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Original Article

Percentage of Children and/or Adolescents of All COVID-19 Cases: A Meta-analysis

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Abstract Since the first report of COVID-19 in Wuhan, China, the disease has rapidly spread to many countries worldwide. The initial reports showed that the incidence rate in adults was higher, while children and adolescents had fewer cases of infection. However, the number of COVID-19 cases has gradually increased in children and adolescents. Therefore, this study aimed to assess the percentage of children and/or adolescents of the total patients diagnosed with COVID-19. PubMed, Embase, Web of Science and the Cochrane Library were searched to find relevant studies. All statistical analyses were conducted using StataMP 14 software. A total of 12 studies met the inclusion criteria. The final results showed that the percentage of children and/or adolescents of all COVID-19 cases was 0.06 [95% confidence interval (CI), 0.04-0.07], which meant an average of 6 cases in children per 10,000 COVID-19 cases. The percentage of children and/or adolescents with COVID-19 was 0.03 (95% CI, 0.01-0.05), 0.09 (95% CI, 0.08-0.09), 0.09 (95% CI, 0.03-0.16) and 0.04 (95% CI, 0.00-0.10) in Asia, South America, North America and Europe, respectively. The present study showed a low percentage of COVID-19 cases of children and/or adolescents, but not without infection risk. Therefore, we should pay attention to the cases of children and/or adolescents during the COVID-19 period and raise our vigilance.

Key words *Children and/or adolescents (teenager, youth, teen); COVID-19 (SARS-CoV-2, 2019-nCoV)*

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Introduction

Viral diseases pose a serious threat to public health and safety. In the last 20 years, two large-scale cross-border outbreaks of β-coronavirus have been reported in animals: one with the severe acute respiratory syndrome (SARS) in 2002 and the other with the Middle East respiratory syndrome (MERS) in 2012.[1,2] The World Health Organization (WHO) announced that the SARS epidemic situation was under control on 5 July 2003. A total of 8096 SARS cases and 774 deaths were reported in 29 countries, and the total mortality rate was 9.6%.[2-4] However, MERS has not been brought under control; 862 of 2506 patients with infections in 27 countries have died since 2012 (fatality rate was about 35%).[3,4] A novel coronavirus (SARS-CoV-2 or 2019 coronavirus) emerged in December 2019, triggering a new global public health concern. Since China's first case of novel coronavirus pneumonia 2019 (COVID-19) in Wuhan, the virus spread rapidly to all countries in the world. As of 15 February 2021, WHO reported 108,484,802 cases of COVID-19, with 2,394,323 deaths and a mortality rate of 3.4%.[5] Although the mortality rate of COVID-19 is significantly lower than that of SARS and MERS, the incidence rate of both is far ahead.

Past surveys showed that children and adolescents had few SARS and MERS infections, and the incidence rate was low. Similarly, few cases were reported in children and adolescents in the early days of the outbreak of COVID-19. However, the number of cases in this age group increased gradually with the spread of this disease. A data from the United States showed that, as of 4 February 2021, 2,934,292 paediatric COVID-19 cases were reported, which represented 12.9% of all cases; in 2 weeks (from 21 January 2021 to 2 February 2021), a 10% increase in the number of cases (257,680 new cases) was observed.[6] However, the percentage of children and/or adolescents with COVID-19 was still significantly lower than that in adults. A report from the Chinese Center for Disease Control and Prevention showed that of the 44,672 patients diagnosed, 965 (2.2%) were children or adolescents aged less than 19 years while 43,707 (97.8%) were adults aged 20 years or older.[3] Research showed that the low detection rates of SARS-CoV-2 RNA in children might be related to the following two reasons: (1) infants and children might display reduced susceptibility to infection compared with adults and (2) mild or asymptomatic disease manifestation in children escaped detection, resulting in an underestimation of the real rate of infection.[7] Therefore, the involvement of children or adolescents in the transmission of COVID-19 could not be excluded. Besides, no specific data or meta-analysis was available to describe the percentage of children and/or adolescents of all COVID-19 cases during the new coronavirus pneumonia outbreak. Therefore, this study was performed to specifically assess the percentage of children and/or adolescents of all patients diagnosed with COVID-19, so as to better guide the treatment of children and adolescents infected with COVID-19 and prevent the spread of the disease.

