Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Background: The association of asthma with the risk for mortality among coronavirus disease 2019 (COVID-19) patients is not clear.

Objective: To investigate the association between asthma and the risk for mortality among COVID-19 patients.

Methods: We performed systematic searches through electronic databases including PubMed, EMBASE, and Web of Science to identify potential articles reporting adjusted effect estimates on the association of asthma with fatal COVID-19. A random-effects model was conducted to estimate pooled effects. Sensitivity analysis, subgroup analysis, meta-regression, Begg’s test, and Egger’s test were also performed.

Results: Based on 62 studies with 2,457,205 cases reporting adjusted effect estimates, COVID-19 patients with asthma had a significantly reduced risk for mortality compared with those without it (15 cohort studies: 829,670 patients, pooled hazard ratio [HR] = 0.88, 95% confidence interval [CI], 0.82-0.95, \(I^2 = 65.9\%\), \(P < .001\); 34 cohort studies: 1,008,015 patients, pooled odds ratio [OR] = 0.88, 95% CI, 0.82-0.94, \(I^2 = 39.4\%\), \(P = .011\); and 11 cross-sectional studies: 1,134,738 patients, pooled OR = 0.87, 95% CI, 0.78-0.97, \(I^2 = 41.1\%\), \(P = .075\)). Subgroup analysis based on types of adjusted factors indicated that COVID-19 patients with asthma had a significantly reduced risk for mortality among studies adjusting for demogrophic, clinical, and epidemiologic variables (pooled OR = 0.87, 95% CI, 0.83-0.92, \(I^2 = 36.3\%\), \(P = .013\); pooled HR = 0.90, 95% CI, 0.83-0.97, \(I^2 = 69.2\%\), \(P < .001\)), but not among studies adjusting only for demographic variables (pooled OR = 0.88, 95% CI, 0.70-1.12, \(I^2 = 40.5\%\), \(P = .097\); pooled HR = 0.82, 95% CI, 0.64-1.06, \(I^2 = 0\%\), \(P = .495\)). Sensitivity analysis proved that our results were stable and robust. Both Begg’s test and Egger’s test indicated that publication bias did not exist.

Conclusions: Our data based on adjusted effect estimates indicated that asthma was significantly related to a reduced risk for COVID-19 mortality.

Key words: Asthma; COVID-19; Mortality; Meta-analysis; Adjusted effect estimate

Introduction

A recent systematic review by Liu et al1 suggested that coronavirus disease 2019 (COVID-19) patients with asthma had a lower risk for death compared with those without it, based on crude effects from six studies. Another systematic review by Shi et al2 based on 12 eligible articles reporting adjusted effects, also indicated that asthma was associated with a significantly reduced risk for COVID-19 mortality. These two studies are interesting.
However, these systematic reviews do not explore sources of heterogeneity; also, more recent primary studies with larger sample sizes have been published. Therefore, an updated meta-analysis based on risk factor-adjusted effects was performed to verify the relationship between asthma and COVID-19 mortality, considering that several factors (sex, age, and underlying comorbidities) significantly affected the clinical outcomes of COVID-19 patients.8–7

METHODS

This meta-analysis was conducted in line with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.8 Systematic searches were carried out in Web of Science, PubMed and EMBASE to identify potential articles as of June 25, 2021. Search terms used were “2019-nCoV” or “SARS-CoV-2” or “COVID-19” or “coronavirus disease 2019” or “severe acute respiratory syndrome coronavirus 2” and “asthma.” Full queries for each bibliographic database are available in Table E1 (in this article’s Online Repository at www.jaci-inpractice.org). We included primary studies comparing COVID-19 patients with asthma versus those without asthma regarding mortality, and in which adjusted effect estimates on the association between asthma and COVID-19 mortality were reported. In the case of a study resulting in more than one publication, only the one with more complete data was included. Duplicated publications, reviews, errata, protocols, comments, case reports, and studies with incomplete data were excluded.

Two independent authors (H. Hou and Y. Li) screened articles and abstracted essential information from all included eligible studies. Any disagreement was resolved by discussion. An assessment of study quality using National Institutes of Health Study Quality Assessment tools was performed by two independent reviewers (Y. Wang and H. Yang). For all included articles, study quality was judged as good, fair, or poor (see Table E2 in this article’s Online Repository at www.jaci-inpractice.org). Basic information, including the first author, study period, prevalence of asthma, country or region, number of cases, age (means and SDs or medians with interquartile ranges), percentage of males, study design, adjusted risk factors, and adjusted effects, was extracted from each eligible article.

We conducted statistical analyses using STATA (version 12.1, StataCorp LP, College Station, Tex) and R (version 3.6.3, The R Foundation, Vienna, Austria). The pooled effect (pooled odds ratio [OR] and/or hazard ratio [HR]) and its 95% confidence interval (CI) were estimated by a random-effects model. Moreover, we presented separate results for the pooled OR and pooled HR. Heterogeneity across studies was assessed by Higgins’s I² statistic and chi-squared-based Q test. Publication bias was investigated by Begg’s test and Egger’s test. Sensitivity analysis was conducted to evaluate the stability of our results by omitting each eligible study one at a time. Meta-regression and subgroup analyses were performed to investigate potential sources of heterogeneity (such as age, sex, region, data collection period (number of months since the first COVID-19 case), hospitalization status, and the types of adjusted factors). Two-tailed P less than .05 was considered statistically significant.

RESULTS

A total of 62 studies9–70 with 2,457,205 patients were included. Basic characteristics of the included studies are presented in Table I. A flowchart of the study search and selection is shown in Figure 1. Sample sizes across the included studies ranged from 132 to 654,858. There were 30 studies conducted in North America (21 in the United States, eight in Mexico, and one in Canada), 15 in Europe (eight in the United Kingdom, two in Spain, and one each in Ireland, Italy, France, Belgium, and Sweden), 11 in Asia (six in Korea and one each in China, Turkey, Iran, Kuwait, and Saudi Arabia), and six in other regions (three in Brazil, one in Nigeria, one in Libya, and one from an international center). There were 39 retrospective cohort studies, 11 cross-sectional studies, nine prospective cohort studies, two case-control studies, and one case series.

