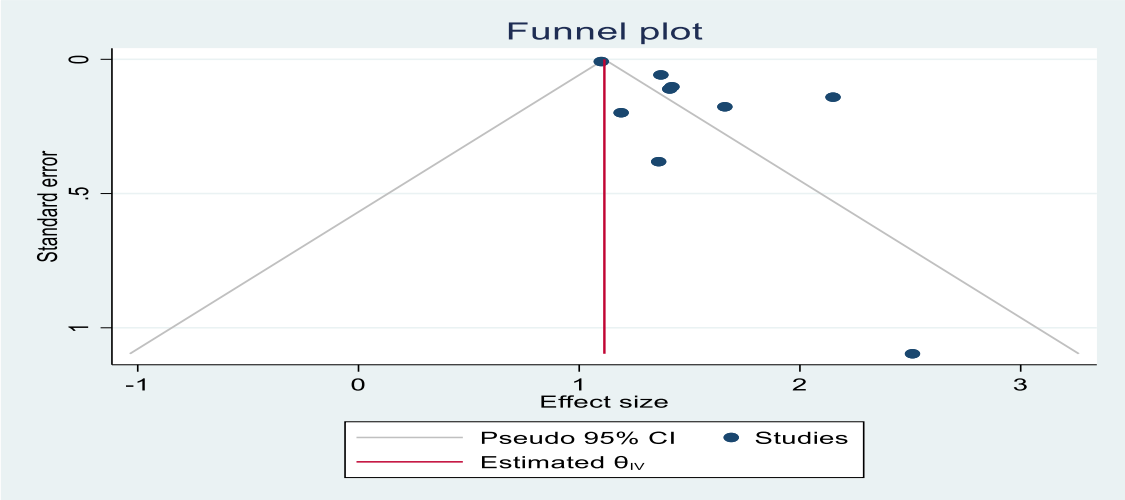

Figure 6 Funnel plot to access the publication bias for sex (male)

Race (black)

Table 8 Meta summary for Race/ethnicity (black)

Study	Effect Size	[95% Conf.	Interval]	% Weight
Baqui et. al.,2021	1.140	1.095	1.185	27.73
Macedo MCF et. al.,2020	0.630	-0.310	1.570	18.60
Kolin et al.,2020	2.530	1.825	3.235	21.74
Lara et al.,2020	2.690	0.745	4.635	8.93
Chung et. al.,2021	1.250	0.640	1.860	22.99
theta	1.511	0.805	2.217	

Test of theta = 0: z = 4.20 Prob > |z| = 0.0000
Test of homogeneity: Q = chi2(4) = 18.56 Prob > Q = 0.0010

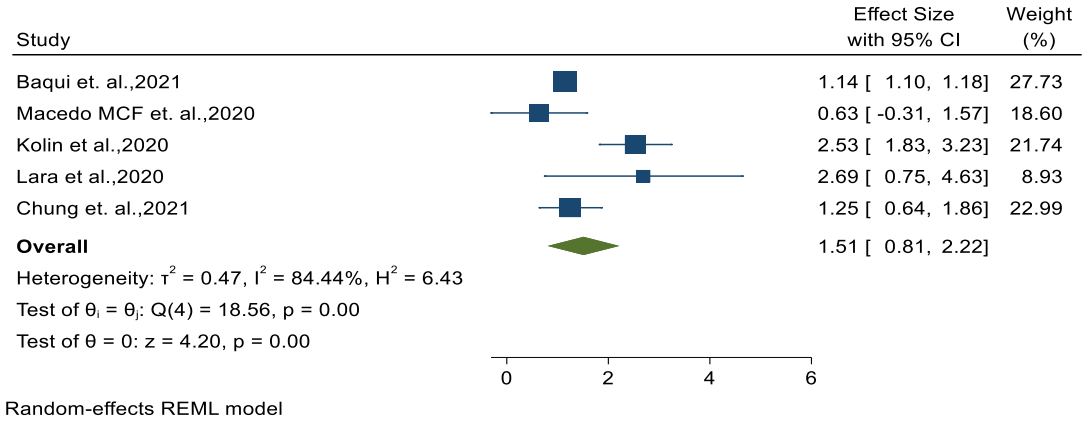

Figure 7 Forest plot of the association COVID-19 and Race/ethnicity (black)

Table 9 Meta regress for race/ethnicity (black)

_meta_es	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
OR	1	.2320993	4.31	0.000	.5450937	1.454906
_cons	0	.26693	0.00	1.000	-.5231732	.5231732

