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International Difference of Tobacco Related COVID-19 Severity

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This study aimed to analyze the correlation between smoking and coronavirus disease 2019 (COVID-19) severity by region and gross domestic product (GDP). The regions were categorized by continent and GDP rankings. Studies conducted between June 3, 2020 and March 27, 2023 were searched to compare the severity of COVID-19 between smokers and non-smokers according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Compared with never-smokers, the smokers' COVID-19 severity scores were 1.48 (confidence interval [CI]: 1.25-1.75) in Asia, 1.24 (CI: 1.05-1.46) in the Middle East, 1.32 (1.21-1.45) in Europe, 1.39 (1.30-1.49) in North America, 1.69 (1.22-2.34) in South America, and 2.87 (1.82-4.53) in Africa. By GDP, the smokers' COVID-19 severity scores were higher than those of never-smokers: 1.42 (1.32-1.53) in high-GDP countries, 1.33 (1.25-1.41) in middle-GDP countries (11th-50th), and 1.53 (0.85-2.76) in low-GDP countries. The COVID-19 severity in smokers was significantly higher in low-GDP countries than in high- and middle-income countries. The high COVID-19 death rate among smokers in the African continent and low-GDP countries is thought to stem from the lack of medical management systems compared with other countries. In addition to medical treatment, environmental or socioeconomic factors can increase the severity.

Keywords: Cigarette smoking, COVID-19, Socioeconomic factor

Introduction

Coronavirus disease 2019 (COVID-19) has affected more than 700 million people, resulting in more than 6.9 million deaths worldwide [1]. Based on previous studies, the risk factors for developing COVID-19 encompass demographic factors (such as old age, male sex, and ethnicity) and the presence of underlying diseases (such as cardiovascular diseases, hypertension, and chronic obstructive pulmonary disease [COPD]) [2]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection may initially progress without symptoms, but can subsequently trigger manifestations including fever, cough, shortness of breath, severe pneumonia, dyspnea, organ dysfunction, and even death [3,4]. Individuals with comorbidities such as hypertension, diabetes, or older age have a poorer prognosis [5]. A previous study established age as the strongest determinant of mortality risk, with a more than 30-fold difference between the oldest and youngest groups. Moreover, smoking and obesity are associated with a higher mortality risk [6].

The World Health Organization (WHO) has reported approximately 1.1 billion current cigarette smokers worldwide [7]. The global prevalence of cigarette smoking among women has increased in recent years, posing a significant public health concern [8]. Smoking is one of the most prevalent causes of death

due to non-communicable diseases [9].

Several studies have explored the correlation between smoking and COVID-19 severity, yielding inconsistent results. One study showed no significant difference between smoking rates and mortality from COVID-19 (p = 0.21) [10]. Zhang et al. [11] observed that among the participants in the severe COVID-19 outcome group, 3.4% were current smokers, and 6.9% were former smokers (n = 58). In the non-severe patient group (n = 82), none were current smokers, while 3.7% were former smokers (odds ratio: 2.23, 95% confidence interval [CI]: 0.65-7.63; p = 0.2). Huang et al. [12] found no significant differences between the intensive care unit (ICU) and non-ICU groups (p = 0.31). Another meta-analysis did not find an association between current smoking status and disease severity [13].

A few studies have analyzed the correlation between smoking and COVID-19 severity by region. One study showed that the severity of COVID-19 differs in various geographical locations, with mortality rates of 0.7 deaths per 100,000 in South Korea and 86.8 per 100,000 in Belgium [14]. Another study found that countries with a high prevalence of male smokers had low COVID-19 mortality and SARS-CoV-2 infection rates within each continent, implying a potential protective effect of active smoking against COVID-19. From the results of this study, COVID-19 mortality was reported in 13 (5-24) per million inhabitants in countries with a male smoking rate of > 45% and 33 (4-133) per million inhabitants in countries with a male smoking rate of < 25% [15].

As a result, the relationship between COVID-19 severity and smoking and the differences between regions remain unclear. This study aimed to analyze the correlation between smoking and COVID-19 severity by region and gross domestic product (GDP). The regions were categorized according to continent and GDP rankings.