Overall results based on adjusted effect estimates demonstrated that COVID-19 patients with asthma had a significantly reduced risk for mortality compared with those without it (15 cohort studies: 829,670 patients, pooled HR = 0.88, 95% CI, 0.82-0.95, I² = 65.9%, P < .001; 34 cohort studies: 1,008,015 patients, pooled OR = 0.88, 95% CI, 0.82-0.94, I² = 39.4%, P = .011; 11 cross-sectional studies: 1,134,738 patients, pooled OR = 0.87, 95% CI, 0.78-0.97, I² = 41.1%, P = .075) (Figure 2). The results of subgroup analysis based on hospitalization status showed that asthma was associated with a significantly reduced risk for mortality in COVID-19 patients when we restricted the analysis to studies that included only hospitalized patients (20 studies: 751,644 patients, pooled OR = 0.87, 95% CI, 0.79-0.95, I² = 44.0%, P = .019; 11 studies: 811,941 patients, pooled HR = 0.87, 95% CI, 0.81-0.94, I² = 68.7%, P < .001) (Figure 3). The significant association was observed in studies reporting ORs but not in those reporting HRs in subgroups that included all laboratory-confirmed patients (36 studies: 1,391,631 patients, pooled OR = 0.88, 95% CI, 0.82-0.94, I² = 31.5%, P = .064; six studies: 24,156 patients, pooled HR = 1.10, 95% CI, 0.80-1.50, I² = 66.2%, P = .011) (Figure 3). The inconsistency of results may be a result of the difference in the number of studies in each subgroup; subgroups with fewer studies tended to conclude more often that asthma was not associated with mortality in COVID-19 patients. Subgroup analysis based on types of adjusted factors indicated that COVID-19 patients with asthma had a significantly reduced risk for mortality among studies adjusting for demographic, clinical, and epidemiologic variables (39 studies: 2,078,426 patients, pooled OR = 0.87, 95% CI, 0.83-0.92, I² = 36.3%, P = .013; 16 studies: 835,345 patients, pooled HR = 0.90, 95% CI, 0.83-0.97, I² = 69.2%, P < .001) (Figure 4), but not among studies adjusting only for demographic variables (nine studies: 97,434 patients, pooled OR = 0.88, 95% CI, 0.70-1.12, I² = 40.5%, P = .097; two studies: 10,883 patients, pooled HR = 0.82, 95% CI, 0.64-1.06, I² = 0%, P = .495) (Figure 4). Further subgroup analysis by region revealed that COVID-19 patients with asthma had a significantly reduced risk for mortality.
| First author | Study period | Country          | Prevalence of asthma, n (%) | Patients, n | Population | Male (%) | Age, y | Study design          | Adjusted-effect (95% confidence interval) | Confounders                                                                 |
|-------------|--------------|------------------|----------------------------|-------------|------------|----------|--------|------------------------|----------------------------------------|--------------------------------------------------------------------------------|
| Shah¹        | March 2 to May 6, 2020 | United States     | 68 (13.0)                  | 522         | All hospitalized patients with confirmed COVID-19 | 41.8      | 63 (50-72) | Case-control study | OR: 0.74 (0.33-1.64) | Age, BMI, sex, race, all baseline comorbidities |
| Arshad¹⁰     | March 10 to May 2, 2020 | United States     | 251 (9.9)                  | 2541        | All hospitalized adult patients with confirmed COVID-19 | 51.1      | 63.7 ± 16.5 | Retrospective cohort study | HR: 0.916 (0.632-1.327) | Hydroxychloroquine alone, azithromycin alone, hydroxychloroquine plus azithromycin, age, sex, race, BMI, lung comorbidity, immunodeficiency comorbidity, cardiovascular comorbidity, CKD, COPD, HTN, cancer comorbidity, DM, percent O₂ saturation <95, admitted to ICU, ventilator, given steroid, given tocilizumab |
| Mato¹¹       | February 17 to April 30, 2020 | International center | 12 (6.1)                  | 198         | All patients diagnosed with confirmed COVID-19 | 63        | 63 (35-92) | Retrospective cohort study | HR: 2.5 (1.1-5.8) | Age, CIRS score, DM, chronic renal disease |
| Poblador-Plou¹² | March 4 to May 17, 2020 | Spain             | NR                         | 4412        | All individuals with laboratory-confirmed infection by SARS-CoV-2 | 41.2      | 67.7 ± 20.7 | Retrospective cohort study | OR: 0.45 (0.18-1.11) OR: 0.68 (0.40-1.17) | Age |
| van Gerwen¹³ | March 1 to May 13, 2020 | United States     | 430 (11.6)                 | 3703        | All adult patients with laboratory-confirmed diagnosis of COVID-19 | 55.3      | 56.8 ± 18.2 | Retrospective cohort study | OR: 0.89 (0.64-1.25) | Age group, sex, race, BMI, smoking status, comorbidities (HTN, CAD, AF, CHF, PVD, CVA/TIA, dementia, DM, hypothyroidism, CKD, malignancy, COPD, and prior VTE) |
| Study | Date Range | Country | Cases | Controls | Methods | OR (95% CI) | Risk Factors |
|-------|------------|---------|-------|----------|----------|-------------|--------------|
| Hernandez-Galdamez | Up to June 27, 2020 | Mexico | 5854 (2.77) | 211,003 | Laboratory-confirmed COVID-19 cases | 54.71 | 45.7 ± 16.3 | Cross-sectional study | 0.82 (0.74-0.90) | Age, sex, CKD, immunosuppression, DM, COPD, HTN, CVD, obesity and smoking |
| Hernandez-Vasquez | Up to May 18, 2020 | Mexico | 1590 (3.1) | 51,053 | Patients with confirmed COVID-19 | 57.6 | 46.6 ± 15.8 | Cross-sectional study | 1.02 (0.84-1.23) | Age, gender, smoking |
| Almazedi | February 24 to April 20, 2020 | Kuwait | 43 (3.9) | 1096 | All patients with confirmed COVID-19 | 81 | 41 (25-75) | Retrospective cohort study | 4.92 (1.03-23.44) | Age, obesity, DM, HTN, chronic renal disease, smoker, qSOFA score, elevated procalcitonin, and elevated CRP |
| Perez-Guzman | February 25 to May 1, 2020 | United Kingdom | 56 (9.1) | 614 | Patients admitted for COVID-19 | 62.21 | 69 ± 25 | Retrospective cohort study | 0.42 (0.19-0.91) | Age |
| Tartof | February 13 to May 23, 2020 | United States | 1273 (18.4) | 6916 | Members diagnosed with COVID-19 | 44.98 | 49.1 ± 16.6 | Retrospective cohort study | Risk ratio: 0.81 (0.54-1.21) | BMI, age, sex, race and ethnicity, smoking, metastatic tumor/cancer, MI, other immune condition, organ transplant, CHF, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, renal disease, HTN, DM status, and time |
| Parra-Bracamonte | January 13 to June 13, 2020 | Mexico | 4028 (2.8) | 142,690 | All cases positive for COVID-19 | 56 | 45 (34.0-57.0) | Cross-sectional study | 0.949 (0.832-1.082) | Age, sex, smoking habits, hospitalization, and comorbidity traits |
| Fox | March 1 to April 24, 2020 | United States | 27 (7.6) | 355 | All hospitalized adult patients with confirmed COVID-19 | 49 | 66.21 ± 14.21 | Retrospective cohort study | 0.714 (0.076-6.670) | Age, BMI, sex, ethnicity, COPD, heart failure, HTN, CAD, AF, and CKD |