Test of residual homogeneity: Q_res = chi2(3) = 0.00 Prob > Q_res = 1.0000

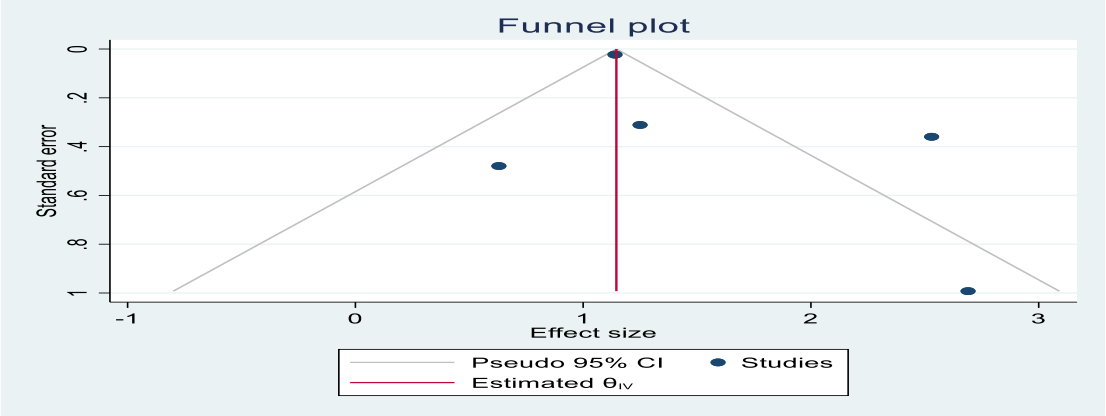

Figure 8 Funnel plot to access the publication bias for the race/ethnicity (black)

Comorbidities

Hypertension

Table 10 Meta summary for the Hypertension

Study	Effect Size	[95% Conf.	Interval]	% Weight
Santos CS, et al.,2020	2.250	0.705	3.795	5.35
Bader El Din et al.,2024	0.830	0.030	1.630	9.05
Caliskan, T et. al.,2020	1.570	0.470	2.670	7.38
Bucholc M et. al.,2022	0.940	0.790	1.090	11.96
Pinki Mishra et al.,2021	2.040	1.015	3.065	7.78
Luoet et. al.,2020	2.570	2.075	3.065	10.72
Jindal, et al.,2022	2.900	1.905	3.895	7.95
de Almeida-Piti..,2020	2.980	2.290	3.670	9.67
Wu et al.,2020	2.670	1.995	3.345	9.76
Yin et al.,2021	2.130	1.780	2.480	11.37
Pizzamiglio et al.,2023	1.370	0.565	2.175	9.02
theta	2.003	1.524	2.482	

Test of theta = 0: z = 8.20 Prob > |z| = 0.0000
Test of homogeneity: Q = chi2(10) = 121.27 Prob > Q = 0.0000