Methods

Search strategy and selection criteria

A systematic literature survey was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The PubMed, Cochrane Library, and Embase databases were searched to find studies published between June 3, 2020, and March 27, 2023. The search terms used were COVID-19, smoking, and synonyms.

(1) Clinical trials, observational studies, and randomized controlled trials, including published or unpublished studies; (2) studies published in English; (3) in vivo studies; (4) studies conducted in patients infected with coronavirus; (5) studies conducted among smokers; (6) studies that examined non-smoking patients; and (7) studies that reported the mortality rates, severe outcomes, hospitalization rates, or the use of oxygen supply were included in the final analysis. Patients without available data were excluded.

Randomized and observational studies reporting the smoking status of COVID-19 patients with different degrees of COVID-19 severity and studies examining individuals using all types of smoke, such as cigarettes, tobacco, or e-cigarettes, were also included in this study.

The literature search, study identification, and data extraction were performed between March 2023 and July 2023. Disagreements were resolved through discussion with all reviewers. The relevant data were extracted by one reviewer using the prepared form and verified for accuracy by another reviewer. The data extracted from the eligible studies included participant characteristics, sample sizes, study designs, data collection period, comorbidities, race, country, participant's age, underlying diseases, type of cigarette used, and criteria for determining severe outcomes.

The clinical endpoints in our study were death, ICU admission, O_2 level, and ventilation outcome. Studies reporting other diseases or topics, reviews, editorials, and nonclinical studies were excluded.

After the initial screening, the four authors independently reviewed the titles and abstracts, and a second screening was conducted by reviewing the full-text records. All discrepancies were resolved by six authors.

Data analysis

A meta-analysis was performed using SPSS Statistic 27.0 (IBM Corp., Chicago, Illinois, USA), and statistical significance was defined as a two-sided p-value of < 0.05. The pooled effects were calculated using fixed- and random-effects models. Statistical heterogeneity among the included studies was assessed using an χ^2 test and a Higgins I^2 value, with an I^2 value of > 75% suggesting high statistical heterogeneity. Publication bias was assessed using funnel plots.

Results

The initial search yielded 5,309 studies, of which 1,114 were unique articles. After screening the titles and abstracts of the remaining 1,114 studies, the full text of 140 articles was reviewed. Overall, 140 studies met the inclusion criteria (Fig. 1). The 140 included studies were conducted in COVID-19 patients, of

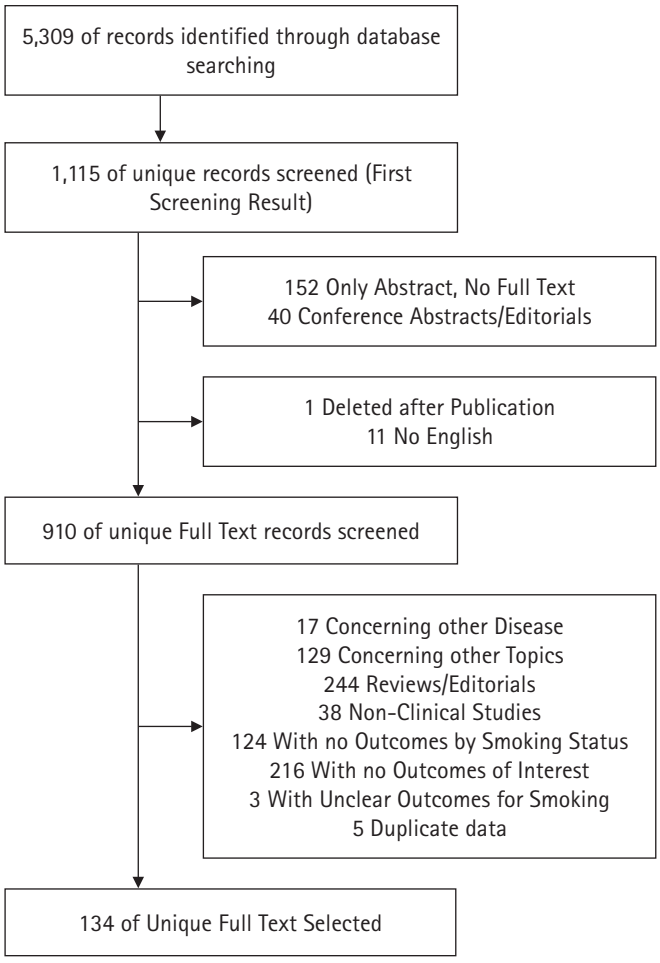


Fig. 1. Flow chart for the process of selecting eligible publications.

whom 16,121,336 reported any smoking history. Among these patients, 5,608,207 were smokers, while 10,513,129 were non-smokers.