(continued)
| First author | Study period | Country   | Prevalence of asthma, n (%) | Patients, n | Population | Male (%) | Age, y | Study design | Adjusted-effect (95% confidence interval) | Confounders                                                                                                                                 |
|-------------|--------------|-----------|-----------------------------|-------------|------------|----------|-------|--------------|-------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Yehia²²     | February 19 to June 25, 2020 | United States | 628 (5.6) | 11,210 | All hospitalized adult patients with confirmed COVID-19 | 49.8 | 61 (46-74) | Retrospective cohort study | HR: 0.91 (0.74-1.12) | Race, age, sex, insurance, Agency for Healthcare Research and Quality Elixhauser Comorbidity Index scores, neighborhood deprivation index scores, cancer, CKD, COPD, CHF, CAD, DM, and obesity |
| Emami²²     | February 20 to March 1, 2020  | Iran      | 25 (2.0) | 1239 | All hospitalized patients with confirmed COVID-19 | 55.9 | 51.48 ± 19.54 | Retrospective cohort study | HR: 1.04 (0.53-2.02) | Age, DM, CVD, chronic liver disease, CKD, cancer, human immunodeficiency virus, smoking, and immunodeficiency disease |
| Trabulus²³  | March 15 to June 1, 2020      | Turkey    | 20 (6.0) | 336  | All hospitalized adult patients with confirmed COVID-19 | 57.1 | 55.0 ± 16.0 | Retrospective cohort study | OR: 3.087 (0.382-24.965) | Age                                                                                                                                 |
| Santos²⁴    | February 20 to June 2, 2020   | Brazil    | 488 (5.7) | 80,102 | All hospitalized patients with confirmed COVID-19 | 57.3 | NR | Retrospective cohort study | HR: 0.71 (0.61-0.81) | ICU, DM, neurological, kidney disease, cardiopathy, race, and pneumopathy                                                                 |
| Ioannou²⁵   | February 28 to June 22, 2020  | United States | 745 (7.4) | 10,131 | Patients with confirmed COVID-19 | 91 | 63.6 ± 16.2 | Retrospective cohort study | HR: 0.80 (0.60-1.05) | All sociodemographic characteristics, comorbid conditions, and symptoms                                                                 |
| Gutierrez²⁶ | Through September 16, 2020   | Mexico    | 17,026 (2.6) | 654,858 | Adult (age ≥20 y) patients with confirmed COVID-19 | 52.21 | 46.1 (45.8-46.3) | Cross-sectional study | OR: 0.85 (0.65-0.81) | Sex, age, indigenous speaker, obese, smoking, COPD, chronic renal disease, CVD, ministry of health, social security, private health provider, and quintiles of share poverty |
| Study | Dates | Country | Participants | Age | BMI | Townsend Score | Study Design | HR (and 95% CI) | Conditions and Treatments |
|-------|-------|---------|--------------|-----|-----|---------------|--------------|----------------|--------------------------|
| Clift 27 | January 24 to April 30, 2020 | United Kingdom | 825,422 (13.57) | 10,776 | All adult patients with laboratory-confirmed diagnosis of COVID-19 | 55.33 | 69.6 ± 17.9 | Prospective cohort study | HR: 0.84 (0.73-0.97) | Age, BMI, Townsend score (linear), ethnic group, domicile (residential care, homeless, neither), and range of conditions and treatments |
| Kim 28 | March 1 to May 12, 2020 | United States | 903 (8.3) | 10,861 | All hospitalized adult patients with confirmed COVID-19 | 59.6 | 65 (54-77) | Prospective cohort study | OR: 0.81 (0.67-0.98) | Age, sex, race and ethnicity, presence of comorbidities, smoking status, hospital type, and BMI groups |
| Tang 29 | March 1 to June 16, 2020 | United States | 54 (7.2) | 752 | All individuals with laboratory-confirmed infection by SARS-CoV-2 | 39.9 | 72.1 ± 11.9 | Retrospective cohort study | HR: 0.64 (0.30-1.40) | Age, sex, race, and facility |
| Ken-Dror 30 | March to April, 2020 | United Kingdom | 42 (12.8) | 429 | All hospitalized adult patients with confirmed COVID-19 | 56.4 | 70 ± 18 | Prospective cohort study | OR: 3.22 (1.16-8.92) | Age, CRP, respiratory rate, diastolic blood pressure, dementia, Akaike information criterion, area under the curve, and sensitivity/specificity |
| Choi 31 | NR | Korea | 96 (2.3) | 4057 | Hospitalized patients with mild to critical COVID-19 nationwide | 42.5 | NR | Prospective cohort study | HR: 2.20 (1.02-4.76) | Age, sex, obesity, systolic blood pressure, diastolic blood pressure, heart rate, temperature, DM, HTN, heart failure, chronic heart disease, COPD, CKD, cancer, chronic liver disease, rheumatic or autoimmune disease, and dementia |
| Nyabera 32 | February 1 to April 30, 2020 | United States | 18 (6.2) | 290 | Older adult inpatients (≥65 y) with laboratory-confirmed COVID-19 infection | 51.7 | 77.6 ± 8.3 | Retrospective cohort study | OR: 0.66 (0.24-1.83) | BMI, age, CAD, COPD, DM, end-stage renal disease, and HTN |