Table 11 Meta regress Odds ratio

```
. meta regress OR

  Effect-size label:  Effect Size
        Effect size:  OR
          Std. Err.:  SE

Random-effects meta-regression                  Number of obs   =        11
Method: REML                                    Residual heterogeneity:
                                                          tau2 = 2.7e-07
                                                       I2 (%)  =     0.00
                                                          H2   =     1.00
                                                R-squared (%)  =   100.00
                                                Wald chi2(1)   =   121.27
                                                Prob > chi2    =   0.0000
------------------------------------------------------------------------------
     _meta_es |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
--------------+---------------------------------------------------------------
           OR |          1   .0908077    11.01   0.000     .8220203     1.17798
        _cons |  -2.22e-16   .1392069    -0.00   1.000    -.2728404     .2728404
------------------------------------------------------------------------------
Test of residual homogeneity: Q_res = chi2(9) = -0.00     Prob > Q_res = 1.0000
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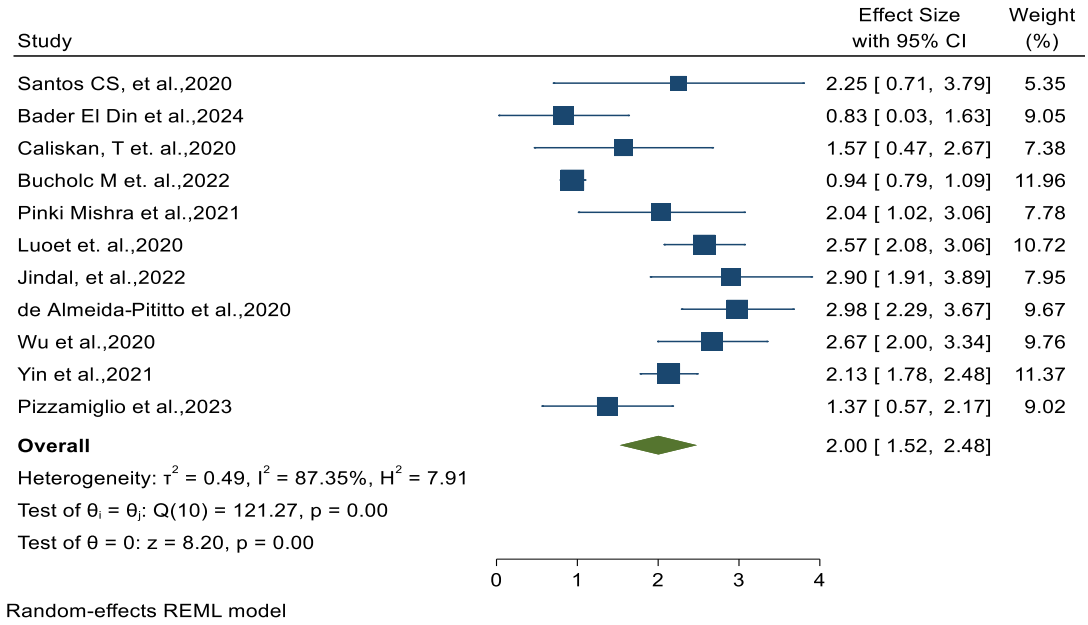

