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Regional and Chronological Variation of Chemosensory Dysfunction in COVID-19: a Meta-Analysis

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ABSTRACT

Background: Olfactory and gustatory dysfunction are frequently reported in patients with coronavirus disease 2019 (COVID-19). However, the reported prevalence of olfactory and/or gustatory dysfunction varies widely, and the reason for the inter-study differences is unclear. Hence, in this meta-analysis, we performed subgroup analyses to investigate the factors that contribute to the inter-study variability in the prevalence of olfactory and gustatory dysfunction.
Methods: Out of 943 citations, we included 55 eligible studies with 13,527 patients with COVID-19 for a meta-analysis. Calculating the data extracted from each study, the weighted summary prevalence of olfactory and gustatory dysfunction was estimated using a Freeman-Tukey transformation with models based on random-effects assumptions. A meta-analysis of variance compared the prevalence of olfactory and gustatory dysfunction according to regional, chronological, demographic, and methodologic factors, respectively.
Results: The overall pooled prevalence rates of olfactory and gustatory dysfunction were 51.4% and 47.5%, respectively, in the random-effect model. In subgroup analyses, the prevalence rates of olfactory and gustatory dysfunction were significantly different among four geographical regions (both $P < 0.001$, respectively). Although the prevalence rates of olfactory and gustatory dysfunction did not significantly differ according to the time of enrollment, the subgroup analyses including only studies from the same geographical region (Europe) revealed a significant difference in olfactory dysfunction according to the time of enrollment.
Conclusion: The regional and chronological differences in the prevalence rates of olfactory and gustatory dysfunctions partly explain the wide inter-study variability.

Keywords: Coronavirus; Smell; Taste; Meta-Analysis; Geographic Location

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread rapidly worldwide since it was first identified in Wuhan, China in 2019. Although most COVID-19 patients have mild clinical manifestations, about 5% progress to critical status with respiratory failure and/or multi-organ failure.[1]
A previous study suggested that the sinonasal tract may play a significant role in the infection, transmission, and pathogenesis of the SARS-CoV-2.[2] In addition, nasal swabs

Author Contributions

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from symptomatic patients with COVID-19 had higher viral loads than throat swabs.[3] As the olfactory sensory neurons directly contact the environment in the nasal cavity, these neurons may be vulnerable to the exposure of the high viral load of SARS-CoV-2 in the nasal cavity.

Olfactory and gustatory dysfunction are frequently reported in patients with COVID-19 and are noted as significant symptoms in COVID-19. The prevalence of olfactory and gustatory dysfunction in previous studies varies from 5.1% to 98.3% and 5.6% to 92.7%, respectively[4]; however, the reason for the inter-study differences is unclear. In addition, a recent meta-analysis showed that the prevalence rates of olfactory and gustatory dysfunction were 52.7% and 54.9% in COVID-19 patients, respectively; however, a significant heterogeneity (I^2 = 98.9% for both, prevalence rates of olfactory and gustatory dysfunction) was detected.[4] In contrast to Europe where the prevalence of olfactory dysfunction was found to be more than 50% in many studies, we noted that most studies conducted in Asia showed the prevalence of olfactory dysfunction to be less than 50%.[5-9] Therefore, we hypothesized that the prevalence rates of olfactory and gustatory dysfunction are geographically and chronologically different, and this may explain the heterogeneity of the prevalence rate of olfactory and gustatory dysfunction. In this meta-analysis, we performed subgroup analysis to investigate factors, such as geographical region and enrollment time, that contributed to the inter-study variability of the prevalence rate of olfactory and gustatory dysfunction.

METHODS

Search strategy

A comprehensive search of PubMed, Embase, and Scopus databases following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline was carried out up to July 9th, 2020.[10] Two authors (S.C.H, J.Y.K) independently performed literature searches to identify candidate studies for the meta-analysis using the terms: ("olfact*" OR "smell" OR "anosmia" OR "hyposmia") AND COVID-19. Only studies published in English were selected.

Selection of studies

The two authors independently screened abstracts and titles of studies identified by the search strategy. Studies that did not satisfy eligibility criteria were discarded; then, eligibility was evaluated in the full-text format. The inclusion criteria of the present systematic review and meta-analysis were as follows: 1) the article reports on prevalence of olfactory or gustatory dysfunction in patients with COVID-19, 2) prevalence of olfactory or gustatory dysfunction are separately reported. The following types of studies were excluded: 1) multicenter studies, including different continents (e.g., Europe and Asia), 2) studies lacking full text (e.g., only abstracts).

Data extraction

Data from included studies were extracted into standardized forms and were independently confirmed by the two authors. For each article, the following information was collected: the name of the first author, year of publication, study design, country where the study was conducted, time patients were enrolled, age, sample size, number of patients with olfactory dysfunction, number of patients with gustatory dysfunction, evaluation method of olfactory dysfunction and/or gustatory function, and the characteristics of the population (general population, hospitalized population, non-hospitalized population, or healthcare workers population). The regions where the individual studies were conducted were categorized

into: East Asia, Europe, North America, Middle East, Latin America, and Africa. The evaluation method was classified into history taking, self-reported survey, validated survey, and validated instrument. The validated surveys were designated as surveys with structured questions about olfactory and/or gustatory dysfunction. The validated instrument included evaluation with psychophysical function tests such as Sniffin' Sticks, UPSIT, and taste test with four solutions (salted, sweet, sour, and bitter solutions).

Risk of bias assessment

Risk of bias was evaluated using a quality assessment checklist for prevalence studies based on nine domains: representation of the national population, representation of the target population, random selection, likelihood of nonresponse, directly collected data from the subject, case definition, validity of the instrument of measurement, similarity in mode of data collection for all subjects, and presence of numerators and denominators in the parameters of interest.[11] Each item was graded as 0 for low risk or 1 for high risk, and the summation of values rated to evaluate the risk of bias were 0–3, 4–6, and 7–9 for low, moderate, and high risk of bias, respectively.