Materials and Methods

Search Strategy

PubMed, Embase, Web of Science and the Cochrane Library databases were comprehensively searched for the studies on the percentage of children and/or adolescents of COVID-19 cases using the following terms: 'COVID-19', 'SARS-CoV-2', 'novel coronavirus 2019', '2019-nCoV', 'children' 'adolescents' 'teenager' 'youth' and 'teen'. In the initial search for studies, the studies that met the inclusion criteria were also selected by reading the references of previous related studies. The search language was limited to English. A total of 9542 studies were retrieved, including one that met the inclusion criteria after reading the references of previous related studies.

Study Selection

Preliminary screening was performed by a researcher. The irrelevant studies were excluded by this researcher after reading the titles and abstracts, and then the full text was read to screen the included studies further. The initial search results were 9543, with 1 retrieved from the references of the included studies. A total of 8048 studies were obtained after excluding repetitive studies. These 8048 studies were screened by titles and abstracts; 6836 were excluded and 1212 were retained. After the full-text screening, 1200 were deleted for various reasons. Finally, after reading and discussion by 2 other researchers, 12 studies were included in the analysis (Figure 1).

Inclusion and Exclusion Criteria

The inclusion criterion was as follows: studies that reported the percentage of children and/or adolescents with COVID-19. Paediatric population was defined as that aged less than 20 years. The percentage of children and/or adolescents with COVID-19 was defined as the percentage of children and/or adolescents of the total patients

diagnosed with COVID-19 during the study period. The included studies should meet this age requirement. In addition, the included studies should have clear information about the author or institution, the year of publication and the country or region of the research population.

The exclusion criteria were as follows: (1) a study irrelevant to the research direction, (2) a study without related data, (3) a letter or medical record report, (4) duplicate data, (5) duplicate studies and (6) reviews, and specified age or age groups that did not meet the requirements.