Figure 9 Forest plot of the association between COVID-19 and hypertension

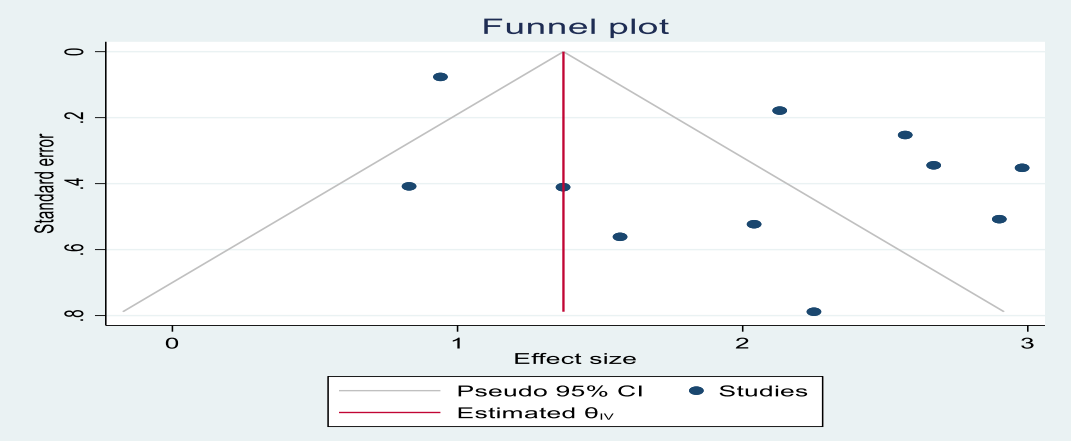

Figure 10 Funnel plot to access publication bias for the hypertension

Diabetes

Table 12 Meta summary for Diabetes

Study	Effect Size	[95% Conf.	Interval]	% Weight
Bader El Din et. al.,2024	1.380	-0.075	2.835	4.34
Baqui et. al.,2021	1.780	1.750	1.810	11.08
Macedo MCF et. al.,2020	1.160	0.940	1.380	10.70
Caliskan T et. al.,2020	1.150	0.230	2.070	6.84
Bucholc M et. al.,2022	1.130	0.925	1.335	10.75
Pinki Mishra et al.,2021	2.070	1.305	2.835	7.75
Luo et. al.,2020	2.540	1.780	3.300	7.79
Jindal, et al.,2022	3.710	2.375	5.045	4.80
de Almeida-Piti..,2020	2.350	1.720	2.980	8.58
Wu et al.,2020	2.140	1.720	2.560	9.81
Yin et al.,2021	2.490	2.060	2.920	9.76
Pizzamiglio et al.,2023	1.050	0.290	1.810	7.79
theta	1.854	1.466	2.243	

Test of theta = 0: z = 9.35 Prob > |z| = 0.0000
Test of homogeneity: Q = chi2(11) = 102.29 Prob > Q = 0.0000

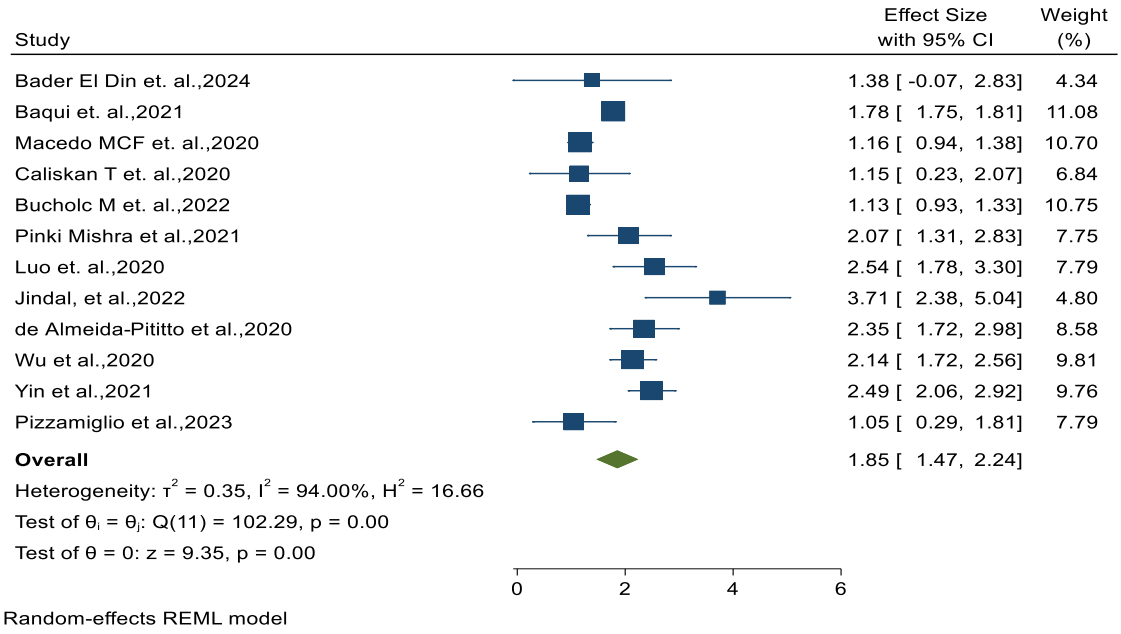

Figure 11 Forest plot of association COVID-19 and diabetes

Table 13 Meta regress odds ratio for diabetes

_meta_es	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
OR	1	.0988738	10.11	0.000	.8062108	1.193789
_cons	0	.1749261	0.00	1.000	-.3428489	.3428489

Test of residual homogeneity: Q_res = chi2(10) = -0.00 Prob > Q_res = 1.0000

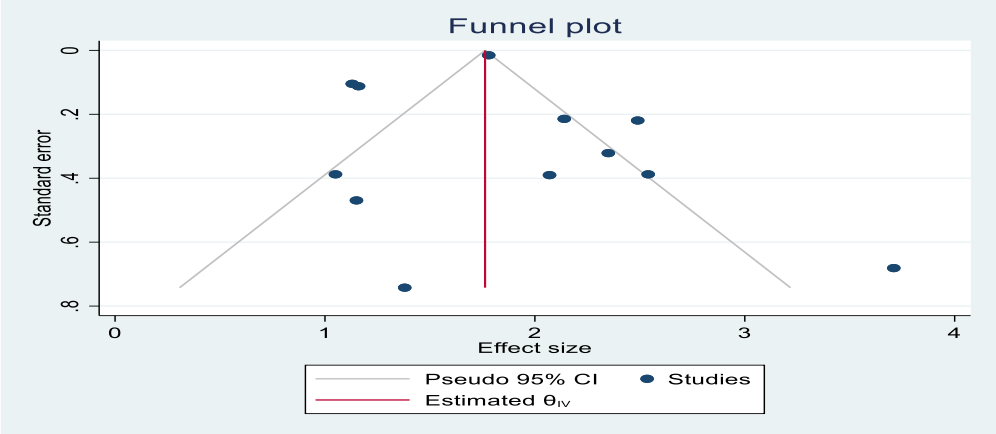

Figure 12 Funnel plot to access publication bias for diabetes