Statistical analysis

Calculating the data extracted from each study, the weighted summary prevalence of olfactory and gustatory dysfunction was estimated using a Freeman-Tukey transformation with models based on random-effects assumptions.[12] Because prevalence would be influenced by the spectrum of populations and the evaluation method of olfactory or gustatory dysfunction in the individual studies, we expected a significant heterogeneity across the included studies. Therefore, we selected a random-effects model to give more conservative estimates. A meta-analysis of variance compared the prevalence of olfactory and gustatory dysfunction according to regional, chronological, demographic, and methodologic factors, respectively. Post-hoc analysis was carried out using Tukey's test for the results of analysis of variance (ANOVA). To assess heterogeneity across the included studies, the Cochran Q statistic test and the I^2 test were carried out. A funnel plot and Egger's test were used to evaluate potential publication bias. All analyses were conducted in R for Windows version 3.6.1 by using the “meta” and “metaphor” packages (R Foundation for Statistical Computing, Vienna, Austria). A P value < 0.05 was considered statistically significant.

RESULTS

Initially, of the 943 citations identified through the search strategy, we included 55 eligible studies for systematic review (**Fig. 1**).[5-9,13-61]

Study characteristics

The characteristics of the included studies are summarized in **Table 1**. The total sample size of the 55 included studies was 13,527 patients with individual sample sizes ranging from 16–3,191 patients. All included studies reported the prevalence of olfactory dysfunction in COVID-19, while 46 studies reported the prevalence of gustatory dysfunction. All included studies were conducted in 2020, and they were performed across 19 countries. There were four regions with at least one study: East Asia (n = 7), Europe (n = 35), North America (n = 8), Middle East (n = 5). The region with the most individual studies was Europe (n = 35), including 16 studies conducted in Italy. Two multicenter studies conducted in Europe were included. Out of 55 included studies, 29 clarified when patients were enrolled. Considering

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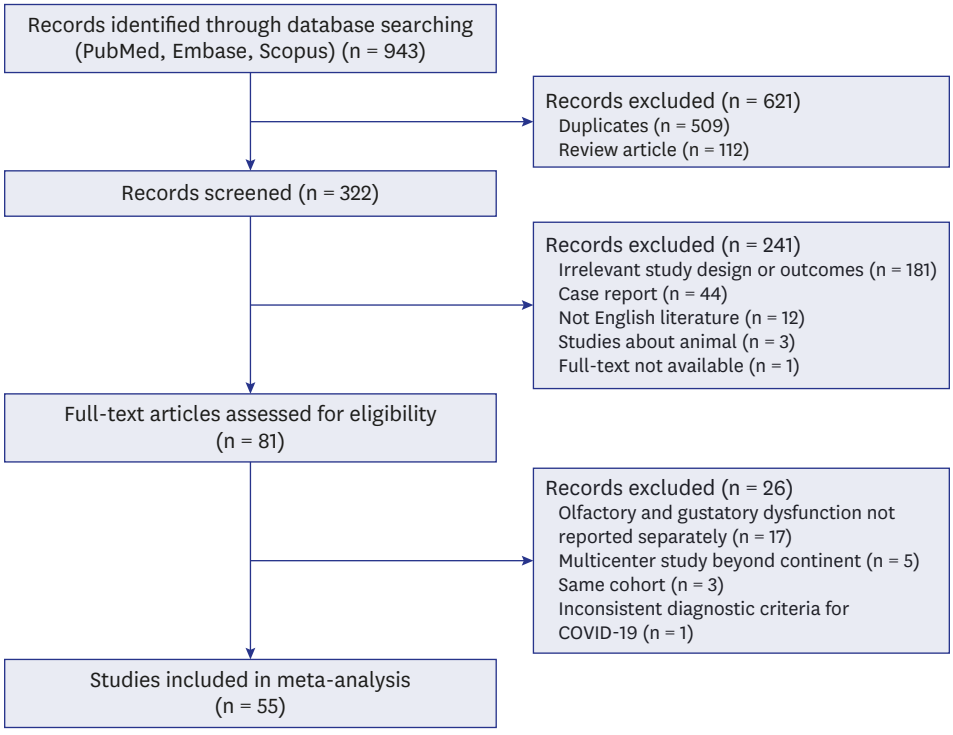

Fig. 1. Study selection diagram.

the characteristics of the population of individual studies, there were 29 studies of the general population, including both hospitalized and non-hospitalized patients, 15 studies of only hospitalized patients, eight studies of only non-hospitalized patients, and three studies of healthcare workers. Ten studies used history taking of olfactory and/or gustatory evaluation, 31 used self-reported surveys, six used validated surveys, and eight used validated instruments. Patients were diagnosed as COVID-19 by real-time polymerase chain reaction in most studies, except four[6,23,49,51] that did not report the testing tool.

Quality assessment

Quality assessment of the individual studies is demonstrated in **Supplementary Table 1**. The mean overall score was 3.5, indicating overall low to moderate risk of procedure bias, and there were 29 and 26 studies with low and moderate risk of procedure bias, respectively. No study had a high risk of methodological bias because the prevalence of olfactory and/or gustatory dysfunction was similarly evaluated in patients. However, the studies with hospitalized, non-hospitalized, or healthcare worker populations that did not represent the general population were commonly evaluated as studies with a moderate risk of bias. Most individual studies were cross-sectional, which contains an implicit risk of bias if the number of patients omitted was not recorded accurately.

The overall prevalence rates of olfactory and gustatory dysfunction in COVID-19 patients

A total of 13,527 patients were identified for assessment of olfactory dysfunction in 55 studies. The prevalence of olfactory dysfunction in individual studies ranged from 5.1% to 99.0%, and the prevalence was 51.4% in the random-effects model with severe inter-study heterogeneity (95% confidence interval [CI], 43.7–59.1; I^2 = 98.6%; **Supplementary Fig. 1A**).