A total of 59 multicenter studies (12 prospective cohort, 37 retrospective cohort, 8 cross-sectional, and 2 case-control studies) and 81 single-center studies (14 prospective cohort, 49 retrospective cohort, 14 cross-sectional, 3 case-control, and 1 randomized control trial) were analyzed. We evaluated the effect of smoking on the rates of COVID-19, death, ICU admission, and O_2 and ventilation use.

Continent

The results were compared by continent. A total of 29 studies performed in Asia evaluated the rates of death, ICU admission, and O_2 or ventilation use between smokers (current or former) and never-smokers (Fig. 2A). Similarly, 30 studies conducted in the Middle East (Fig. 2B), 36 in Europe (Fig. 2C), 25 in North America (Fig. 2D), 9 in South America (Fig. 2E), and 5 in Africa (Fig. 2F) were evaluated. All results classified by continent were significant, with those from African studies being particularly noteworthy.

GDP

The results were compared based on the national GDP. A total of 59 studies were performed in high-GDP income (1st-10th GDP) countries (Fig. 3A), 52 in middle-GDP countries (11th-50th) (Fig. 3B), and 12 in low-GDP countries (GDP 51th and below) (Fig. 3C). The COVID-19 severity in smokers was significantly higher in low-GDP countries than high- and middle-income countries.

Discussion

The COVID-19 severity among smokers differs by region and national income. When region is classified by continent, the COVID-19 severity scores of ever-smokers were 1.48 (CI: 1.25–1.75) in Asia, 1.24 (CI: 1.05–1.46) in the Middle East, 1.32 (1.21–1.45) in Europe, 1.39 (1.30–1.49) in North America, 1.69 (1.22–2.34) in South America, and 2.87 (1.82–4.53) in Africa compared with never-smokers. Meanwhile, the COVID-19 severity was lower in Middle Eastern countries but higher in African countries. The high prevalence of smokeless (chewing) tobacco and waterpipe smoking in the Middle East could be a possible cause of lower severity in Middle Eastern countries [16]. Conversely, the increasing prevalence of smoking due to the low tobacco tax could explain the higher severity in the African continent [17].

COVID severity in smokers differed according to the GDP ranking. The smokers' COVID-19 severity scores were higher compared with never-smokers: 1.42 (1.32–1.53) in high-GDP countries, 1.33 (1.25–1.41) in middle-GDP countries (11th–50th), and 1.53 (0.85–2.76) in low-GDP countries. The COVID-19 severity among smokers was significantly higher in low-GDP countries than in high- and middle-income countries.

This study suggests that smoking increases the severity of COVID-19, with minimal disparity observed between continental and national GDP levels. To date, several studies have demonstrated the risk of respiratory infections from smoking. For instance, smokers are more susceptible to respiratory infections, such as invasive pneumococcal disease [18], community-acquired pneumonia [19], influenza [20], and common colds [21]. Smoking has significant effects on the respiratory tract, immune system, skin, and soft tissues, both locally and systemically. These effects can influence susceptibil-