(continued)
| First author | Study period       | Country       | Prevalence of asthma, n (%) | Patients, n | Population | Male (%) | Age, y | Study design         | Adjusted-effect (95% confidence interval) | Confounders                                                                 |
|-------------|--------------------|---------------|----------------------------|-------------|------------|----------|--------|----------------------|---------------------------------------------|--------------------------------------------------------------------------------|
| Lee         | January 20 to May 27, 2020 | Korea        | 686 (9.4)                  | 7272        | Adult COVID-19 patients | 40.3     | NR     | Retrospective cohort study | OR: 1.06 (0.71-1.59) | Age, sex, and CCI |
| Murillo-Zamora | March 4 to August 15, 2020 | Mexico      | NR                        | 66,123      | All hospitalized adult patients with confirmed COVID-19 | 60.7     | NR     | Retrospective cohort study | HR: 0.92 (0.85-0.99) | Sex, age, clinically diagnosed pneumonia at hospital admission, tobacco use, obesity, COPD, type 2 DM arterial HTN, immunosuppression, and CKD |
| Ling        | January 27 to August 7, 2020 | United Kingdom | 52 (11.7)                  | 444         | All hospitalized adult patients with confirmed COVID-19 | 55.1     | 74 (63-83) | Cross-sectional study   | OR: 0.31 (0.13-0.71) | Age, sex, obesity, ethnicity, and presence of DM (types 1 and 2 combined) |
| Izurieta    | April 1 to May 8, 2020 | United States | 962,666 (3.8)             | 27,961      | All elderly patients (ages ≥65 y) with confirmed COVID-19 | 48.8     | 75 (70-85) | Retrospective cohort study | OR: 0.93 (0.85-1.03) | Sex, age, area deprivation index national rank, circulation rate, population density, vaccination, presence of medical conditions, frailty conditions, immune compromised status, and race |
| Lundon      | March 28 to April 26, 2020 | United States | 403 (4.5)                  | 8928        | All individuals with laboratory-confirmed infection by SARS-CoV-2 | 46.2     | 58.0 ± 18.8 | Cross-sectional study   | OR: 0.68 (0.51-0.91) | Age, sex, race and ethnicity, New York City borough, English as preferred language, smoking status, COPD, HTN, obesity, DM, CKD, human immunodeficiency virus, and cancer |
| Study | Date | Country | Sample Size | Prevalence | Duration | Cohort Type | OR (95% CI) | Risk Factors |
|-------|------|---------|-------------|------------|----------|-------------|------------|-------------|
| Schwartz | January 21 to September 30, 2020 | Canada | 2655 (4.7) | 56,606 | All individuals with laboratory-confirmed infection by SARS-CoV-2 | 48.4 | NR | Cross-sectional study | OR: 0.85 (0.66-1.09) Sexual (male vs female), age (<30 y, 30-44 y, 60-75 y, compared with 45-59 y), comorbidities (COPD, renal disease, cardiac disease, DM, immune compromised or cancer, obesity, or other comorbidities, compared with no comorbidities), working or residing in long-term care home (yes vs no), and symptoms (fever and/or cough, other symptoms, or missing symptoms compared with asymptomatic) |
| Martos-Benítez | January 1 to May 13, 2020 | Mexico | NR | 38,324 | All individuals with laboratory-confirmed infection by SARS-CoV-2 | 58.3 | 46.9 ± 15.7 | Retrospective cohort study | OR: 0.86 (0.64-1.16) Age, sex, smoking habit, time from symptoms onset to medical contact, COPD, high blood pressure, CVD, DM, obesity, CKD, and other comorbidities |
| Oh | January 1 to June 4, 2020 | Korea | NR | 7780 | Adult (age ≥20 y) patients with confirmed COVID-19 | NR | NR | Retrospective cohort study | OR: 1.03 (0.76-1.41) COPD, interstitial lung disease, lung cancer, lung disease d/t external agent, obstructive sleep apnea, tuberculosis of lung, age, income level, sex, residence, underlying disability, CCI, HTN, DM, peripheral vascular disease, renal |
| First author | Study period | Country | Prevalence of asthma, n (%) | Patients, n | Population | Male (%) | Age, y | Study design | Adjusted-effect (95% confidence interval) | Confounders |
|--------------|--------------|---------|-----------------------------|-------------|------------|----------|--------|-------------|-------------------------------------|-------------|
| Park\(^{11}\) | February 15 to April 24, 2020 | Korea | 2269 | Patients hospitalized with COVID-19 | 35.9 | 55.5 ± 20.2 | Retrospective cohort study | OR: 2.13 (0.74-6.13) | Age, male, respiratory rate, fever, altered consciousness, hemoptysis, sore throat, malaise, COPD, CKD, malignancy, chronic neurological disorder, and preexisting cardiovascular risk factor/CVD |
| Ahlstrom\(^{12}\) | March 6 to May 27, 2020 | Sweden | 261 (2.6) | All adult patients with laboratory-confirmed diagnosis of COVID-19 | 74 | 61 (52-69) | Case-control study | HR: 1.52 (1.04-2.22) | Simplified acute physiology score 3, age, sex, ischemic heart disease, nonischemic heart disease, HTN, type 1 DM, type 2 DM, stroke, chronic renal disease, COPD, immunosuppressed, and cancer |
| Author(s)   | Study Dates      | Country | Sample Size | Criteria                                                                                   | Design                  | HR (95% CI)                                                                 | Factors considered                                                                                           |
|------------|-------------------|---------|-------------|--------------------------------------------------------------------------------------------|-------------------------|----------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|
| Lopez Zuniga & colleagues | February 4 to April 30, 2020 | Spain   | NR 318      | All adult patients with laboratory-confirmed diagnosis of COVID-19                         | Prospective cohort study | HR: 2.235 (0.554-9.02)                                                   | Age, sex, HTN, COPD, immunosuppression, chronic heart disease, AF, obesity, tumor, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, needed high oxygen volume, DM, qSOFA, hydroxychloroquine azithromycin, lopinavir/ritonavir, interferon, corticosteroids, tocilizumab, vitamin D supplementation, and anticoagulation therapy |
| Mollalo & colleagues | January 22 to November 22, 2020 | United States | NR NR | All individuals with laboratory-confirmed infection by SARS-CoV-2                           | Cross-sectional study    | OR: 4.584 (2.583-8.137) OR: 0.818 (0.461-1.452) | Age, sex, race, BMI, and comorbidities including HTN, CAD, DM, CKD, ESRD on dialysis, CHF, any cancer, any liver disease, hyperlipidemia, and history of stroke |
| Lohia & colleagues | March 10 to June 30, 2020 | United States | 134 (7.2) | 1871 All adult patients with laboratory-confirmed diagnosis of COVID-19                   | Retrospective cohort study | OR: 0.98 (0.61-1.58)                                                      | Age, sex, race, BMI, and comorbidities including HTN, CAD, DM, CKD, ESRD on dialysis, CHF, any cancer, any liver disease, hyperlipidemia, and history of stroke |
| Cedano & colleagues | March 3 to April 22, 2020 | United States | 7 (5) | 132 All adult patients admitted to ICU with severe COVID-19 infection                     | Retrospective cohort study | OR: 2.13 (0.10-45.4)                                                      | Age, male sex, arterial HTN, DM, COPD, CAD, systolic heart failure, diastolic heart failure, CKD, end-stage kidney disease, BMI, and mechanical ventilation |