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Table 1. Summary of the included studies

Authors	Region	Country	Study design	The time of enrollment	Population	Age	Evaluating method	Sample size
Liang et al.[7]	East Asia	China	CS	03-16-2020 to 04-12-2020	Hospitalized population	25.5[b]	Self-reported survey	86
Mao et al.[8]	East Asia	China	CS	01-16-2020 to 02-19-2020	Hospitalized population	52.7[a]	History taking	214
Chung et al.[56]	East Asia	China (Hongkong)	Retrospective case-control study	04-06-2020 to 04-09-2020	Hospitalized population	Unknown	Validated survey	18
Kim et al.[5]	East Asia	Korea	CS	03-12-2020 to 03-16-2020	Non-hospitalized population	26[b]	Self-reported survey	213
Lee et al.[6]	East Asia	Korea	CS	03-08-2020 to 03-31-2020	General population	44[a]	History taking	3,191
Noh et al.[9]	East Asia	Korea	CS	NA	Non-hospitalized population	38[a]	History taking	199
Chua et al.[20]	East Asia	Singapore	CS	03-23-2020 to 04-04-2020	General population	Unknown	Self-reported survey	31
Lechien et al.[31]	Europe	Four European countries	CS	NA	General population	36.9[a]	Validated survey	417
Lechien et al.[32]	Europe	Five European countries	CS	NA	General population	39.2[a]	Self-reported survey	1,420
Iravani et al.[26]	Europe	France	Retrospective case series	03-01-2020 to 03-17-2020	General population	47[a]	Self-reported survey	114
Lechien et al.[30]	Europe	France	CS	NA	General population	41.7[a]	Validated instrument	86
Renaud et al.[43]	Europe	France	CS	NA	General population	35[b]	Self-reported survey	97
Zayet et al.[54]	Europe	France	Retrospective case-control study	NA	Non-hospitalized population	40[a]	Self-reported survey	95
Zayet et al.[55]	Europe	France	Retrospective case-control study	02-26-2020 to 03-14-2020	General population	57[a]	Self-reported survey	70
Brandstetter et al.[18]	Europe	Germany	CS	NA	Healthcare workers	Unknown	Self-reported survey	31
Hintschich et al.[57]	Europe	Germany	CS	NA	General population	Unknown	Validated instrument	41
Luers et al.[36]	Europe	Germany	CS	03-22-2020 to 03-28-2020	Non-hospitalized population	38[a]	Self-reported survey	72
Tsivgoulis et al.[48]	Europe	Greece	CS	03-19-2020 to 04-08-2020	Hospitalized population	55[a]	Validated instrument	22
De Maria et al.[22]	Europe	Italy	CS	NA	Non-hospitalized population	Unknown	Self-reported survey	92
Dell'Era et al.[23]	Europe	Italy	CS	03-10-2020 to 03-30-2020	General population	50[b]	Validated survey	355
Freni et al.[24]	Europe	Italy	CS	NA	General population	37.7[a]	Validated survey	50
Gelardi et al.[25]	Europe	Italy	Retrospective case series	NA	General population	49.7[a]	History taking	72
Karadaş et al.[28]	Europe	Italy	CS	NA	Hospitalized population	46.5[a]	History taking	239
Lagi et al.[29]	Europe	Italy	CS	02-25-2020 to 03-26-2020	Hospitalized population	62[b]	History taking	68
Liguori et al.[35]	Europe	Italy	CS	NA	Hospitalized population	55[a]	History taking	103
Meini et al.[37]	Europe	Italy	CS	NA	Hospitalized population	65[a]	Self-reported survey	100
Mercante et al.[38]	Europe	Italy	CS	03-05-2020 to 03-23-2020	General population	52.6[a]	Self-reported survey	204
Paderno et al.[59]	Europe	Italy	CS	NA	General population	55[a]	Self-reported survey	508
Paderno et al.[39]	Europe	Italy	CS	03-27-2020 to 04-01-2020	Non-hospitalized population	45[a]	Self-reported survey	151
Petrocelli et al.[41]	Europe	Italy	CS	03-16-2020 to 05-02-2020	General population	43.6[a]	Validated instrument	300
Vacchiano et al.[49]	Europe	Italy	CS	NA	Hospitalized population	59[b]	Self-reported survey	108
Vaira et al.[50]	Europe	Italy	CS	03-31-2020 to 04-06-2020	General population	49.2[a]	Validated instrument	72

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Table 1. (Continued) Summary of the included studies

Authors	Region	Country	Study design	The time of enrollment	Population	Age	Evaluating method	Sample size
Vaira et al.[51]	Europe	Italy	Retrospective case series	NA	General population	48.5[a]	Validated instrument	256
Vaira et al.[52]	Europe	Italy	CS	NA	Healthcare workers	47.2[a]	Validated instrument	33
Tostmann et al.[47]	Europe	Netherland	Retrospective case-control study	03-10-2020 to 03-23-2020	Healthcare workers	Unknown	Self-reported survey	79
Sierpiński et al.[46]	Europe	Poland	CS	NA	Non-hospitalized population	50[b]	Self-reported survey	1,942
Abalo-Lojo et al.[13]	Europe	spain	CS	NA	General population	Unknown	Self-reported survey	131
Beltrán-Corbellini et al.[16]	Europe	Spain	CS	03-23-2020 to 03-25-2020	Hospitalized population	61.6[a]	Self-reported survey	79
Izquierdo-Domínguez et al.[27]	Europe	Spain	CS	03-21-2020 to 04-21-2020	General population	56.8[a]	Validated survey	846
Speth et al.[2]	Europe	Switzerland	CS	03-03-2020 to 04-17-2020	General population	46.8[a]	Self-reported survey	103
Altin et al.[15]	Europe	Turkey	CS	03-25-2020 to 04-20-2020	Hospitalized population	54.2[a]	History taking	81
Patel et al.[40]	Europe	UK	CS	03-01-2020 to 04-01-2020	General population	45.6[a]	Self-reported survey	141
Carignan et al.[19]	North America	Canada	Retrospective case-control study	NA	General population	57.1[b]	Self-reported survey	134
Lee et al.[33]	North America	Canada	CS	03-15-2020 to 04-06-2020	General population	38[b]	Self-reported survey	56
Aggarwal et al.[14]	North America	USA	CS	NA	Hospitalized population	67[b]	History taking	16
Dawson et al.[21]	North America	USA	CS	NA	General population	Unknown	Self-reported survey	42
Pinna et al.[42]	North America	USA	Retrospective case series	03-01-2020 to 04-30-2020	Hospitalized population	59.6[a]	History taking	50
Yan et al.[60]	North America	USA	CS	03-03-2020 to 03-29-2020	General population	Unknown	Self-reported survey	59
Yan et al.[61]	North America	USA	Retrospective case series	03-03-2020 to 04-08-2020	General population	Unknown	Self-reported survey	128
Yan et al.[53]	North America	USA	CS	03-09-2020 to 04-29-2020	General population	Unknown	Self-reported survey	46
Moein et al.[58]	Middle East	Iran	Retrospective case-control study	03-21-2020 to 04-05-2020	Hospitalized population	46.6[a]	Validated instrument	60
Biadsee et al.[17]	Middle East	Israel	CS	NA	Non-hospitalized population	36.3[a]	Self-reported survey	128
Levinson et al.[34]	Middle East	Israel	CS	03-10-2020 to 03-23-2020	Hospitalized population	34[b]	Self-reported survey	42
Sakalli et al.[44]	Middle East	Turkey	CS	NA	General population	37.8[a]	Self-reported survey	172
Sayin et al.[45]	Middle East	Turkey	Retrospective case-control study	NA	General population	37.8[a]	Validated survey	64

CS = cross-sectional, NA = not available.
[a]Mean age; [b]Median age.