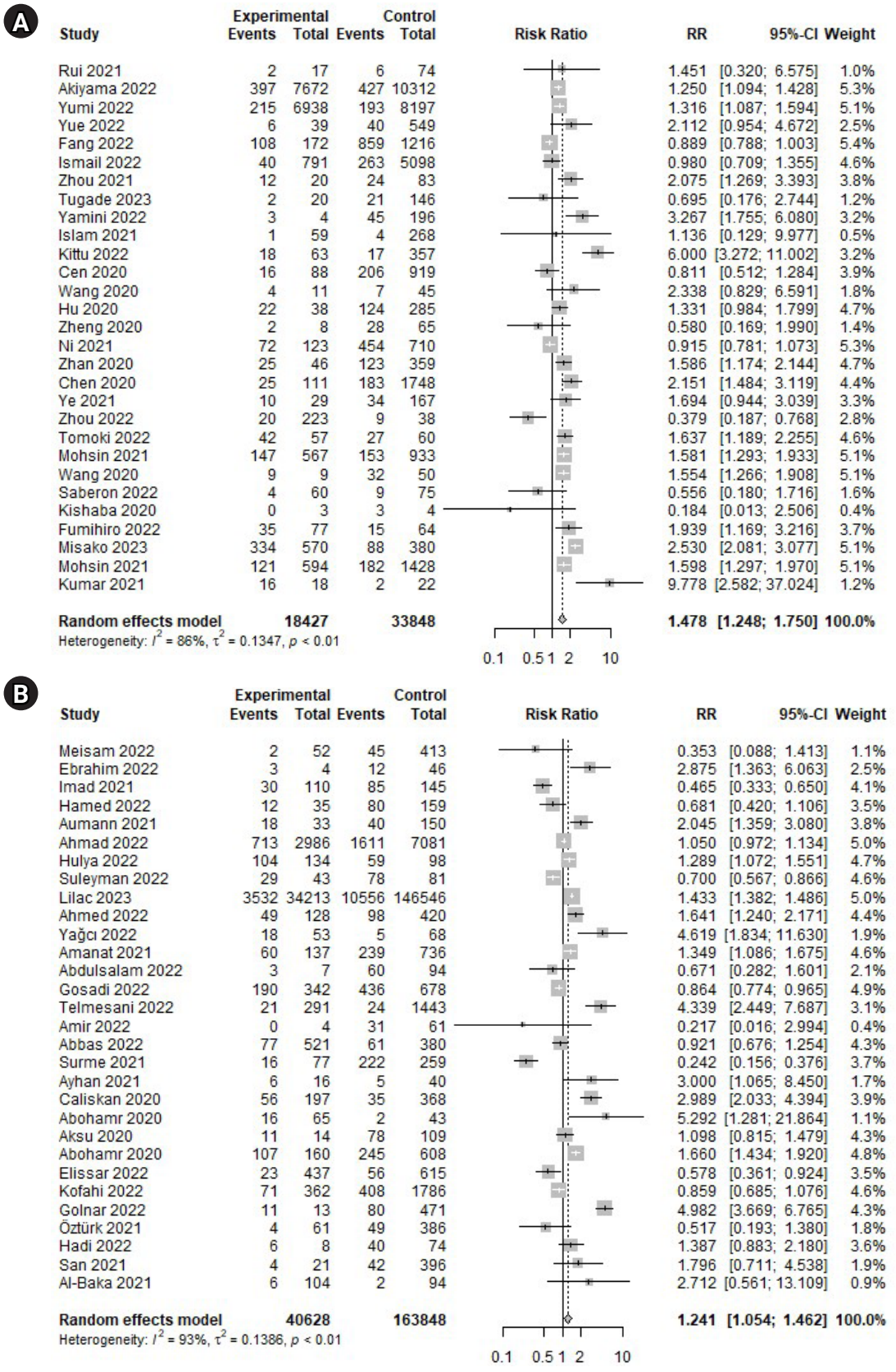