Cardiovascular disease

Table 14 Meta summary for the cardiovascular disease

Study	Effect Size	[95% Conf.	Interval]	% Weight
Santos CS, et al.,2020	2.730	0.380	5.080	6.10
Baqui et. al.,2021	1.820	1.785	1.855	15.60
Macedo MCF et. al.,2020	0.940	0.760	1.120	15.46
Pinki et al.,2021	2.780	-0.045	5.605	4.80
Luo et. al.,2020	3.860	2.450	5.270	9.99
Jindal, et al.,2022	3.170	2.095	4.245	11.77
De Almeida-Piti..,2020	4.020	2.470	5.570	9.30
Wu et al.,2020	3.150	2.320	3.980	13.06
Yin et al.,2021	2.760	2.105	3.415	13.92
theta	2.657	1.914	3.401	

Test of theta = 0: z = 7.01 Prob > |z| = 0.0000
Test of homogeneity: Q = chi2(8) = 130.72 Prob > Q = 0.0000

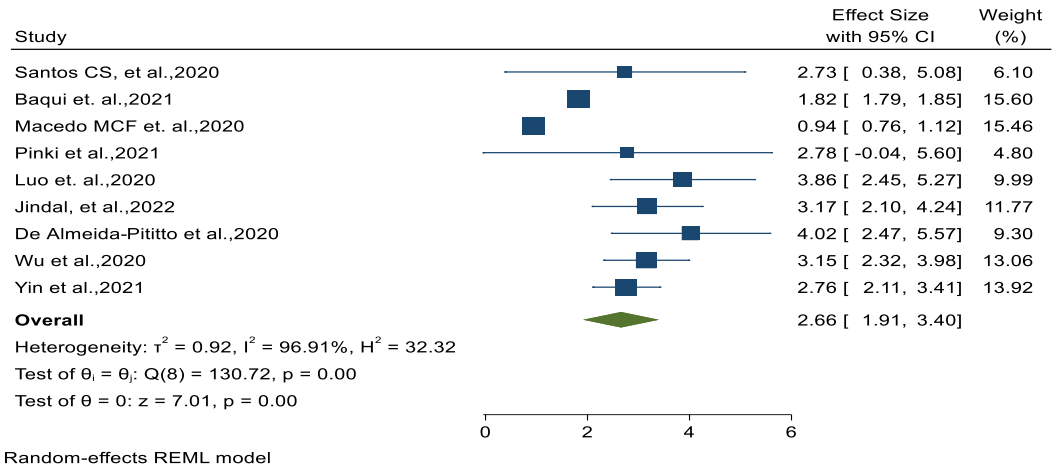

Figure 13 Forest plot of the association between COVID-19 and cardiovascular disease

Table 15 Meta regress odds ratio for cardiovascular disease

_meta_es	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
OR	1	.0874658	11.43	0.000	.8285702	1.17143
_cons	-4.44e-16	.1581411	-0.00	1.000	-.3099509	.3099509

Test of residual homogeneity: Q_res = chi2(7) = -0.00 Prob > Q_res = 1.0000

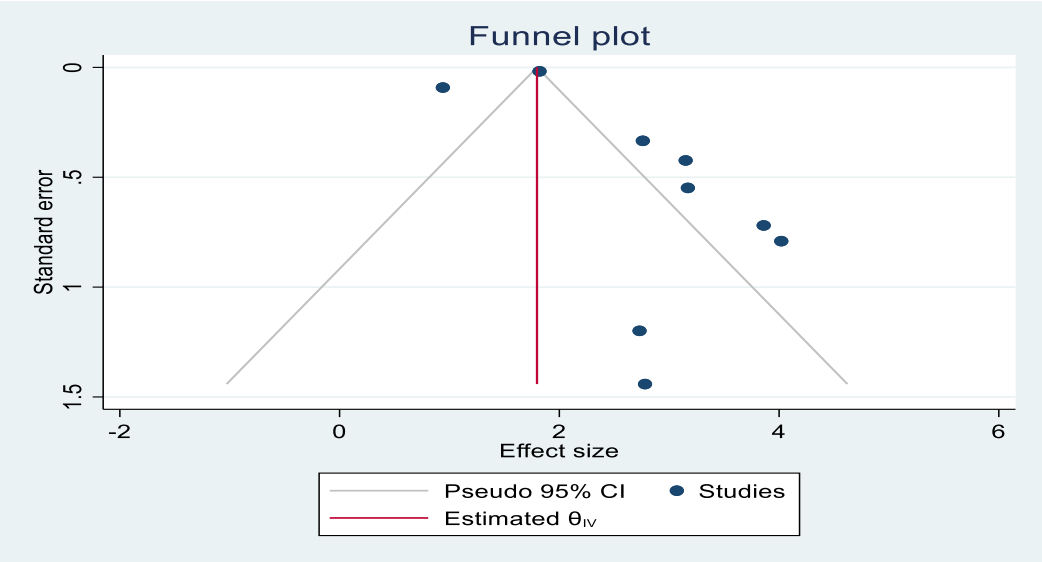

Figure 14 Funnel plot to access the publication bias for the cardiovascular disease

Chronic kidney disease

Table 16 Meta summary for the chronic kidney disease

Study	Effect Size	[95% Conf.	Interval]	% Weight
Angulo-Aguado et al.,2022	5.170	-17.360	27.700	0.05