Evaluation of gustatory dysfunction was identified in 46 included studies of 13,014 patients. The prevalence of gustatory dysfunction in individual studies ranged from 5.1% to 89.4%, and the random-effects model demonstrated a 47.5% prevalence with severe inter-study heterogeneity (95% CI, 39.7–55.3; I^2 = 98.6%; **Supplementary Fig. 1B**).

Subgroup analyses according to the region

The prevalence rates of olfactory and gustatory dysfunction of the four different regions were 25.3% and 19.4% in East Asia, 57.5% and 53.1% in Europe, 41.8% and 46.2% in North America, and 59.8% and 47.9% in the Middle East, respectively, with a significant difference among the regions (both $P < 0.001$; **Fig. 2A and B**). Post-hoc analysis revealed that the

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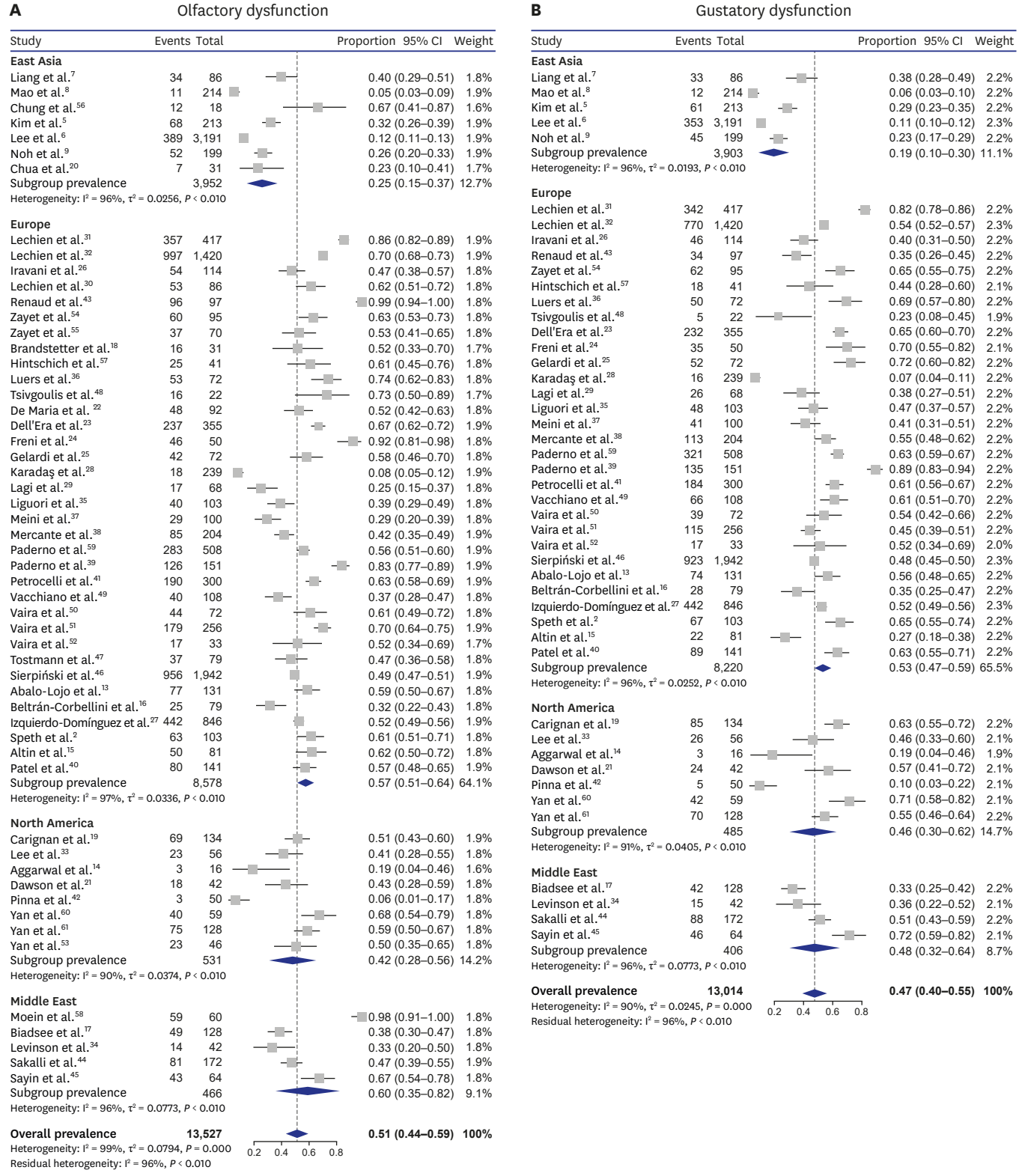

Fig. 2. Subgroup analysis on region. (**A**) Forest plot meta-analysis of the prevalence of olfactory dysfunction of four regions (East Asia, Europe, North America, and Middle East) showed 25.3%, 57.5%, 41.8%, and 59.8% pooled subgroup prevalence rates in the random-effect model, respectively ($P < 0.001$ for subgroup difference). (**B**) Forest plot meta-analysis of the prevalence of gustatory dysfunction of four regions (East Asia, Europe, North America, and Middle East) showed 19.4%, 53.1%, 46.2%, and 47.9% pooled subgroup prevalence rates in the random-effect model, respectively ($P < 0.001$ for subgroup difference). The diamonds represent pooled prevalence rates with 95% CI, and the estimates of individual studies are represented as squares, with 95% CIs represented as horizontal lines.
CI = confidence interval.