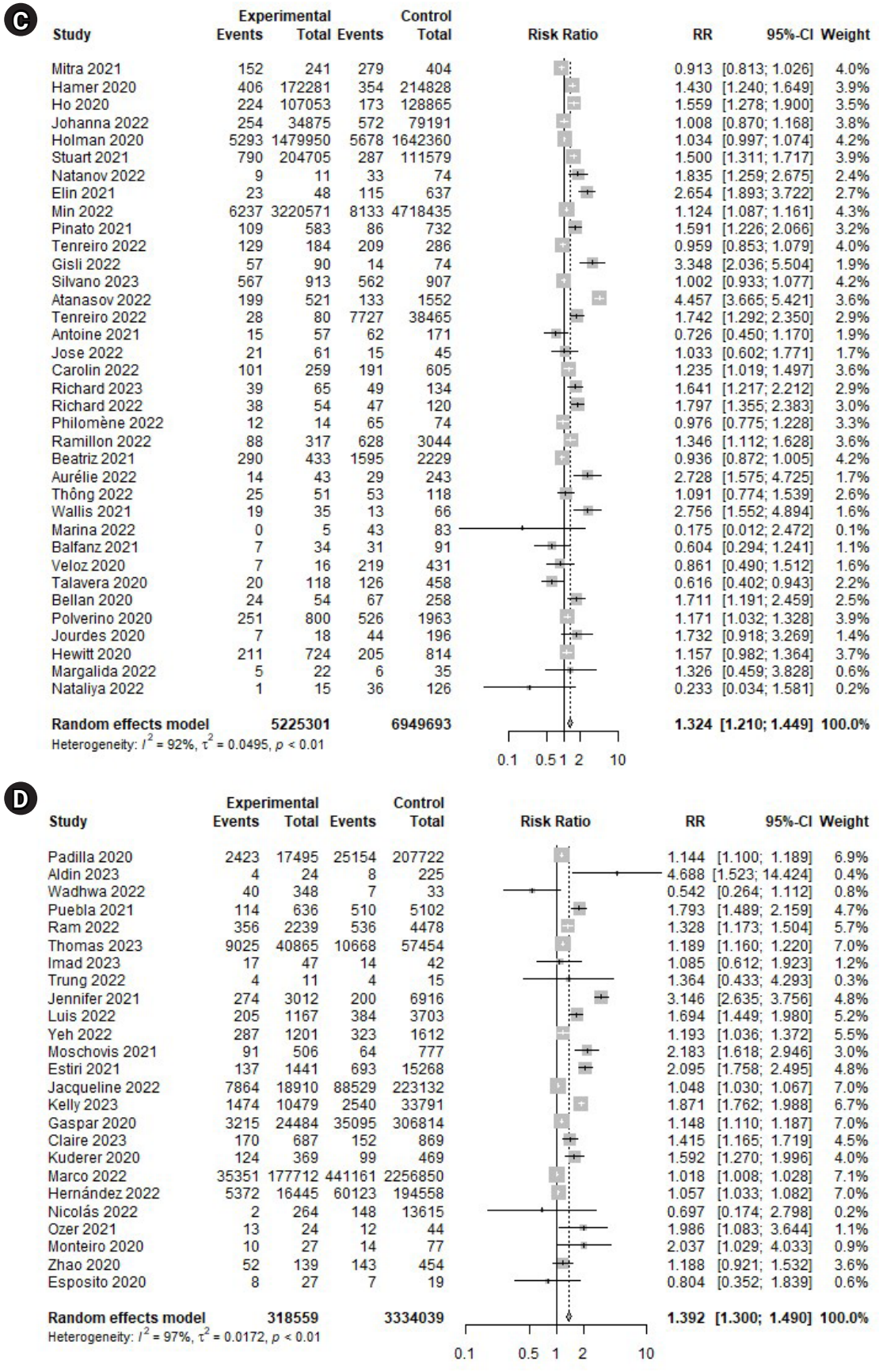