(continued)
| First author | Study period | Country       | Prevalence of asthma, n (%) | Patients, n | Population | Male (%) | Age, y | Study design | Adjusted-effect (95% confidence interval) | Confounders                                                                 |
|------------|-------------|--------------|-----------------------------|------------|------------|----------|-------|--------------|------------------------------------------|-----------------------------------------------------------------------------|
| Girardin47 | March 2 to May 24, 2020 | United States | 493 (11.7)                  | 4446       | All hospitalized patients with confirmed COVID-19 | 58.1     | 62 ± 18 | Case series  | HR: 0.83 (0.67-1.04)                      | Age, ethnic minority, male sex, low income, smoking, obesity, COPD, sleep apnea, HTN, DM, peripheral artery disease, CAD, autoimmune disease, and cancer |
| Cao48      | March to September 2020 | United States | 72 (21.0)                   | 343        | All adult patients with laboratory-confirmed diagnosis of COVID-19 | 56       | 60.7 ± 15.9 | Prospective cohort study | OR: 0.72 (0.31-1.57)                    | Age, race (Black or not Black), sex, COPD, and obesity                     |
| Ho49       | March 7 to June 7, 2020  | United States | 468 (4.4)                   | 10,523     | All adult patients with laboratory-confirmed diagnosis of COVID-19 | 54.2     | 58.4 ± 18.8 | Retrospective cohort study | OR: 0.64 (0.53-0.77)                    | Age, sex, BMI, race, COVID-19 disease severity, CCI, COPD, CRP (>150), interleukin-6 (>80), ferritin (>2000), D-dimer (>2.0 μg/L), use of anticoagulation, use of corticosteroids, and smoking (current and former) |
| Guan50     | December 2019 to May 6th, 2020 | China       | 830 (2.1)                   | 39,420     | All hospitalized patients with confirmed COVID-19 | 49.9     | 55.7     | Retrospective cohort study | OR: 0.84 (0.48-1.48)                    | Presence of any other systemic comorbidities, female sex, and age           |
| Bloom51    | January 17 to August 17, 2020 | United Kingdom | 7859 (10.4)                  | 75,463     | All hospitalized patients with confirmed COVID-19 | 55.4     | NR       | Prospective cohort study | HR: 1.17 (0.73-1.86) HR: 0.99 (0.61-1.58) HR: 0.94 (0.62-1.43) HR: 1.02 (0.67-1.54) HR: 1.96 (1.25-3.08) HR: 0.97 (0.89-1.05) HR: 0.86 (0.80-0.92) HR: 1.13 (1.01-1.28) HR: 0.97 (0.89-1.06) | Age, sex, ethnicity, deprivation, obesity, smoking, chronic cardiac disease, CKD, and malignancy |
| Osibogun52 | February 27 to July 6, 2020 | Nigeria     | 45 (2.1)                    | 2184       | All hospitalized patients with confirmed COVID-19 | 65.8     | 43 (33-55) | Retrospective cohort study | OR: 1.52 (0.41-5.57)                    | Age and sex                                                                  |
| Author(s) | Dates | Location | Sample Size | All hospitalized patients with confirmed COVID-19 | All hospitalized patients with confirmed COVID-19 | Study Design | Test Statistic | Findings |
|----------|-------|----------|-------------|--------------------------------------------------|--------------------------------------------------|-------------|--------------|----------|
| de Souza | February 26 to August 10, 2020 | Brazil | 4566 (7.15) | 44,128 | 54.2 | NR | Retrospective cohort study | HR: 0.79 (0.73-0.85) | Male sex, age, fever, cough, dyspnea, respiratory distress, blood oxygen saturation <95%, diarrhea, other symptom, cardiac disease, liver disease, immunodepression, DM, neuropathy, nephropathy, kidney disease, other comorbidity, flu vaccine, ICU admission, invasive mechanical ventilation, and noninvasive ventilation |
| Mulhem | March 13 to April 29, 2020 | United States | 429 (13.3) | 3219 | 49 | 65.2 (52.6-77.2) | Retrospective cohort study | OR: 1.14 (0.84-1.55) | Gender, age, race, current smoking and comorbidities |
| Topless | March 16 to August 24, 2020 | United Kingdom | 40,898 (8.6) | 2118 | NR | NR | Retrospective cohort study | OR: 1.11 (0.80-1.53) | Current age, sex, ethnicity, Townsend deprivation index, BMI, and smoking status |
| Bennett | March 2 to September 14, 2020 | Ireland | 467 (2.4) | 19,789 | 43.6 | NR | Retrospective cohort study | OR: 0.82 (0.50-1.35) | Age (linear, quadratic, and cubic), chronic heart disease, chronic neurological disease, chronic respiratory disease, and CKD |

(continued)
| First author               | Study period                  | Country       | Prevalence of asthma, n (%) | Patients, n | Population | Male (%) | Age, y | Study design       | Adjusted-effect (95% confidence interval) | Confounders                                                                                                                                                                                                 |
|---------------------------|-------------------------------|---------------|----------------------------|-------------|------------|----------|--------|-------------------|--------------------------------|-------------------------------------------------------------------------------------|
| Lieberman-Cribbin         | February 29 to April 24, 2020 | United States | 272 (4.4)                   | 6250        | NR         | NR       | Cross-sectional study | OR: 0.82 (0.53-1.26) | Age                                                                                     |
| Calmes                    | March 18 to April 17, 2020    | Belgium       | 57 (9.6)                    | 596         | 49.3       | 58.8 ± 18.9 | Retrospective cohort study | OR: 0.74 (0.24-2.3) | Age, sex, cardiopathy, immunosuppressive disease, and COPD                              |
| Choi                      | Up to May 15, 2020            | Korea         | 218 (2.9)                   | 7590        | 40.8       | NR       | Retrospective cohort study | OR: 1.317 (0.708–2.451) | Age, sex, and underlying diseases                                                      |
| Kim                       | February to May 2020          | Korea         | 70 (3.2)                    | 2200        | 35.7       | 56.7 ± 19.0 | Cross-sectional study | OR: 1.762 (0.813-3.822) | Age and sex                                                                             |
| Study | Country | Date Range | Study Population | OR (95% CI) | Explanatory Variables |
|-------|---------|------------|------------------|-------------|-----------------------|
| Alwai | Saudi Arabia | March 15 to August 15, 2020 | All hospitalized patients with confirmed COVID-19 | 1.656 (0.624-4.395) | Age, smoking history, underlying comorbidity (COPD, DM, HTN, heart failure, other heart disease, CKD, chronic liver disease, cancer, autoimmune disease, dementia, and other psychological disorder), and medication (antiretroviral, hydroxychloroquine, systemic steroid, and azithromycin) |
| Vera-Zertuche | Mexico | February 24 to April 26, 2020 | All individuals with laboratory-confirmed infection by SARS-CoV-2 | 0.63 (0.24-1.70) | Sex, age, and time from symptom onset to care, social lag index, aging index, afro-descendant/100 inhabitants, indigenous language-speaking/100 inhabitants, affiliation to health services/100 inhabitants, members per household, hospitals/10,000 inhabitants, and hospital beds/10,000 inhabitants |

(continued)
| First author | Study period          | Country     | Patients, n | Population                                           | Male (%) | Age, y | Study design   | Adjusted-effect (95% confidence interval) | Confounders                                                                 |
|--------------|-----------------------|-------------|-------------|------------------------------------------------------|----------|--------|----------------|---------------------------------------------|-----------------------------------------------------------------------------|
| Elhadi       | May 29 to December 30, 2020 | Libya       | 51 (11)     | All adult COVID-19 patients admitted to ICUs         | 51.6     | 69     | Prospective cohort study | HR: 0.66 (0.40-1.10) | Age, BMI, comorbidities, laboratory findings during admission, qSOFA score, type of intubation during admission, developed sepsis/septic shock at during ICU admission, inotropes/vasopressor, antibiotic, and major complications or events |
| Cummins      | February 1 to June 30, 2020 | United Kingdom | 244 (13.7) | All adult (age ≥16 y) patients with laboratory-confirmed diagnosis of COVID-19 | 55.2     | NR     | Retrospective cohort study | OR: 1.03 (0.70-1.50) | Age, sex, ethnicity, top 30% most deprived areas, obese, smoker (current), AF, cancer, chronic heart disease, CKD, COPD, dementia, depression, type 1 DM, type 2 DM, epilepsy, heart failure, HTN, learning disability, severe mental illness, peripheral arterial disease, and stroke |
| Castro       | By 14 December 2020    | Brazil      | 14,567 (2.8) | All hospitalized patients with confirmed COVID-19    | 56.0     | 61     | Retrospective cohort study | OR: 0.81 (0.77-0.86) | Age, sex, ethno-racial self-classification, region, ICU, obesity, DM, chronic liver disease, chronic neurological disease, chronic lung disease, immunodeficiency, and CKD |
| Study (Reference) | Period | Country | N | Age | Description | Methodology | OR | CI | Comorbidities |
|------------------|--------|---------|---|-----|-------------|-------------|----|----|--------------|
| Beltramo66 | March 1 to April 30, 2020 | France | 3273 (3.7) | 89,530 | All hospitalized patients with confirmed COVID-19 | Retrospective cohort study | 0.82 (0.71-0.94) | Lung cancer, COPD, pulmonary sarcoidosis, ILD, emphysema, sleep apnea, chronic respiratory failure, and pulmonary HTN |
| Robles-Pérez67 | March to December 2020 | Mexico | 2403 (3.2) | 75,595 | All Social Security workers with confirmed COVID-19 | Retrospective cohort study | 0.96 (0.51-1.79) | Age, sex, and presence of comorbidities |
| De Rosa68 | February 27 to June 15, 2020 | Italy | 23 (1.5) | 1538 | Hospitalized adult patients with confirmed COVID-19 | Retrospective cohort study | 1.45 (0.44-4.78) | Age, sex, smoking, DM, HTN, CVD, COPD, immunodepression, P/F, lymphocytopenia, LDH, eGFR, D-dimer, and CRP |
| Marciniak69 | January 17, 2020 to February 15, 2021 | United Kingdom | NR | 73,832 | Hospitalized adult patients with confirmed COVID-19 | Prospective cohort study | 0.90 (0.85-0.96) | Age, sex, and comorbidities |
| Kelly70 | March 2 to October 31, 2020 | United States | 1487 (5.4) | 27,640 | All veterans with confirmed COVID-19 | Retrospective cohort study | 0.88 (0.65-1.19) | Age, sex, race, ethnicity, marital status, clinical factors, health care facility, and month of COVID-19 diagnosis |

AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; CCI, Charlson comorbidity index; CHF, congestive heart failure; CIRS, cumulative illness rating scale score; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease comorbidity; CRP, C-reactive protein; CVD, cardiovascular disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HR, hazard ratio; HTN, hypertension; ICU, intensive care unit; IQR, interquartile range; LDH, lactate dehydrogenase; MI, myocardial infarction; NR, not reported; OR, odds ratio; P/F, arterial oxygen tension/inspired oxygen fraction; qSOFA, quick sequential organ failure assessment. Values of age are presented as means ± SDs or medians (IQRs).
compared with patients without asthma among North American patients (24 studies: 1,355,172 patients, pooled OR = 0.87, 95% CI, 0.82-0.92, I² = 15.8%, P = .243; six studies: 95,203 patients, pooled HR = 0.90, 95% CI, 0.84-0.96, I² = 0%, P = .808 (Figure 5) and South American patients (3 studies: 646,397 patients, pooled HR = 0.80, 95% CI, 0.72-0.90, I² = 83.1%, P = .003) (Figure 5), but not among Asian patients (9 studies: 68,669 patients, pooled OR = 1.13, 95% CI, 0.92-1.38, I² = 1.0%, P = .542; 2 studies: 5296 patients, pooled HR = 1.47, 95% CI, 0.71-3.07, I² = 51.7%, P = .150) (Figure 5) or European patients (11 studies: 195,083 patients, pooled OR = 0.86, 95% CI, 0.73-1.01, I² = 56.0%, P = .012; 4 studies: 88,538 patients, pooled HR = 1.07, 95% CI, 0.89-1.29, I² = 52.1%, P = .099) (Figure 5). Age (OR: τ² = 0.010, t = −0.62, P = .542; HR: τ² = 0.008, t = −0.63, P = .540) (Figure 6, A and B), sex (OR: τ² = 0.007, t = −0.14, P = .889; HR: τ² = 0.016, t = 0.33, P = .743) (Figure 6, C and D), and data collection periods (OR: τ² = 0.007, t = −0.28, P = .777; HR: τ² = 0.017, t = −0.82, P = .428) (Figure 6, E and F) could not explain potential sources of heterogeneity by meta-regression. We did not observe potential publication bias in Begg’s test (OR: P = .394; HR: P = .343) (Figure 7, A and B) or Egger’s test (OR: P = .142; HR: P = .265) (Figure 7, C and D). Sensitivity analysis proved that our results were stable.

DISCUSSION
This meta-analysis on the basis of adjusted effects estimates found that COVID-19 patients with asthma had a significantly reduced risk for mortality compared with those without asthma, which suggests that asthma might be an independent protective factor for developing fatal outcomes among COVID-19 patients. Meta-regression and subgroup analyses showed that none of these factors (such as age, sex, region, hospitalization status, data collection period, and the types of adjusted factors) could explain the potential sources of heterogeneity. Although the detailed mechanisms underlying the association between asthma and the reduced risk for COVID-19 mortality are unclear, several possibilities exist: (1) COVID-19 patients with asthma may receive more medical care in clinical practice; (2) the use of inhaled corticosteroids, allergen immunotherapy, and biological agents might be beneficial through suppressing viral replication and alleviating inflammation; and (3) type 2 immune response in patients with asthma might counteract the severe acute respiratory syndrome coronavirus 2 infection-induced inflammatory process. Further studies should focus on underlying mechanisms of preexisting asthma reducing the risk for fatal COVID-19. The association between having asthma and lower COVID-19 mortality may also have resulted from study bias, including selection bias (eg, a lack of representativeness), information bias (asthma underreporting or overreporting), and
FIGURE 2. Forest plots indicating that coronavirus disease 2019 (COVID-19) patients with asthma had a significantly reduced risk for mortality compared with those without it. Arrow indicates that the 95% confidence interval (CI) for effect size in the study was equal to or greater than the x-axis value. Sizes of the shaded area reflect the study-specific statistical weights. (A) Pooled odds ratio (OR). (B) Pooled hazard ratio (HR). *Combined effects based on subgroups.
FIGURE 3. Subgroup analysis by hospitalization status: (A) pooled odds ratio (OR) and (B) pooled hazard ratio (HR). *Combined effects based on subgroups. CI, confidence interval.
FIGURE 4. Subgroup analysis by type of adjusted factors: (A) pooled odds ratio (OR) and (B) pooled hazard ratio (HR). *Combined effects based on subgroups. CI, confidence interval.
FIGURE 5. Subgroup analysis based on region: (A) pooled odds ratio (OR) and (B) pooled hazard ratio (HR). *Combined effects based on subgroups. CI, confidence interval.
confounding bias (e.g., asthma may have been relatively under-represented among patients with other comorbidities that predispose more often to COVID-19 mortality, such as diabetes, obesity, or smoking, because asthma is common among younger patients).