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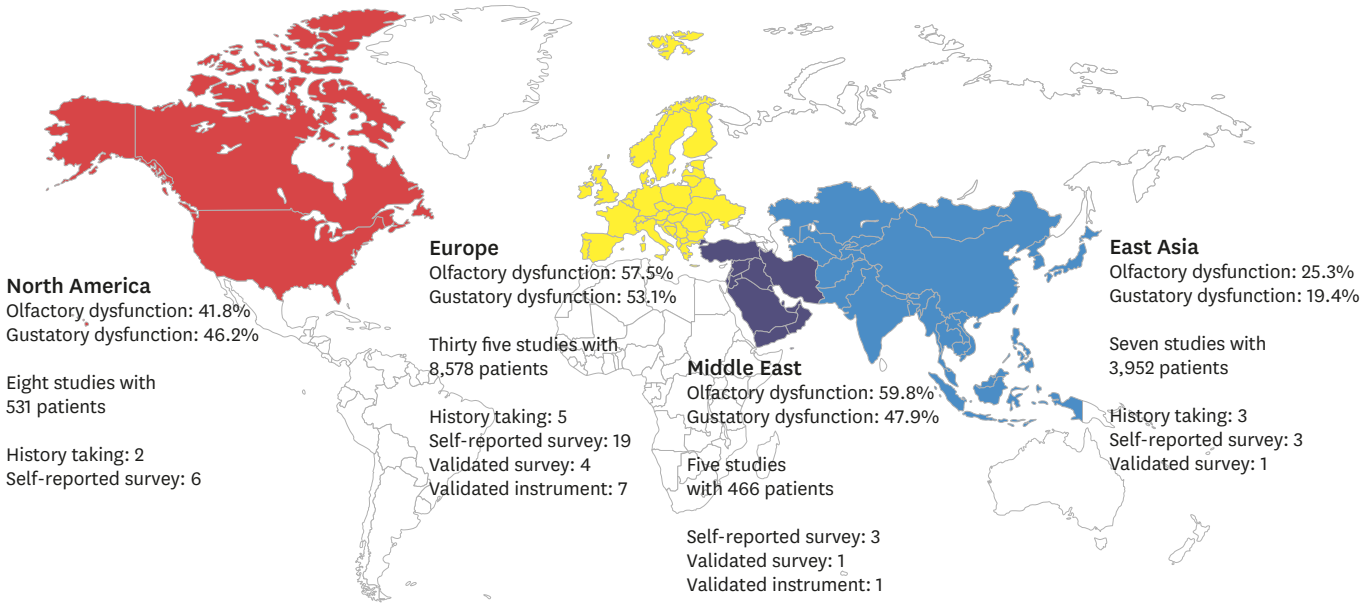

Fig. 3. World map of the prevalence rates of olfactory and gustatory dysfunction in coronavirus disease 2019 patients. The colored regions indicate the geographically classified regions in this study (aqua blue: East Asia, yellow: Europe, red: North America, navy: Middle East). The prevalence rates of olfactory and gustatory dysfunction, number of included studies and patients, and number of studies according to the evaluation method are presented for each region.

prevalence of olfactory dysfunction in East Asia was significantly lower than that in Europe or the Middle East ($P = 0.001$ and $P = 0.021$, respectively), and prevalence of gustatory dysfunction in East Asia was significantly lower than that in Europe or North America ($P = 0.001$ and $P = 0.048$, respectively). Considering the possibility that olfactory or gustatory dysfunction was not accurately recorded when the history taking was used as the evaluation method, an ANOVA was performed without the studies conducted with history taking as the evaluation method, and the results also showed a significant difference among the regions ($P = 0.005$ and $P < 0.001$, respectively; **Supplementary Fig. 2A and B**). The regional prevalence rates of olfactory and gustatory dysfunction are shown in **Fig. 3**.

Subgroup analyses according to the time of enrollment

The time of enrollment was clarified in 29 out of 55 studies. The time of enrollment in the included studies ranged from January 16, 2020 to May 2, 2020. The beginning date of the time of enrollment in the included studies ranged from January 16, 2020 to April 6, 2020, and the end date ranged from February 9, 2020 to May 2, 2020. After calculating the median date (mid-date) between the beginning and end date of the time of enrollment, the individual studies were categorized into three groups: 1st period (mid-date February 2, 2020 to March 17, 2020), 2nd period (mid-date March 20, 2020 to March 29, 2020), and 3rd period (mid-date March 30, 2020 to April 9, 2020). The numbers of included studies of olfactory and gustatory dysfunction in each period were n = 10 and n = 8 for the 1st period, n = 11 and n = 9 for the 2nd period, and n = 8 and n = 6 for the 3rd period, respectively. The prevalence rates of olfactory and gustatory dysfunction for the three periods were 39.5% and 40.9% for the 1st period, 57.7% and 51.2% for the 2nd period, and 49.0 and 40.5% for the 3rd period, respectively; however, no significant difference was found with regard to the time of enrollment ($P = 0.391$ and $P = 0.778$; **Fig. 4A and B**). As the region can be a potential confounding factor, we performed ANOVA for the studies conducted in Europe (n = 16). The ANOVA of the studies from Europe demonstrated that there were significant differences in the prevalence rates of olfactory dysfunction among the three periods ($P = 0.013$; **Fig. 4C**); however, there was no