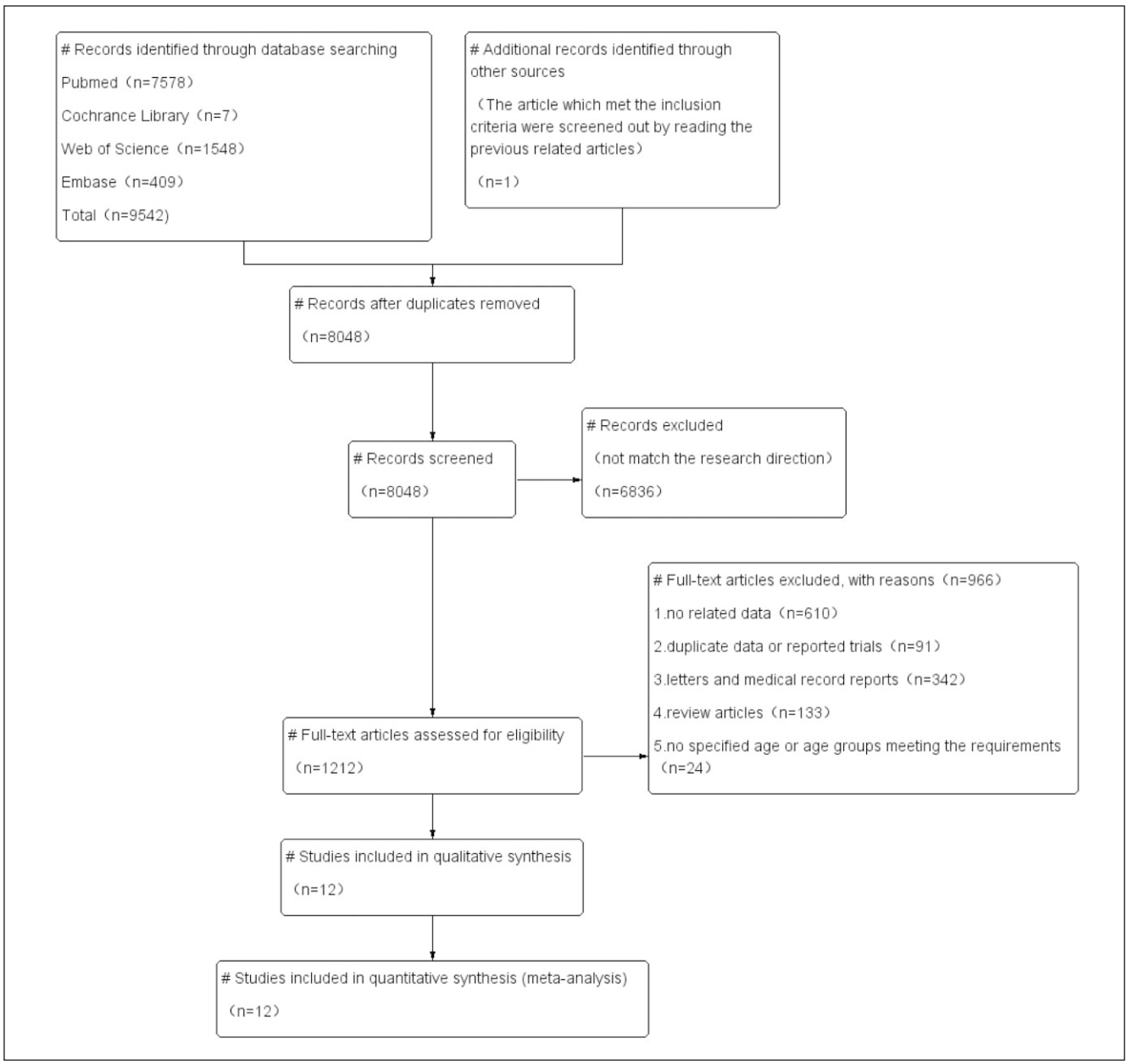

Figure 1 Flow chart of the screening process. The initial search results were 9543, with 1 retrieved from the references of the included studies. A total of 8084 studies were obtained after excluding repetitive studies. These 8084 studies were screened by titles and abstracts; 6863 were excluded, and 1212 were obtained. After the full-text screening, 610 studies without relevant data, 91 studies with repeated data, 342 letters or medical record reports, 24 studies with no specified age or age groups meeting the requirements and 133 reviews were further excluded. Finally, 12 studies were included in the analysis.

Data Extraction

A total of 12 studies were included in this study. The collected data included the name of the first author or institution, the year of publication, the country, the age of the participants, the total number of participants and the percentage of children and/or adolescents with COVID-19.

Quality Assessment

In this study, the Joanna Briggs Institute critical capital checklist for students reporting progress data was used to evaluate the quality of all included published studies.[8] All the evaluations were conducted by two co-authors in strict accordance with the standards. The results of the quality evaluation of these published studies are shown in Table 1.

Statistical Analysis

All statistical analyses were conducted using StataMP 14 software. The percentage of cases and 95% confidence interval (CI) of COVID-19 in children and/or adolescents were calculated and analysed using single-rate descriptive analysis and random-effects model. Egger's test was used to analyse whether the included studies had publication bias. Also, the subgroup analysis of the percentage of children and/or adolescents with COVID-19 among different states and countries was also performed.

Results

Characteristics of the Included Studies

The characteristics of all included studies are shown in Table 2, including the first author or institution, the year of publication, the number of patients aged 0-19 years, the total number of positive COVID-19 cases and the country of the study population. The sample size of the included studies ranged from 102 to 3,998,055.