A strength of this study was the large number of included studies (62 eligible articles) with 2,457,205 cases reporting adjusted effect estimates, which consider the influences of confounding factors such as age, sex, and underlying diseases on the association between asthma and mortality among COVID-19 patients.
patients. However, several limitations should be acknowledged. First, most included studies were from North America, and one should be cautious when extrapolating the findings to other regions. Second, most of the eligible studies were designed retrospectively. Thus, further well-designed prospective studies with large sample sizes are warranted to verify the findings. Third, the pooled effects were estimated based on risk factor-adjusted effects, but the adjusted risk factors were not fully consistent across the included studies. We performed subgroup analysis according to the types of adjusted factors, which yielded inconsistent results. These results may have been because the number of studies adjusting only for demographic variables was significantly smaller than the number of studies adjusting for demographic, clinical, and epidemiologic variables, which warrants further studies based on more primary studies and larger sample sizes. Fourth, we did not investigate the effects of medication on the association between asthma and COVID-19 mortality, which should be addressed in the future when sufficient data are available. Fifth, there was heterogeneity across studies, which was why we performed meta-regression and further subgroup analyses but did not identify potential sources of heterogeneity. In addition, excluding articles that were not written in English might be a source of publication bias. However, publication bias was not detected by Begg’s test or Egger’s test. Our data indicate that asthma is related to a significantly reduced risk for COVID-19 mortality. Thus, routine interventions and treatment for asthma patients infected with severe acute respiratory syndrome coronavirus 2 should be continued. We hope the updated data will contribute to more accurate elaboration and substantiation of findings from the study of Liu et al.¹

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**FIGURE 7.** Publication bias was evaluated by Begg’s test: (A) pooled odds ratio (OR); (B) pooled hazard ratio (HR) and Egger’s test; (C) pooled OR; (D) pooled HR.
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| Database       | Search strategies                                                                 |
|---------------|----------------------------------------------------------------------------------|
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| EMBASE        | ("coronavirus disease 2019" OR 'covid-19' OR 'sars-cov-2' OR '2019-ncov' OR 'novel coronavirus') AND ("asthma") AND ("mortality" OR "fatality" OR "death" OR "non-survivor" OR "deceased") |
| Web of Science| TS = ("coronavirus disease 2019" OR "covid-19" OR "sars-cov-2" OR "2019-ncov" OR "novel coronavirus") AND ("asthma") AND ("mortality" OR "fatality" OR "death" OR "non-survivor" OR "deceased") |
| First author | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | Score |
|--------------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|------|
| Arshad SE | Yes | Yes | Yes | No | Yes | Yes | No | Yes | NR | Yes | NR | NR | Yes | i |
| Mato ARE | Yes | Yes | Yes | No | Yes | No | Yes | NR | NR | NR | Yes | i |
| Poblador-Plou B | Yes | Yes | Yes | No | Yes | Yes | No | Yes | NR | Yes | NR | NR | Yes | i |
| van Gerwen M | Yes | Yes | No | Yes | No | Yes | No | NR | Yes | NR | Yes | Yes | i |
| Hernandez-Galdamez DR | Yes | No | Yes | No | Yes | NA | No | Yes | NR | NA | Yes | i |
| Hernandez-Vasquez A | Yes | NR | Yes | No | Yes | NA | No | Yes | NR | Yes | NA | Yes | i |
| Almazedi SE | Yes | Yes | No | Yes | No | Yes | NA | Yes | NR | Yes | Yes | Yes | i |
| Perez-Guzman PN | Yes | Yes | Yes | No | Yes | No | Yes | No | NR | Yes | NR | Yes | Yes | i |
| Tartof SY | Yes | Yes | NR | No | Yes | No | Yes | NR | Yes | NR | Yes | Yes | i |
| Parra-Bracamonte GM | Yes | NR | Yes | No | NR | NA | No | Yes | NR | NA | Yes | i |
| Fox T | Yes | Yes | Yes | No | Yes | No | Yes | NR | Yes | NR | Yes | i |
| Yehia BR | Yes | Yes | NR | No | Yes | Yes | No | NR | Yes | NR | Yes | Yes | i |
| Emami A | Yes | Yes | Yes | No | Yes | No | Yes | NR | Yes | NR | Yes | Yes | i |
| Trabulus S | Yes | Yes | No | Yes | No | Yes | No | NR | Yes | Yes | Yes | Yes | i |
| Santos MM | Yes | Yes | NR | Yes | No | Yes | No | Yes | NR | Yes | Yes | Yes | i |
| Ioannou GN | Yes | Yes | No | Yes | No | Yes | No | NR | Yes | NR | Yes | Yes | i |
| Gutierrez JP | Yes | Yes | NR | Yes | No | NR | No | Yes | NR | Yes | NR | Yes | Yes | i |
| Clift AK | Yes | Yes | NR | No | Yes | Yes | No | NR | Yes | NR | Yes | Yes | i |
| Kim TS | Yes | Yes | Yes | No | Yes | Yes | No | Yes | NR | Yes | Yes | Yes | i |
| Tang OL | Yes | Yes | Yes | No | Yes | No | Yes | NR | Yes | Yes | Yes | Yes | i |
| Ken-Dror GE | Yes | Yes | NR | Yes | No | Yes | No | NR | Yes | Yes | Yes | Yes | i |
| Choi HG | Yes | Yes | NR | No | Yes | NR | No | Yes | NR | Yes | Yes | Yes | i |
| Nyabera A | Yes | Yes | NR | Yes | No | NR | No | NR | NR | NR | Yes | Yes | i |
| Lee SC | Yes | Yes | Yes | No | Yes | No | Yes | Yes | Yes | Yes | NR | Yes | Yes | ii |
| Murillo-Zamora E | Yes | Yes | NR | Yes | No | Yes | No | Yes | NR | Yes | NR | Yes | Yes | i |
| Ling SF | Yes | Yes | NR | No | Yes | NA | No | Yes | NR | NA | Yes | Yes | i |
| Izurieta HS | Yes | Yes | NR | Yes | No | Yes | No | Yes | NR | Yes | Yes | Yes | i |
| Lunden DJ | Yes | Yes | Yes | No | NR | NA | No | Yes | NR | Yes | Yes | Yes | i |
| Schwartz KL | Yes | Yes | NR | Yes | No | NR | No | No | Yes | NR | Yes | Yes | i |
| Martos-Benítez FD | Yes | Yes | NR | Yes | No | Yes | No | Yes | NR | Yes | Yes | Yes | i |
| Oh TK | Yes | Yes | NR | Yes | No | Yes | No | Yes | NR | Yes | NR | Yes | Yes | i |
| Park BE | Yes | Yes | NR | Yes | No | Yes | No | Yes | NR | Yes | Yes | Yes | i |
| Lopez Zaniga MA | Yes | Yes | Yes | No | Yes | No | Yes | NR | Yes | Yes | Yes | Yes | i |
| Collado A | Yes | Yes | Yes | No | NR | NA | No | Yes | NR | NA | Yes | Yes | i |
| Lohia P | Yes | Yes | NR | Yes | No | Yes | No | Yes | NR | Yes | Yes | Yes | i |
| Cedano F | Yes | Yes | NR | Yes | No | Yes | No | Yes | NR | Yes | Yes | Yes | i |
| Cao L | Yes | Yes | NR | Yes | No | Yes | No | Yes | NR | Yes | Yes | Yes | Yes | i |
| Ho KS | Yes | Yes | Yes | No | Yes | No | Yes | No | NR | Yes | Yes | Yes | Yes | i |
| Guan WJ | Yes | Yes | NR | Yes | No | Yes | No | Yes | NR | Yes | Yes | Yes | Yes | i |
| Bloom CI | Yes | Yes | NR | Yes | No | Yes | Yes | Yes | Yes | Yes | NR | Yes | Yes | ii |
| Osibogun A | Yes | Yes | NR | Yes | No | Yes | No | No | NR | Yes | Yes | Yes | Yes | i |
| de Souza FSH | Yes | Yes | NR | Yes | No | Yes | No | Yes | NR | Yes | Yes | Yes | Yes | i |
| Mulhem E | Yes | Yes | NR | Yes | No | Yes | No | Yes | NR | Yes | Yes | Yes | Yes | i |
| Topless RK | Yes | Yes | NR | Yes | No | Yes | No | Yes | NR | Yes | Yes | Yes | Yes | i |
| Bennett KE | Yes | Yes | NR | Yes | No | Yes | No | Yes | NR | Yes | Yes | Yes | Yes | i |
| Lieberman-Cribbin W | Yes | Yes | NR | Yes | Yes | NR | No | No | NR | Yes | Yes | Yes | Yes | i |
| Calmes D | Yes | Yes | NR | Yes | No | NR | No | No | Yes | NR | Yes | Yes | Yes | i |
| Choi Y | Yes | Yes | NR | Yes | No | Yes | No | NR | Yes | Yes | Yes | Yes | Yes | i |
| Kim S | Yes | Yes | Yes | No | Yes | NA | No | Yes | NR | Yes | Yes | Yes | Yes | i |
| Alwafi H | Yes | Yes | Yes | No | Yes | No | Yes | No | NR | Yes | Yes | Yes | Yes | i |
| Vera-Zertuche JM | Yes | Yes | NR | Yes | No | Yes | No | Yes | NR | Yes | Yes | Yes | Yes | i |
| Elhadi M | Yes | Yes | NR | Yes | No | Yes | No | Yes | NR | Yes | Yes | Yes | Yes | i |
| Cummins L | Yes | Yes | Yes | No | Yes | NR | No | Yes | NR | Yes | Yes | Yes | Yes | i |