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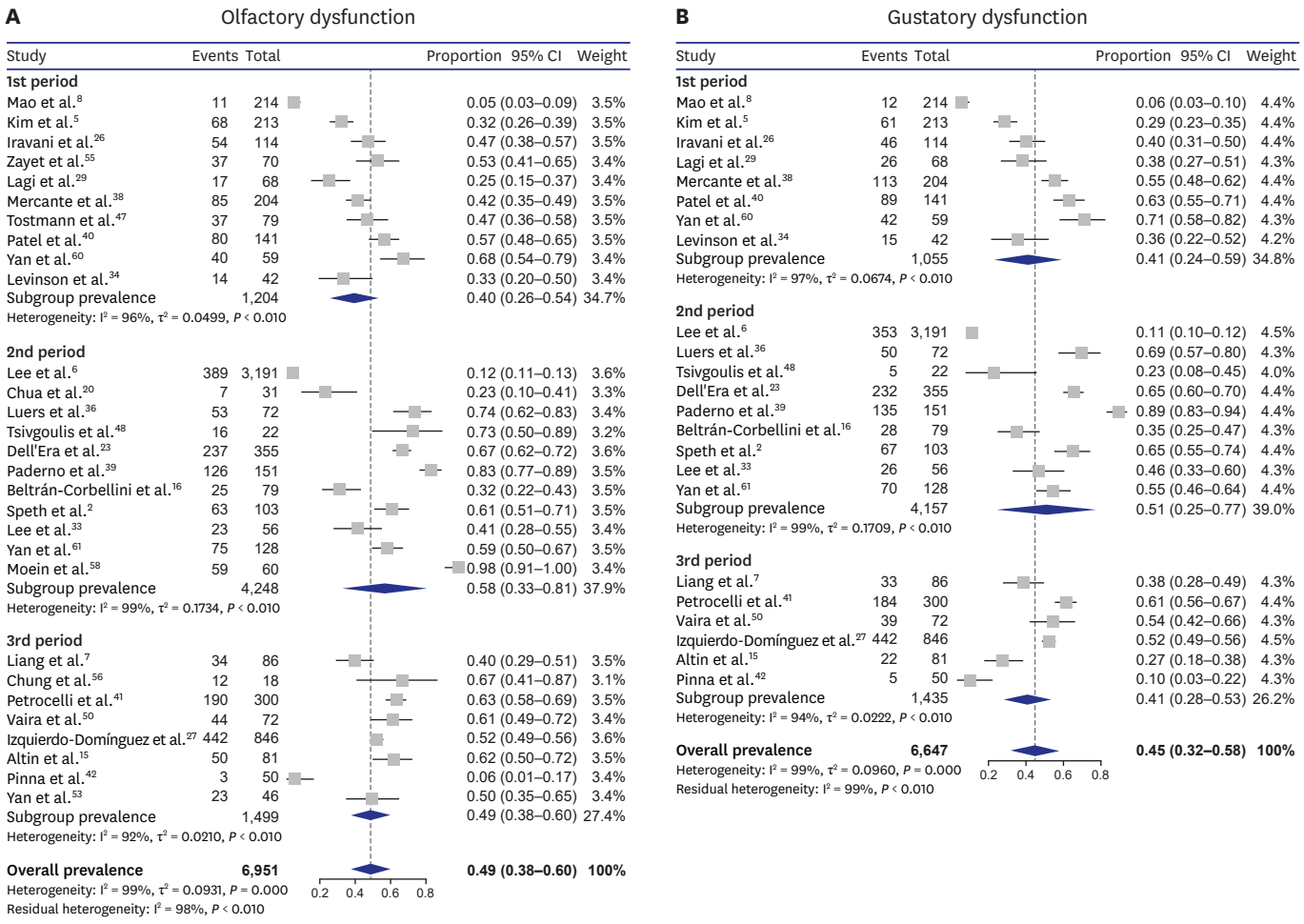

Fig. 4. Subgroup analysis on the time of enrollment. The time of enrollment was clarified in 29 out of 55 studies. After calculating the median date (mid-date) between beginning and end date of the time of enrollment, the individual studies were categorized into three groups: 1st period (mid-date February 2, 2020 to March 17, 2020), 2nd period (mid-date March 20, 2020 to March 29, 2020), and 3rd period (mid-date March 30, 2020 to April 9, 2020). (**A**) Forest plot meta-analysis of the prevalence of olfactory dysfunction of the three periods showed 39.5%, 57.7%, and 49.0% pooled subgroup prevalence rates in the random-effect model, respectively (P = 0.391 for subgroup difference). (**B**) Forest plot meta-analysis of the prevalence of gustatory dysfunction of the three periods showed 40.9%, 51.2%, and 40.5% pooled subgroup prevalence rates in the random-effect model, respectively (P = 0.778 for subgroup difference). (**C**) Forest plot meta-analysis of the prevalence of olfactory dysfunction only including studies conducted in Europe for the three periods showed 45.2%, 65.4%, and 59.0% pooled subgroup prevalence rates in the random-effect model, respectively (P = 0.013 for subgroup difference). (**D**) Forest plot meta-analysis of the prevalence of gustatory dysfunction of the three periods showed 49.8%, 60.2%, and 49.3% pooled subgroup prevalence rates in the random-effect model, respectively (P = 0.538 for subgroup difference). The diamonds represent pooled prevalence rates with 95% CI, and the estimates of individual studies are represented as squares, with 95% CIs represented as horizontal lines.
CI = confidence interval.

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significant difference in the prevalence of gustatory dysfunction (**Fig. 4D**). Post-hoc analysis revealed that the prevalence of olfactory dysfunction in the 2nd period was significantly higher than that in the 1st period (P = 0.046). Furthermore, the chronological difference among the studies from Europe was significant even when studies in which history taking was used as an evaluation method were omitted (P = 0.038, **Supplementary Fig. 3**). The chronological prevalence rates of olfactory and gustatory dysfunction are shown in **Fig. 5**.

Subgroup analyses according to evaluation method

The prevalence rates of olfactory and gustatory dysfunction according to the four different evaluation methods were 23.4% and 23.5% for history taking, 52.1% and 53.2% for self-reported surveys, 72.9 and 68.5% for validated surveys, and 69.2 and 48.4% for the validated