Meta-analysis

Figure 2 shows that the percentage of children and/or adolescents with COVID-19 was 0.06 (95% CI, 0.04-0.07), which meant an average of 6 cases in children per 10,000 COVID-19 cases. The heterogeneity of COVID-19 was high, and therefore the random-effects model was used. Egger's test showed that the P>|t| index was 0.386 in COVID-

Table 1 Quality (risk of bias) assessment of included pandemic studies

Study	1. Was the sample frame appropriate to address the target population?	2. Were study participants recruited in an appropriate way?	3. Was the sample size adequate?	4. Were the study subjects and setting described in detail?	5. Was data analysis conducted with sufficient coverage of the identified sample	6. Were valid methods used for the identification of the condition?	7. Was the condition measured in a standard, reliable way for all participants?	8. Appropriate statistical analysis?	9. Was the response rate adequate?
Wu 2020[3]	Y	N	Y	Y	UN	Y	NA	NA	NA
Kasuga 2020[9]	N	N	Y	N	UN	Y	NA	NA	NA
Lee 2020[10]	Y	N	Y	N	UN	Y	NA	NA	NA
Mizumoto 2020[11]	N	N	N	Y	UN	Y	Y	Y	Y
Nikpouraghdam 2020[12]	N	N	N	Y	UN	Y	Y	Y	Y
Gujski 2020[13]	N	N	N	Y	UN	Y	Y	N	NA
Ortenzi 2020[14]	Y	N	Y	Y	UN	Y	NA	NA	NA
Undurraga 2021[15]	Y	N	Y	Y	UN	Y	NA	Y	NA
Martins-Filho 2021[16]	Y	N	Y	Y	UN	Y	NA	N	NA
Paquette 2020[17]	Y	N	Y	Y	UN	Y	NA	NA	NA
Alaska Department 2021[18]	Y	N	Y	Y	UN	Y	NA	NA	NA
Stokes 2020[19]	Y	N	Y	Y	UN	Y	NA	NA	NA

Abbreviations: Y, Yes; N, No; NA, not applicable; UN, unclear.

Table 2 Characteristics of all included studies

Continent	Article	Country	Age (year)	Percentage of children and/or adolescents cases n (%)	Total number of patients with COVID-19
Asia	Wu 2020[3]	China	0-19	965 (2.2)	44672
	Kasuga 2020[9]	Japan	0-19	152 (2.9)	5195
	Lee 2020[10]	The Republic of Korea	0-19	987 (7.2)	13672
	Mizumoto 2020[11]	Japan	0-19	6 (0.9)	634
	Nikpouraghdam 2020[12]	Iran	0-19	10 (0.3)	2964
Europe	Gujski 2020[13]	Poland	0-19	86 (7.4)	1157
	Ortenzi 2020[14]	Italy	0-19	1355 (1.4)	94312
South America	Undurraga 2021[15]	Latin America (Chile)	0-19	40418 (9.1)	444 921
	Martins-Filho 2021[16]	Brazil	0-19	335279 (8.4)	3998055
North America	Paquette 2020[17]	Canada	0-19	938 (3.9)	24079
	Alaska Department 2021[18]	Alaska	0-19	10337 (18.9)	54736
	Stokes 2020[19]	America	0-19	69703 (5.3)	1320488