Fig. 2. Evaluation of the rate of death, intensive care unit admission, and O_2 or ventilation use between smokers (current or former) and never-smokers by Asian (A), Middle Eastern (B), European (C), North American (D), South American (E), and African (F). RR, risk ratio; 95% CI, confidence interval. (Continued to the next page)



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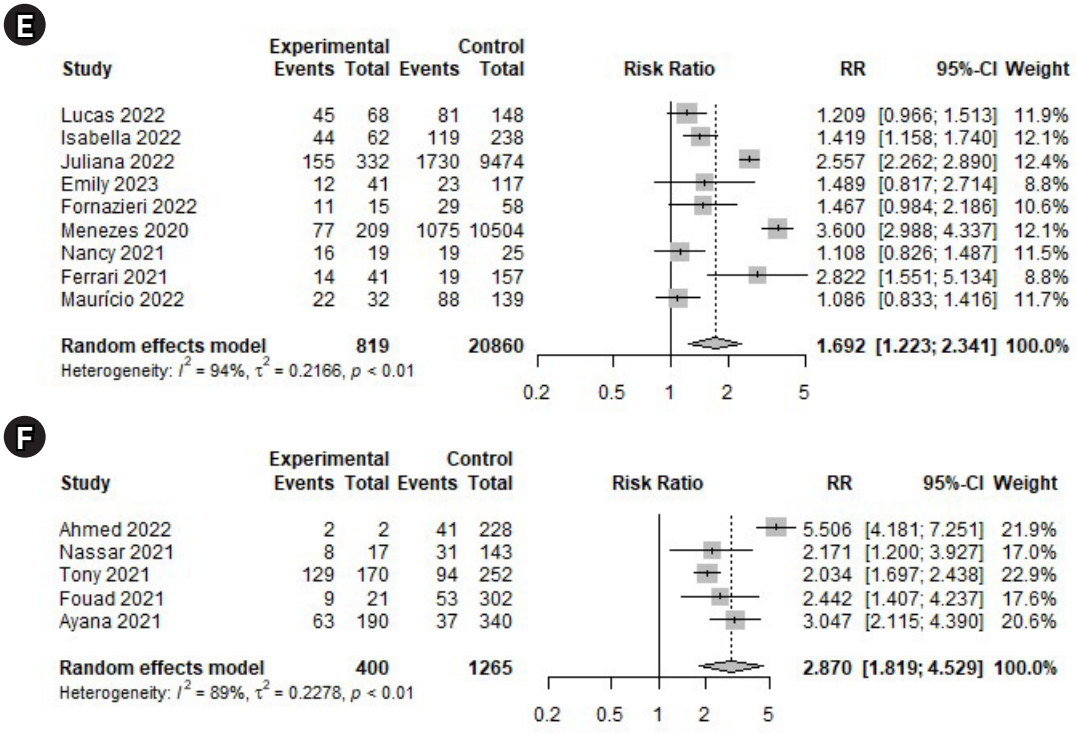

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ity to contracting infection and the progression of infection [22]. Various smoking mechanisms increase the risk of viral infections. These mechanisms include changes in the immune response; changes in airway biology, such as the activation of the epithelium; and significant structural changes in the respiratory tract, such as impaired mucociliary clearance, mucus hypersecretion, fibrosis, and epithelial barrier dysfunction [23-26].

Angiotensin-converting enzyme 2 (ACE2) may be the key factor that links smoking with the progression of COVID-19. The entry of coronaviruses into human cells involves a multifaceted process, encompassing various distinct domains of spike (S) protein that mediate viral attachment to the cell surface, receptor engagement, protease processing, and membrane fusion [27]. ACE2 is abundantly present in the epithelia of the lungs and small intestines and serves as an entry point for SARS-CoV [28]. The binding of S proteins to human cells is facilitated by the ACE2 receptor in several viruses, such as SARS-CoV and SARS-CoV-2 [29-31]. A previous study demonstrated the upregulation of pulmonary ACE2 gene expression in ever-smokers compared with never-smokers, regardless of the tissue subset or COPD status [32]. A recent meta-analysis indicated a heightened risk of COVID-19 progression (30%-50%) among current and ex-smokers compared with never-smokers. These results suggested that 6.2 million deaths due to COVID-19 worldwide are caused by tobacco smoking [33].

The pooled prevalence rates of smokers in Oceania, Asia, Europe, America, and Africa were 36%, 14%, 38%, 31%, and 32%, respectively [34]. We compared the smokers' COVID severity by continent and GDP level. One study showed that the severity of COVID-19 differs in various geographical locations, with mortality rates of 0.7 deaths per 100,000 in South Korea and 86.8 per 100,000 in Belgium [14]. Another study comparing the COVID-19 severity by region concluded that smoking had a protective effect against COVID-19. The COVID-19 mortality rates were 13 (5-24) per million inhabitants in countries with a high male smoking prevalence (>45%) and 33 (4 COVID-19 133) in countries with a low male smoking prevalence (<25%) [15]. The high COVID-19 death rate among smokers in the African continent and low-GDP countries is attributed to the lack of medical management systems compared with other countries. In addition to medical treatment, environmental or socioeconomic factors can increase the severity. However, no available study has compared the COVID-19 severity according to the type and amount of smoking.