Macedo MCF et. al.,2020	2.410	1.505	3.315	33.94
Pinki Mishra et al.,2021	2.160	0.895	3.425	17.37
LUOET AL.,2020	2.200	0.935	3.465	17.37
Jindal, et al.,2022	4.100	-0.660	8.860	1.23
Wu et al.,2020	3.040	1.920	4.160	22.16
Yin et al.,2021	3.600	1.720	5.480	7.87
theta	2.586	2.058	3.113	

Test of theta = 0: z = 9.61 Prob > |z| = 0.0000
Test of homogeneity: Q = chi2(6) = 3.13 Prob > Q = 0.7928

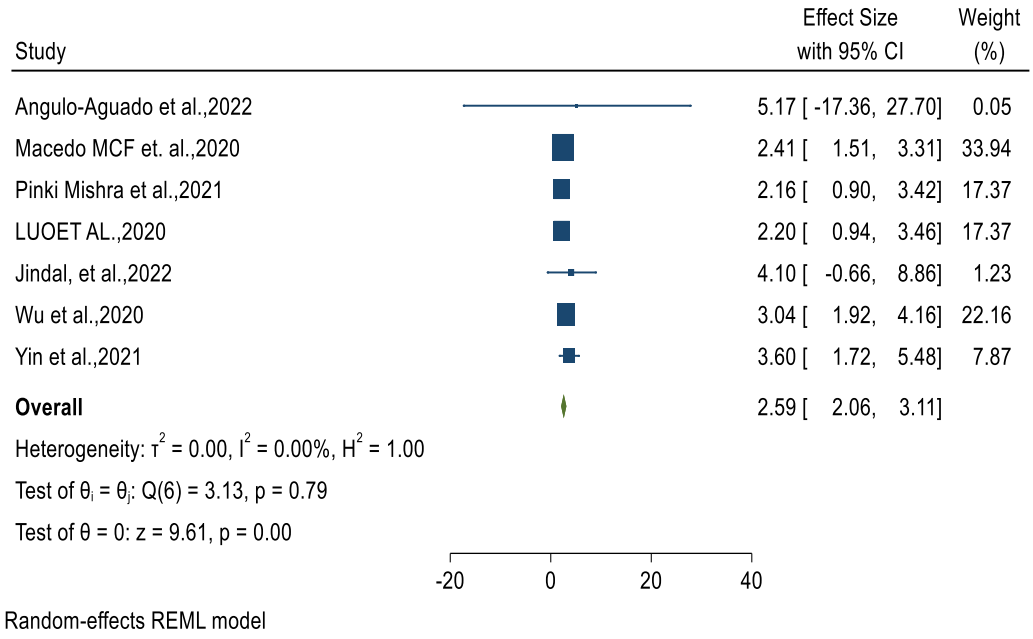

Figure 15 Forest plot association between COVID-19 and the chronic kidney disease

Table 17 Meta regress odds ratio for chronic kidney disease

_meta_es	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
OR	1	.56554	1.77	0.077	-.1084379	2.108438
_cons	0	1.486777	0.00	1.000	-2.914029	2.914029

Test of residual homogeneity: Q_res = chi2(5) = -0.00 Prob > Q_res = 1.0000

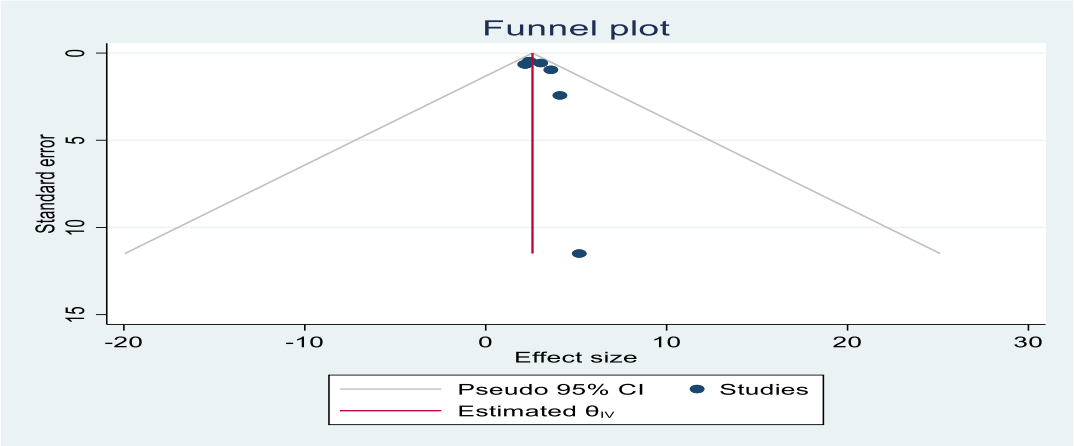

Figure 16 Funnel plot to access the publication bias for the chronic kidney disease

Cancer

Table 18 Meta summary for the Cancer

Study	Effect Size	[95% Conf.	Interval]	% Weight
LUOET AL.,2020	2.420	1.715	3.125	17.14
Wu et al.,2020	3.050	1.585	4.515	8.42
L. Sun et al.,2020	2.160	0.630	3.690	7.94
V. De Rubeis et. al.,2024	1.130	1.025	1.235	24.69
Kondili et. al.,2022	1.720	1.055	2.385	17.75
M. F. Guerra Veloz et al.,2020	2.050	-0.265	4.365	4.22
L. Jiao et. al.,2023	1.320	0.790	1.850	19.84
theta	1.776	1.254	2.298	

Test of theta = 0: z = 6.67 Prob > |z| = 0.0000