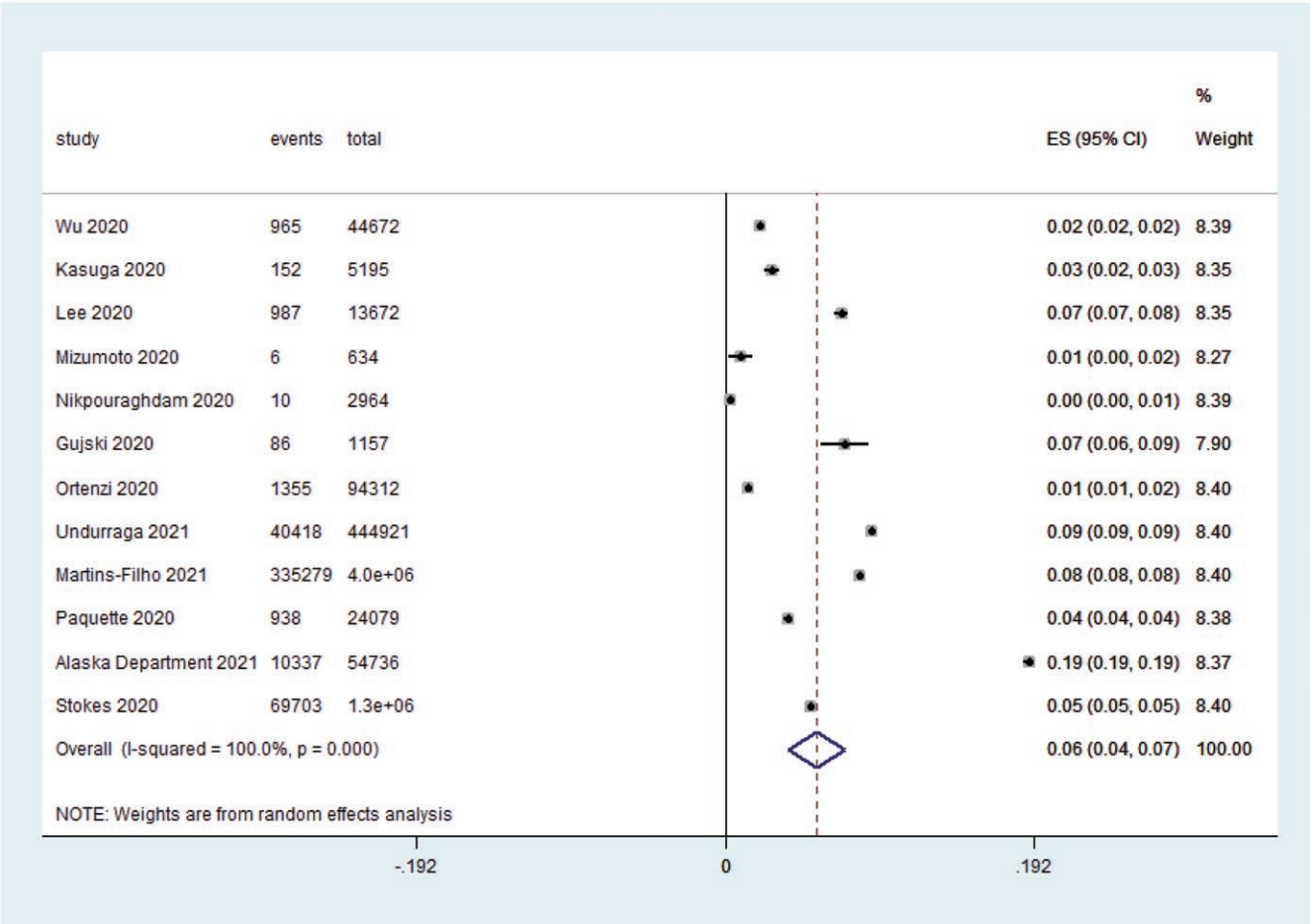

Figure 2 Percentage of children and/or adolescents of all cases diagnosed with COVID-19 was calculated by the single-rate meta-analysis method 1.

19, which was greater than 0.05, indicating no significant publication bias. Figure 3 shows that the percentage of children and/or adolescents with COVID-19 was 0.03 (95% CI, 0.01-0.05; I^2 = 99.5%), 0.09 (95% CI, 0.08-0.09; I^2 = 99.6%), 0.09 (95% CI, 0.03-0.16; I^2 = 100%) and 0.04 (95% CI, 0.00-0.10; I^2 = 98.3%) in Asia, South America, North America and Europe, respectively.