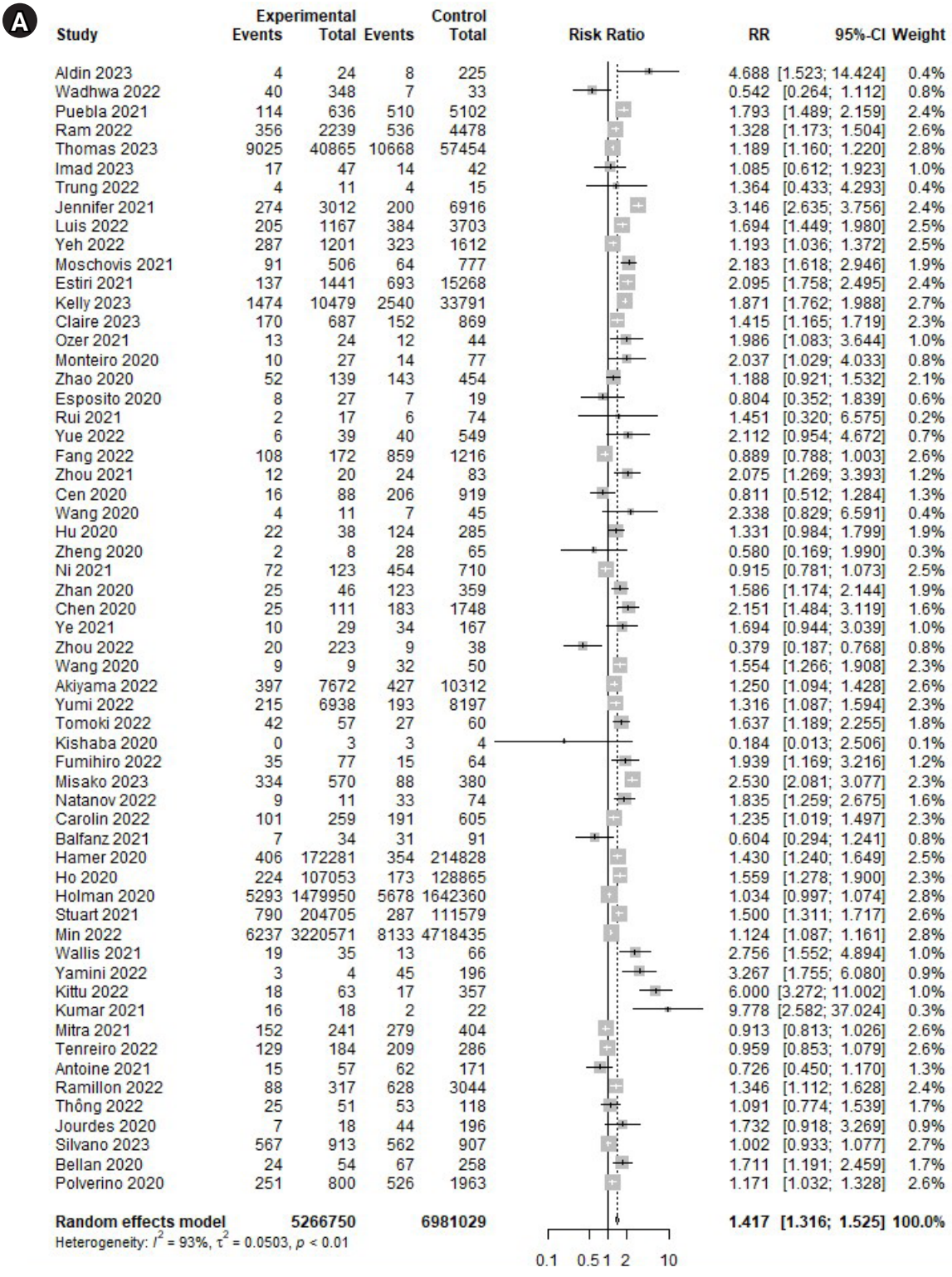

Fig. 3. COVID-19 severity in high-income (GDP 10th place or higher) countries (A), middle-income countries (GDP 11th–50th) (B), and low-income countries (GDP 51th and below) (C). RR, risk ratio; 95% CI, confidence interval. (Continued to the next page)