Test of homogeneity: Q = chi2(6) = 23.89 Prob > Q = 0.0005

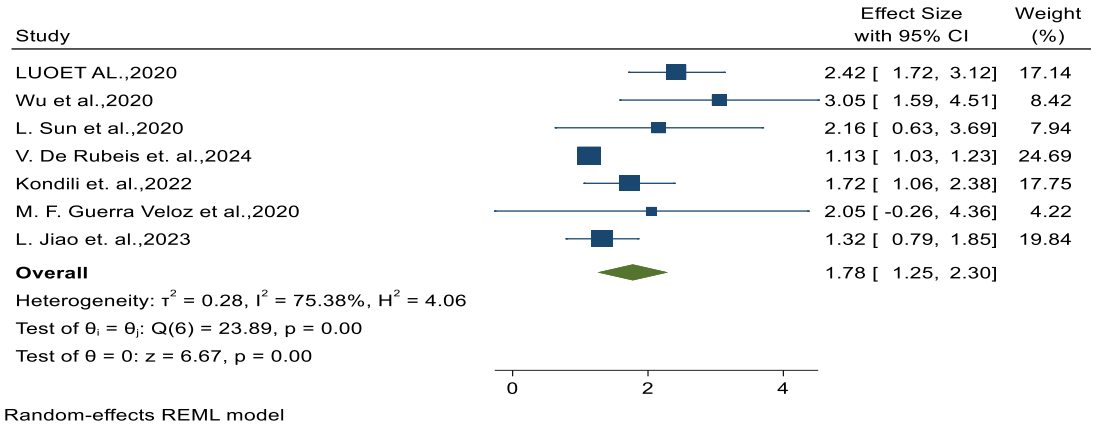

Figure 17 Forest plot of the association between COVID-19 and Cancer

Table 19 Meta regress odds ratio

_meta_es	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
OR	1	.2046151	4.89	0.000	.5989618	1.401038
_cons	0	.2490741	0.00	1.000	-.4881762	.4881762

Test of residual homogeneity: Q_res = chi2(5) = -0.00 Prob > Q_res = 1.0000

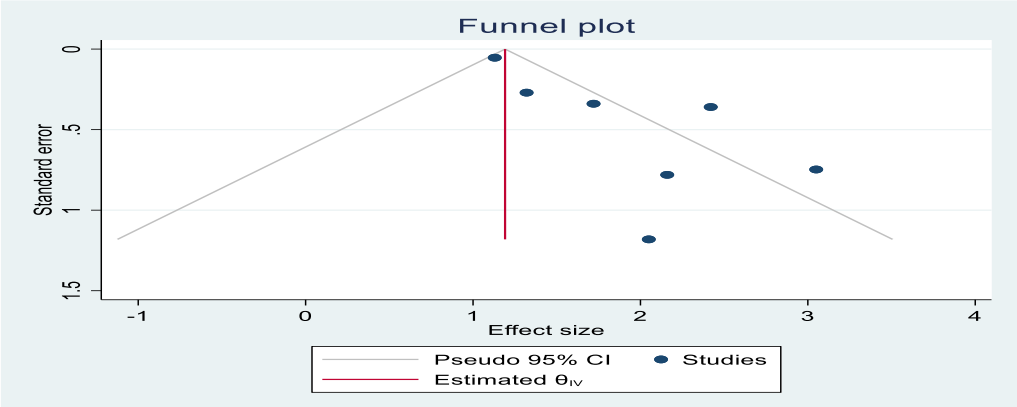

Figure 18 Funnel plot to access the publication bias for the Cancer

BMI (Obesity)

Table 20 Meta summary for the BMI/Obesity

Study	Effect Size	[95% Conf.	Interval]	% Weight
Angulo-Aguado et al.,2022	2.310	-0.040	4.660	0.35
Baqui et. al.,2021	1.160	1.115	1.205	41.06
Bucholc M et. al.,2022	5.270	1.975	8.565	0.18
Pizzamiglio et al.,2023	2.240	0.705	3.775	0.82
V. De Rubeis et. al.,2024	1.150	1.085	1.215	39.26
MF Guerra Veloz et al.,2020	1.230	-0.170	2.630	0.98
L Jiao et. al.,2023	1.450	1.190	1.710	17.35
theta	1.227	1.087	1.368	

Test of theta = 0: z = 17.14 Prob > |z| = 0.0000
Test of homogeneity: Q = chi2(6) = 13.63 Prob > Q = 0.0340

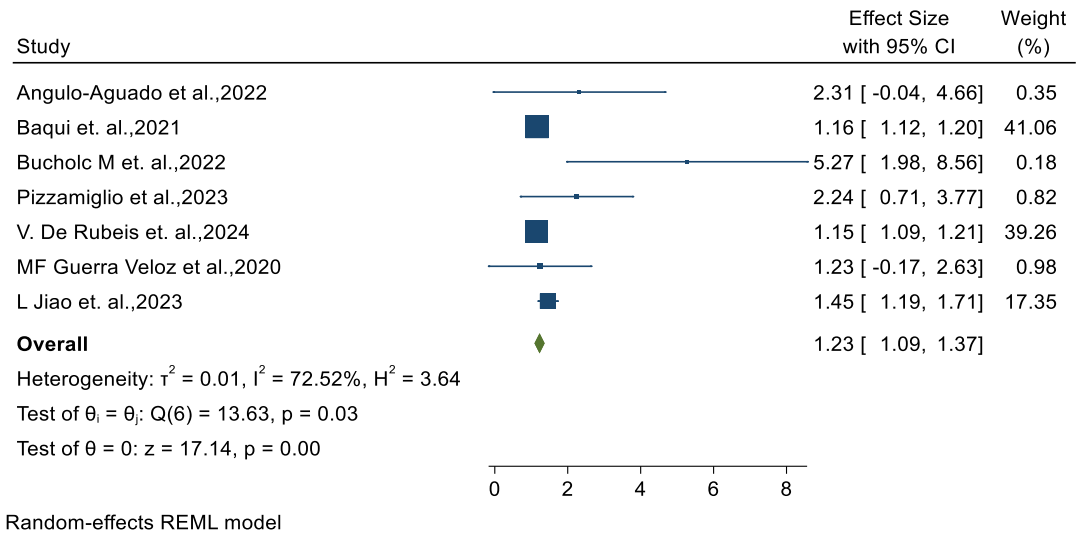

Figure 19 Forest plot of the association between COVID-19 and BMI/Obesity

Table 21 Meta regress odds ratio

_meta_es	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
OR	1	.2708444	3.69	0.000	.4691548	1.530845
_cons	-2.22e-16	.3158221	-0.00	1.000	-.6189999	.6189999