This study showed that the percentage of children and/or adolescents with COVID-19 was low, but not without infection risk. Therefore, the involvement of children or adolescents in the transmission of COVID-19 could not be excluded.

Discussion

This analysis included 12 studies. It reported the percentage of children and/or adolescents of the total patients diagnosed with COVID-19. The findings indicated that the percentage of children and/or adolescents with

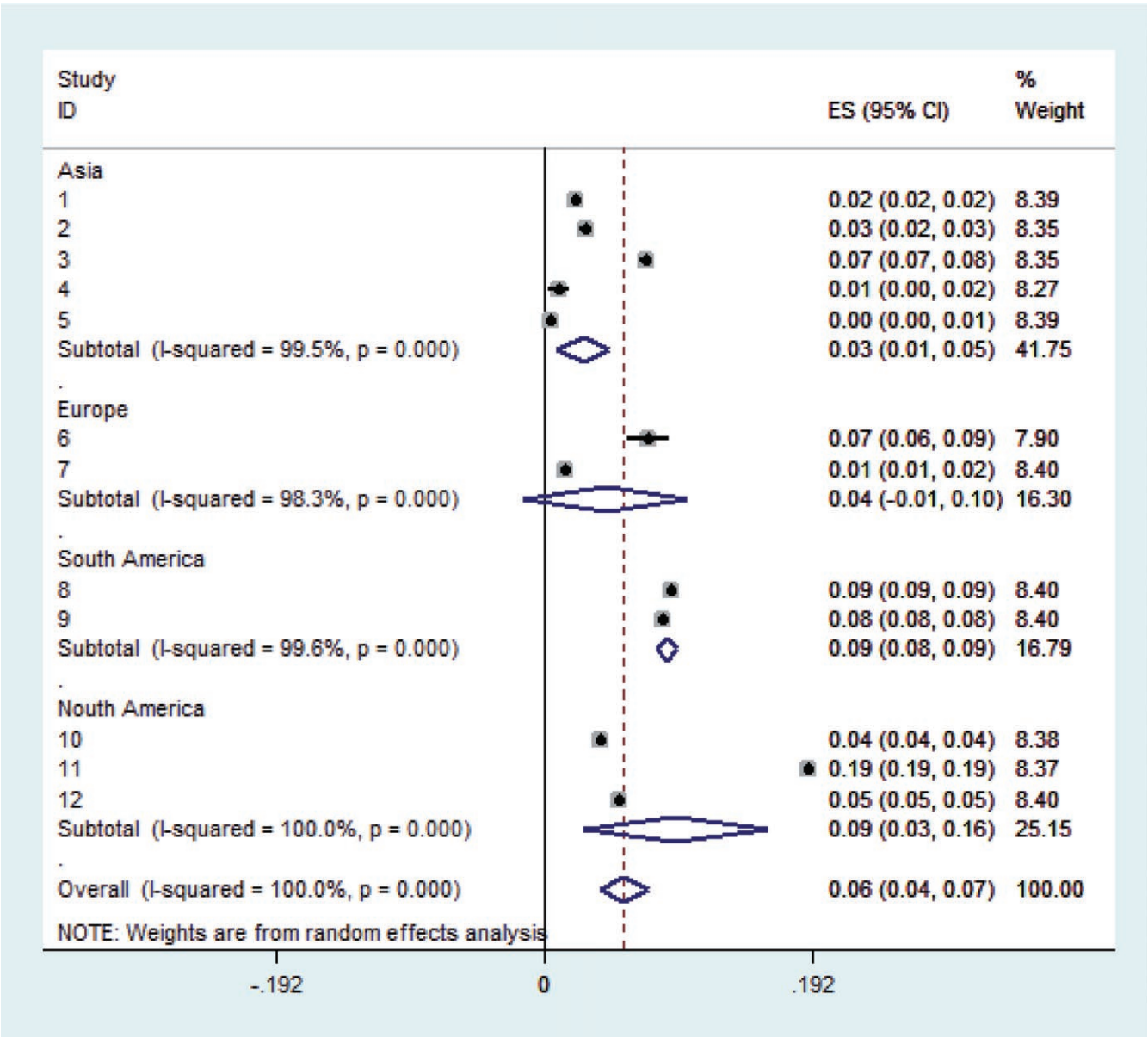

Figure 3 Between continents, the percentage of children and/or adolescents of all cases diagnosed with COVID-19 was calculated by the subgroup analysis.

COVID-19 was 0.06 (95% CI, 0.04-0.07). Besides, it was 0.03 (95% CI, 0.01-0.05; I^2 = 99.5%), 0.09 (95% CI, 0.08-0.09; I^2 = 99.6%), 0.09 (95% CI, 0.03-0.16; I^2 = 100%) and 0.04 (95% CI, 0.00-0.10; I^2 = 98.3%) in Asia, South America, North America and Europe, respectively. This low percentage of children and/or adolescents with COVID-19 indicated that children and adolescents might have low susceptibility to the new coronavirus, but still a certain risk of infection existed.

Internationally, the prevalence of confirmed COVID-19 cases is significantly lower in children than in adults;[20] however, emerging data suggest that more young children are being infected.[6,21] Some possible reasons for the low percentage of children and/or adolescents with COVID-19 are as follows. First, similar to SARS-CoV, the presence of angiotensin-converting enzyme-2 (ACE-2) protein is required for SARS-CoV-2 to enter the cells.[20,22-24] Relevant reports have pointed out that undifferentiated cells have a low expression of ACE-2 and are rarely infected by the SARS virus, whereas highly differentiated cells have a high expression of ACE-2 and are infected by the SARS virus more quickly. ACE-2 is not mature in young children and hence may not function as a receptor for SARS-CoV-2. In addition, ACE2-induced intracellular response of alveolar epithelial cells in children may be lower than that in adults.