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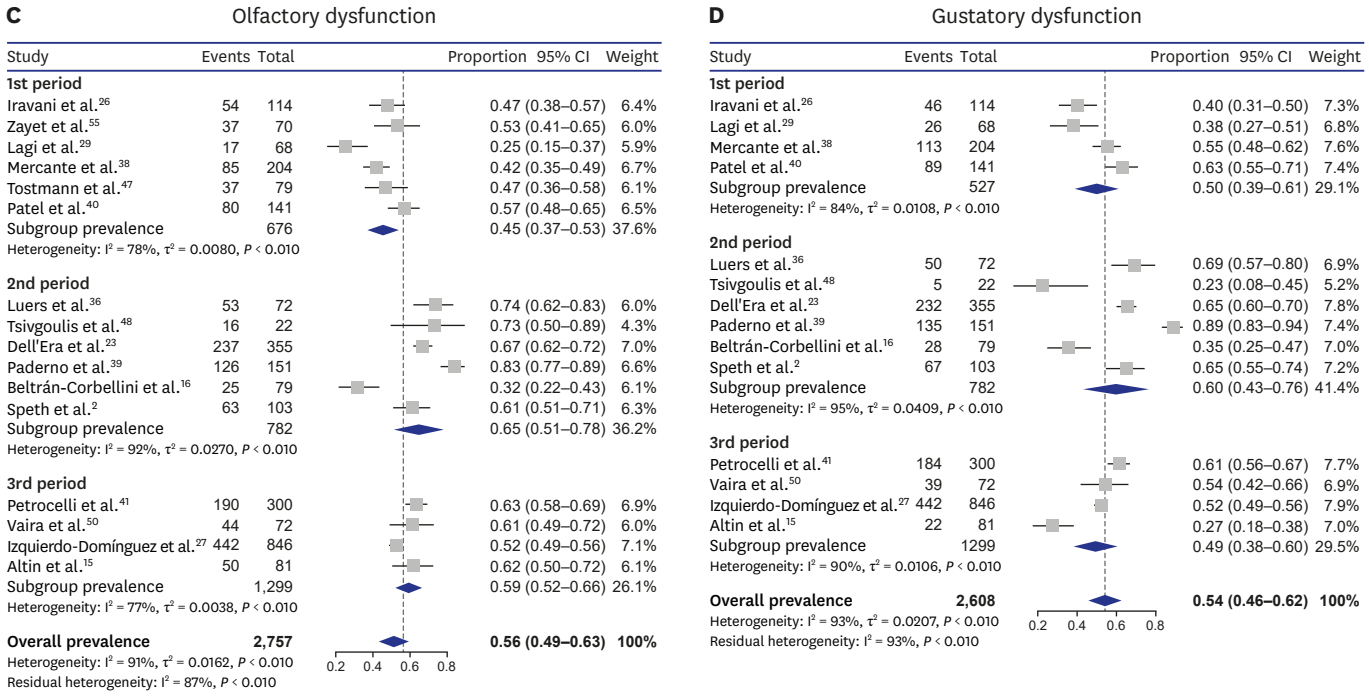

Fig. 4. (Continued) Subgroup analysis on the time of enrollment. The time of enrollment was clarified in 29 out of 55 studies. After calculating the median date (mid-date) between beginning and end date of the time of enrollment, the individual studies were categorized into three groups: 1st period (mid-date February 2, 2020 to March 17, 2020), 2nd period (mid-date March 20, 2020 to March 29, 2020), and 3rd period (mid-date March 30, 2020 to April 9, 2020). (**A**) Forest plot meta-analysis of the prevalence of olfactory dysfunction of the three periods showed 39.5%, 57.7%, and 49.0% pooled subgroup prevalence rates in the random-effect model, respectively (P = 0.391 for subgroup difference). (**B**) Forest plot meta-analysis of the prevalence of gustatory dysfunction of the three periods showed 40.9%, 51.2%, and 40.5% pooled subgroup prevalence rates in the random-effect model, respectively (P = 0.778 for subgroup difference). (**C**) Forest plot meta-analysis of the prevalence of olfactory dysfunction only including studies conducted in Europe for the three periods showed 45.2%, 65.4%, and 59.0% pooled subgroup prevalence rates in the random-effect model, respectively (P = 0.013 for subgroup difference). (**D**) Forest plot meta-analysis of the prevalence of gustatory dysfunction of the three periods showed 49.8%, 60.2%, and 49.3% pooled subgroup prevalence rates in the random-effect model, respectively (P = 0.538 for subgroup difference). The diamonds represent pooled prevalence rates with 95% CI, and the estimates of individual studies are represented as squares, with 95% CIs represented as horizontal lines.
CI = confidence interval.

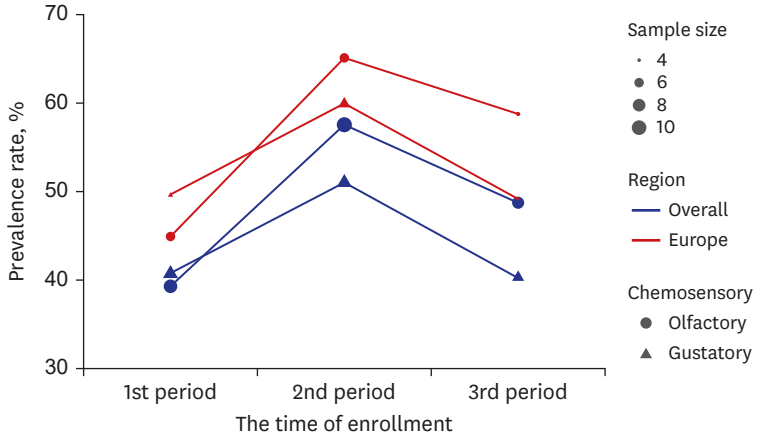

Fig. 5. The pooled prevalence of olfactory and gustatory dysfunction was presented chronologically. The overall and European pooled prevalence rates of olfactory and gustatory dysfunction are shown, discriminated by color. The prevalence rates of both olfactory and gustatory tended to increase from the 1st to 2nd period but decreased from the 2nd to 3rd period.

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instruments, respectively, and there was a significant difference among the regions (both $P < 0.001$, respectively; **Fig. 6A and B**). In a post-hoc analysis, the prevalence of olfactory dysfunction evaluated by history taking was lower than that evaluated by other methods (all $P < 0.001$, respectively), and the prevalence evaluated by the self-reported survey was lower than that evaluated by validated survey ($P = 0.033$). In addition, the prevalence of gustatory dysfunction by history taking was lower than that evaluated by the self-reported survey, validated survey, and validated instruments ($P < 0.001$, $P < 0.001$, and $P = 0.004$, respectively).

Subgroup analyses according to the characteristics of the population

The prevalence rates of olfactory and gustatory dysfunction according to the four population groups were 58.7% and 56.2% in the general population, 36.7% and 28.3% in hospitalized patients, 52.3% and 51.1% in non-hospitalized patients, and 48.9% and 51.5% in health care workers, respectively (**Fig. 7A and B**). Interestingly, a significant difference was found in the prevalence of gustatory dysfunction depending on the characteristics of the population ($P = 0.013$) but not in that of olfactory dysfunction ($P = 0.173$). Post-hoc analysis showed that the prevalence of gustatory dysfunction of the hospitalized patients was significantly lower than that of the general population ($P = 0.030$).

Assessment of publication bias

The funnel plot demonstrated potential publication bias in the analysis (**Supplementary Fig. 4A and B**). In Egger's test, there was a potential publication bias for the prevalence rates of olfactory and gustatory dysfunction ($P = 0.031$, $P = 0.028$). However, asymmetry in the funnel plots may be attributed to the various factors that elicited different prevalence rates, such as region, time of enrollment, and evaluation method, rather than publication bias.