Test of residual homogeneity: Q_res = chi2(5) = -0.00 Prob > Q_res = 1.0000

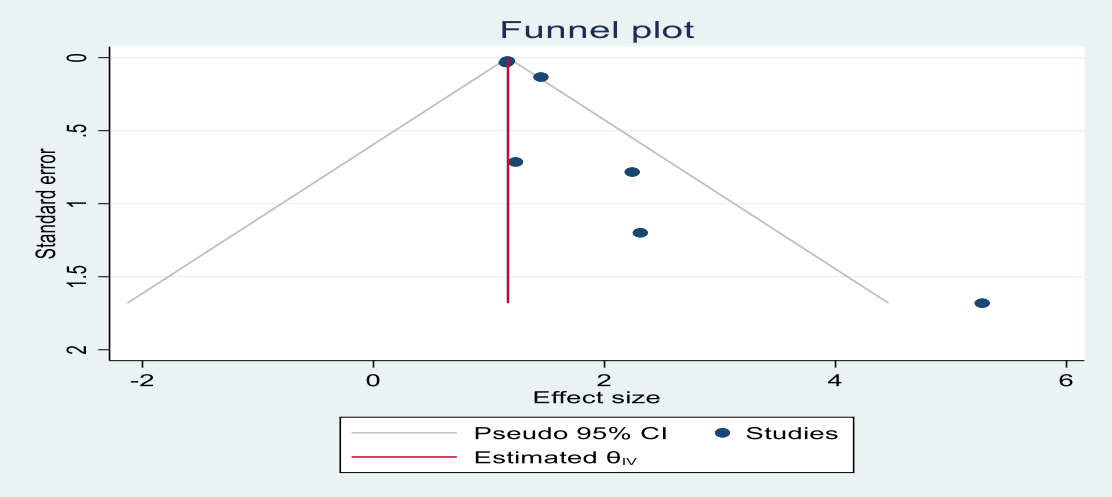

Figure 20 Funnel plot to access the publication bias for the BMI/obesity

Vitamin D

Table 22 Meta summary for the vitamin-D

Study	Effect Size	[95% Conf.	Interval]	% Weight
Mirghani et. al.,2024	1.100	0.655	1.545	12.99
Autier P et. al.,2025	0.920	0.855	0.985	15.42
MM García-Zendeja..,2023	2.790	-2.425	8.005	0.57
H. Sh. Ahmed et al.,2024	1.510	1.195	1.825	14.12
Wang et. al.,2021	2.180	1.315	3.045	8.97
Kaya MO et al.,2021	2.420	0.395	4.445	3.11
Li S., et al.,2020	2.330	1.990	2.670	13.92
Heidari et. al.,2021	1.060	1.030	1.090	15.47
Rathod, et al.,2023	1.070	1.020	1.120	15.44
theta	1.438	1.038	1.838	

Test of theta = 0: z = 7.05 Prob > |z| = 0.0000
Test of homogeneity: Q = chi2(8) = 87.75 Prob > Q = 0.0000

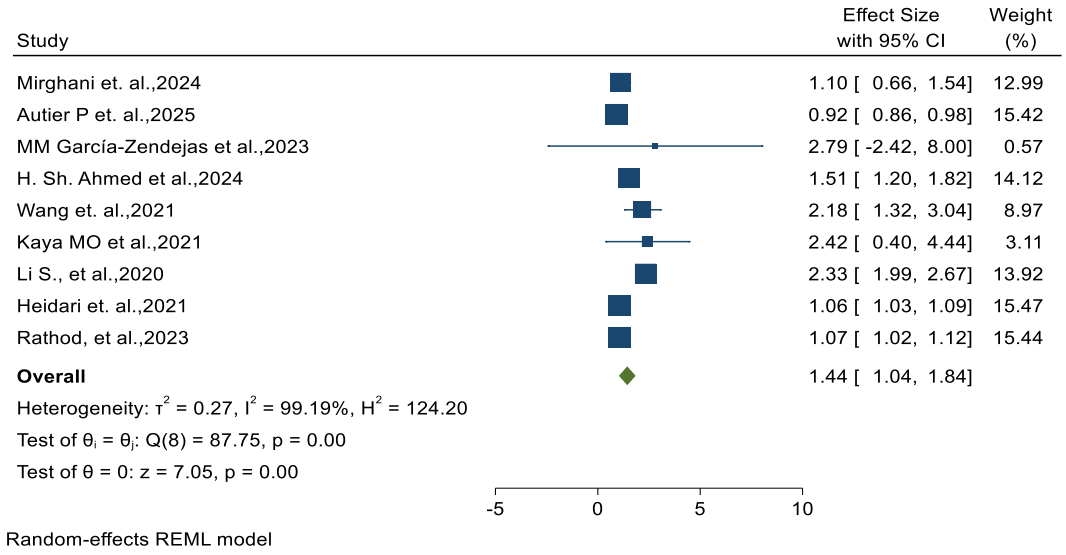

Figure 21 Forest plot of the association between COVID-19 and vitamin D

Table 23 Meta regress odds ratio

_meta_es	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
OR	1	.1067603	9.37	0.000	.7907536	1.209246
_cons	0	.1131243	0.00	1.000	-.2217196	.2217196

Test of residual homogeneity: Q_res = chi2(7) = -0.00 Prob > Q_res = 1.0000

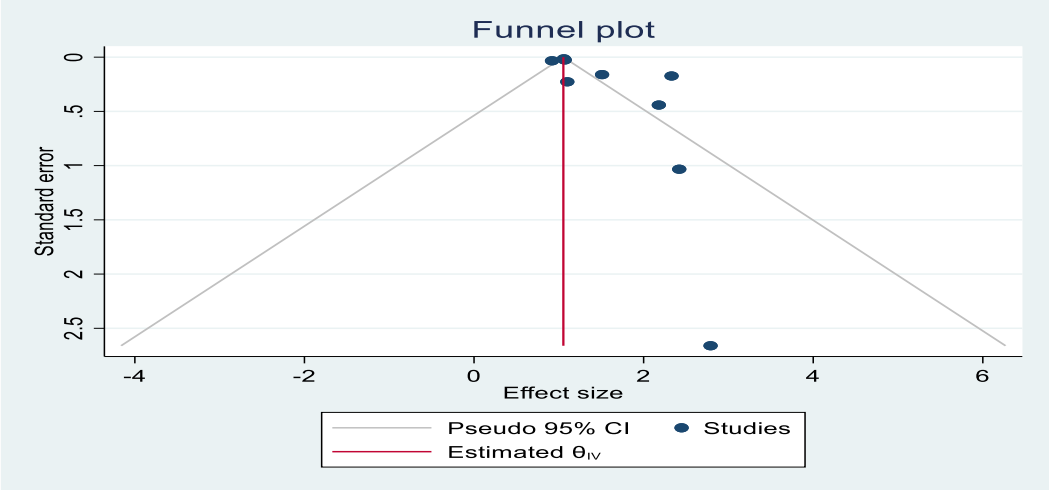

Figure 22 Funnel plot to access the publication bias for the vitamin D

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