[23,24] Another possible reason is the higher number of CD4 cells and the lower number of CD8 T lymphocytes. The infection of SARS virus type 2 in elderly men is related to the decrease in the number of CD4 cells compared with the higher number of CD4 cells in young people.[23] In addition, studies show that a greater proportion of children have an asymptomatic disease; hence, it is also likely that the true number of paediatric cases is underestimated.[7,20, 25] Therefore, we need to be extra vigilant towards the cases in children and adolescents.

Although the conclusion of this study was consistent with the actual situation, the study still had some limitations. First, most studies on children and adolescents had no specific age and gender classification, and therefore subgroup analysis was difficult. Second, many studies could not be included in this study due to different age grouping criteria for different studies. Besides, since we included only English studies, many non-English reports might have been missed. Finally, only 12 studies with an age limit of 0-19 years were available, and the sample size was significantly different, which might be the reason for the heterogeneity in this study. Large-sample studies should be conducted in the future to analyse the differences in the percentage of COVID-19 cases between children and adolescents.

Conclusion

This study showed that the percentage of children and/or adolescents of all patients diagnosed with COVID-19 was low, but not without infection risk.

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Declaration of Interest

The authors have no conflicts of interest to disclose. All listed authors contributed to the planning, performance and reporting of this study.

Consent to Participate

Informed consent was obtained from all individual participants included in the study.

Author Contributions

Wen Wen, Hai-fu Zhang and Yong-ran Cheng: data curation, software and methodology. Chun-yi Wang and Meng-yun Zhou: methodology and writing. Xing-wei Zhang: methodology and writing. Lan Ye: data curation and writing. Ming-wei Wang, Zhan-hui Feng, Yan-hong Luo and Juan Chen: methodology, supervision, project administration and writing. All authors read and approved the final manuscript.

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