(continued)
TABLE E2. (Continued)

| First author                  | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | Score |
|------------------------------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|-------|
| Castro MC                     | Yes | Yes | Yes | NR | No | Yes | Yes | No | Yes | NR | Yes | NR | Yes | Yes | i    |
| Beltram G                     | Yes | Yes | Yes | Yes | No | Yes | Yes | No | Yes | NR | Yes | NR | Yes | Yes | i    |
| Robles-Pérez E               | Yes | Yes | NR | Yes | No | Yes | Yes | No | Yes | NR | NR | NR | Yes | i    |
| De Rosa FG                   | Yes | Yes | NR | Yes | No | Yes | Yes | No | Yes | NR | NR | NR | Yes | i    |
| Marciniak SJ                 | Yes | Yes | NR | Yes | No | Yes | Yes | No | Yes | NR | NR | NR | Yes | i    |
| Kelly JD                     | Yes | Yes | NR | Yes | No | Yes | Yes | No | Yes | NR | NR | NR | Yes | i    |
| Case-control studies         |    |    |    |    |    |    |    |    |    |    |    |    |    |    |       |
| Shah I                      | Yes | Yes | No | Yes | Yes | Yes | Yes | No | Yes | NR | Yes | i   |
| Ahlstrom B                   | Yes | Yes | Yes | Yes | No | Yes | Yes | No | Yes | NR | Yes | i   |
| Case series studies          |    |    |    |    |    |    |    |    |    |    |    |    |    |    |       |
| Girardin J                   | Yes | Yes | NR | NR | Yes | Yes | NR | NR | Yes | Yes | i   |

NA: not applicable; NR: not reported.

For cohort and cross-sectional studies, quality was rated as 0 for poor (0-4 of 14 questions), i for fair (5-10 of 14 questions), or ii for good (11-14 of 14 questions): (1) Was the research question or objective in this paper clearly stated? (2) Was the study population clearly specified and defined? (3) Was the participation rate of eligible persons at least 50%? (4) Were all of the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants? (5) Was a sample size justification, power description, or variance and effect estimates provided? (6) For the analyses in this paper, were the exposure(s) of interest measured before the outcome(s) being measured? (7) Was the time frame sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed? (8) For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (eg, categories of exposure, or exposure measured as continuous variable)? (9) Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? (10) Was the exposure(s) assessed more than once over time? (11) Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? (12) Were the outcome assessors blinded to the exposure status of participants? (13) Was loss to follow-up after baseline 20% or less? (14) Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)? For case-control studies, quality was rated as 0 for poor (0-3 of 12 questions), i for fair (4-8 of 12 questions), or ii for good (9-12 of 12 questions): (1) Was the research question or objective in this paper clearly stated and appropriate? (2) Was the study population clearly specified and defined? (3) Did the authors include a sample size justification? (4) Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same time frame)? (5) Were the definitions, inclusion and exclusion criteria, algorithms, or processes used to identify or select cases and controls valid, and implemented consistently across all study participants? (6) Were the cases clearly defined and differentiated from controls? (7) If less than 100% of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible? (8) Was there use of concurrent controls? (9). Were the investigators able to confirm that the exposure or risk occurred during the development of the study (or event that defined a participant as a case) as an event that occurred after the exposure? (10) Were the measures of exposure or risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants? (11) Were the assessors of exposure or risk blinded to the case or control status of participants? (12) Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, was the investigators account for matching during study analysis? For case series studies, quality was rated as 0 for poor (0-2 of nine questions), i for fair (3-6 of nine questions), or ii for good (7-9 of nine questions): (1) Was the study question or objective clearly stated? (2) Was the study population clearly specified and defined? (3) Were the investigators able to control for confounding variables? (4) Did the investigators account for matching during study analysis? For cohort and cross-sectional studies, quality was rated as 0 for poor (0-4 of 14 questions), i for fair (5-10 of 14 questions), or ii for good (11-14 of 14 questions): (1) Was the research question or objective in this paper clearly stated? (2) Was the study population clearly specified and defined? (3) Were the investigators able to control for confounding variables? (4) Did the investigators account for matching during study analysis? (5) Was a sample size justification, power description, or variance and effect estimates provided? (6) For the analyses in this paper, were the exposure(s) of interest measured before the outcome(s) being measured? If matching was used, did the investigators account for matching during study analysis? For case series studies, quality was rated as 0 for poor (0-2 of nine questions), i for fair (3-6 of nine questions), or ii for good (7-9 of nine questions): (1) Was the study question or objective clearly stated? (2) Was the study population clearly specified and defined? (3) Were the investigators able to control for confounding variables? (4) Did the investigators account for matching during study analysis? (5) Was a sample size justification, power description, or variance and effect estimates provided? (6) For the analyses in this paper, were the exposure(s) of interest measured before the outcome(s) being measured? If matching was used, did the investigators account for matching during study analysis? (7) Was the length of follow-up adequate? (8) Were the statistical methods well-described? (9) Were the results well-described?

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