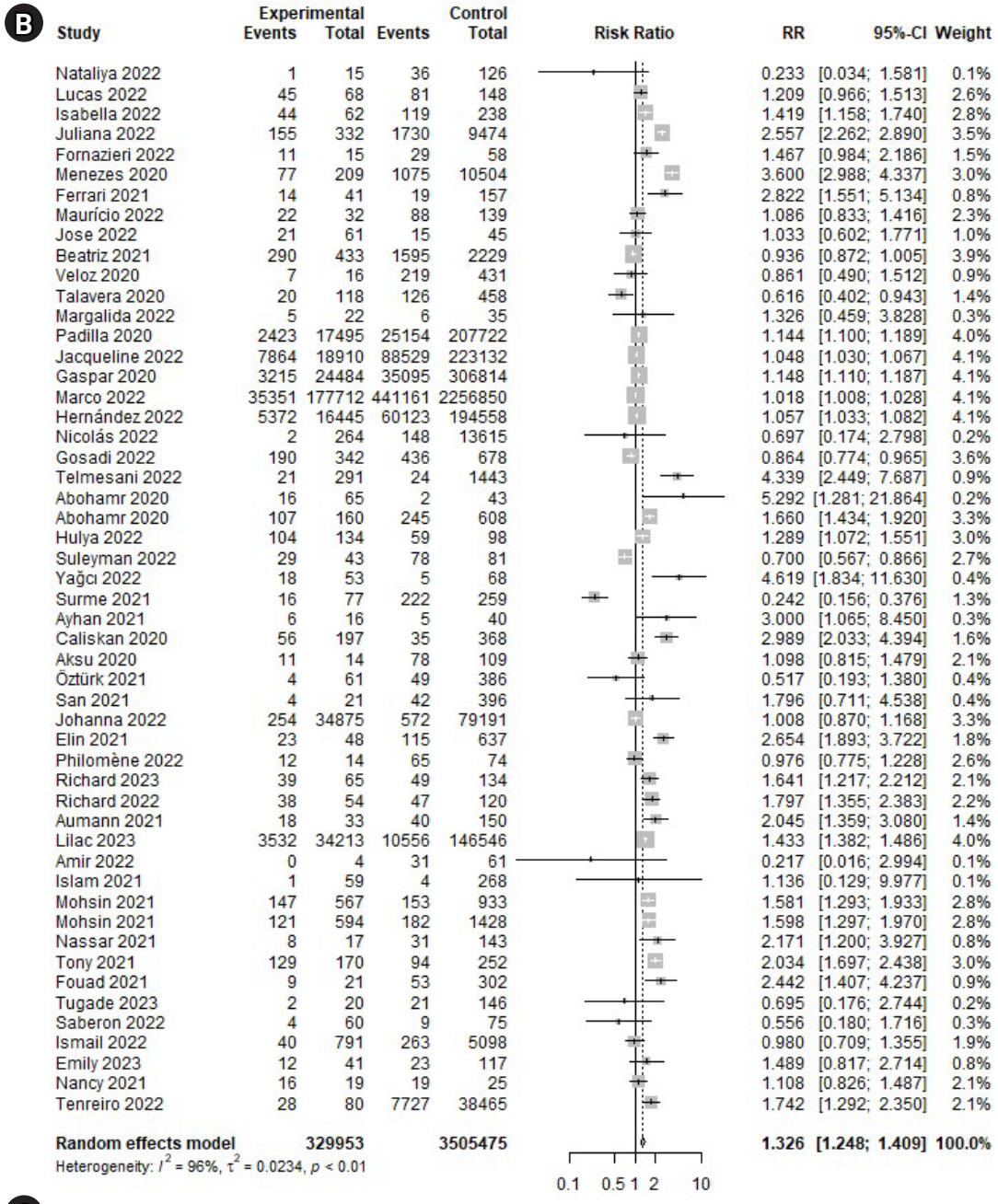

Fig. 3. Continued.

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Ethics approval

Not applicable.

Conflict of interest

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