DISCUSSION

Olfactory and gustatory dysfunction were not recognized as typical symptoms of COVID-19 in the early phase of virus' spread. However, as olfactory and gustatory dysfunction were frequently found in patients with COVID-19, these symptoms became significant. Furthermore, as a previous study reported, 17% of COVID-19 patients with anosmia were otherwise asymptomatic, meaning that isolated olfactory or gustatory dysfunction could be used as potential early indicators of SARS-CoV-2 infection during the COVID-19 pandemic.[62] Possible mechanisms of olfactory dysfunctions in COVID-19 patients are conductive anosmia, disruption of olfactory epithelium following local infection, and retrograde propagation to higher-order neurons in the olfactory pathway.[63] However, there is limited evidence to conclusively determine the mechanism of olfactory dysfunction in COVID-19.[63] Considering gustatory dysfunction in COVID-19, it is unclear whether gustatory dysfunction is a distinct clinical feature of SARS-CoV-2 or occurs secondary to olfactory dysfunction. Although olfactory and gustatory dysfunction were noted frequently in COVID-19, the prevalence rates of olfactory and gustatory dysfunction were variable among previous studies. In this meta-analysis, subgroup analysis was performed to explain the variability of the prevalence rate of olfactory and gustatory dysfunction among patients with COVID-19.

In this meta-analysis, the prevalence rates of olfactory and gustatory dysfunction in COVID-19 patients were 51.4% and 47.5%, with severe inter-study heterogeneity (both $I^2 = 98.6\%$, respectively), respectively. We performed subgroup analysis based on region, time of enrollment, demographics, and the evaluation method to explain the inter-study heterogeneity.

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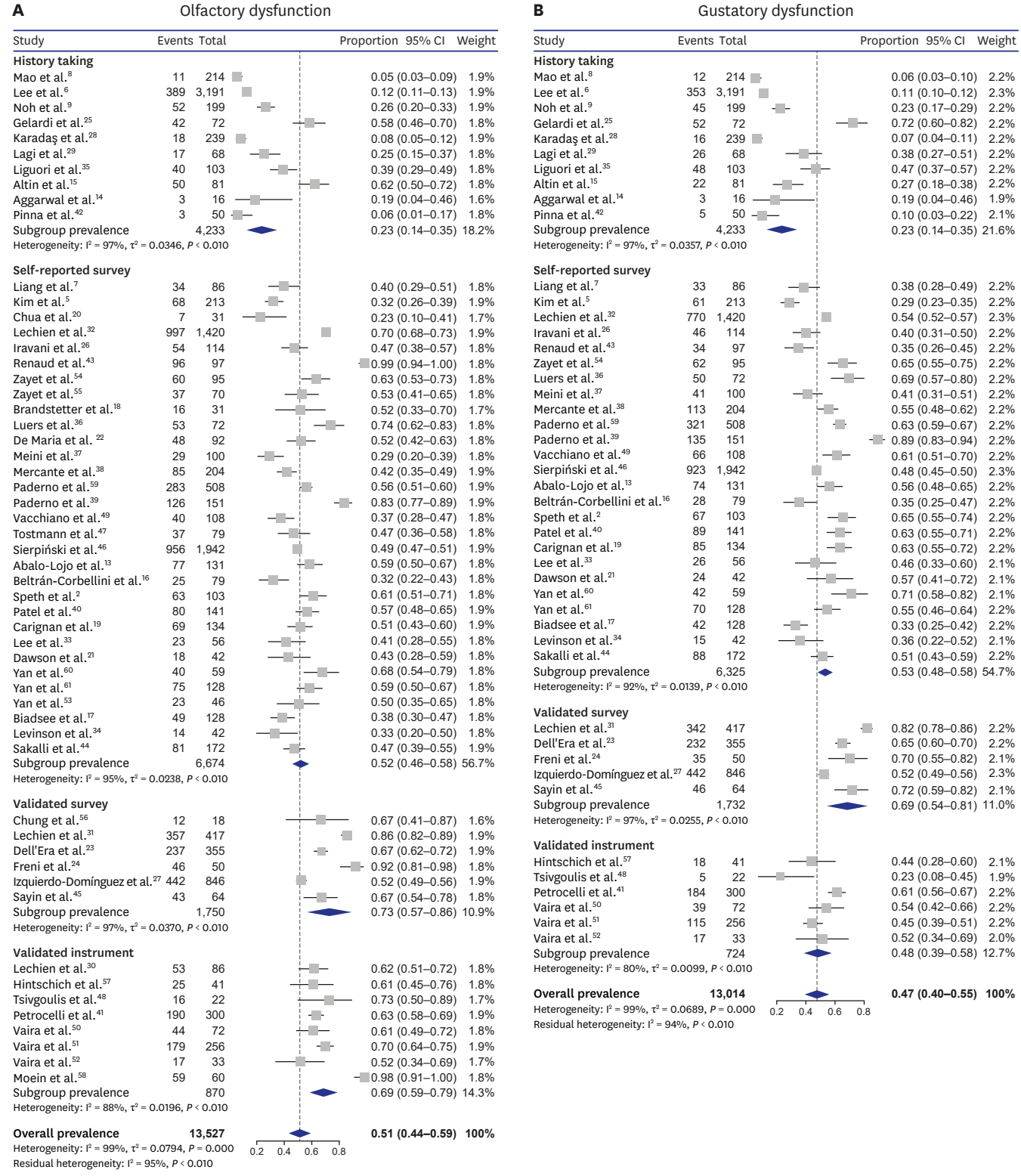

Fig. 6. Subgroup analysis on the evaluation method. The evaluation method was classified into history taking, self-reported survey, validated survey, and validated instrument. (**A**) Forest plot meta-analysis of the prevalence rates of olfactory dysfunction of the four evaluation methods showed 23.4%, 52.1%, 72.9%, and 69.2% pooled subgroup prevalence rates in random-effect model, respectively ($P < 0.001$ for subgroup difference). (**B**) Forest plot meta-analysis of the prevalence rates of gustatory dysfunction of the four evaluation methods showed 23.5%, 53.2%, 68.5%, and 48.4% pooled subgroup prevalence rates in random-effect model, respectively ($P < 0.001$ for subgroup difference). The diamonds represent pooled prevalence rates with 95% CI, and the estimates of individual studies are represented as squares, with 95% CIs represented as horizontal lines.
CI = confidence interval.

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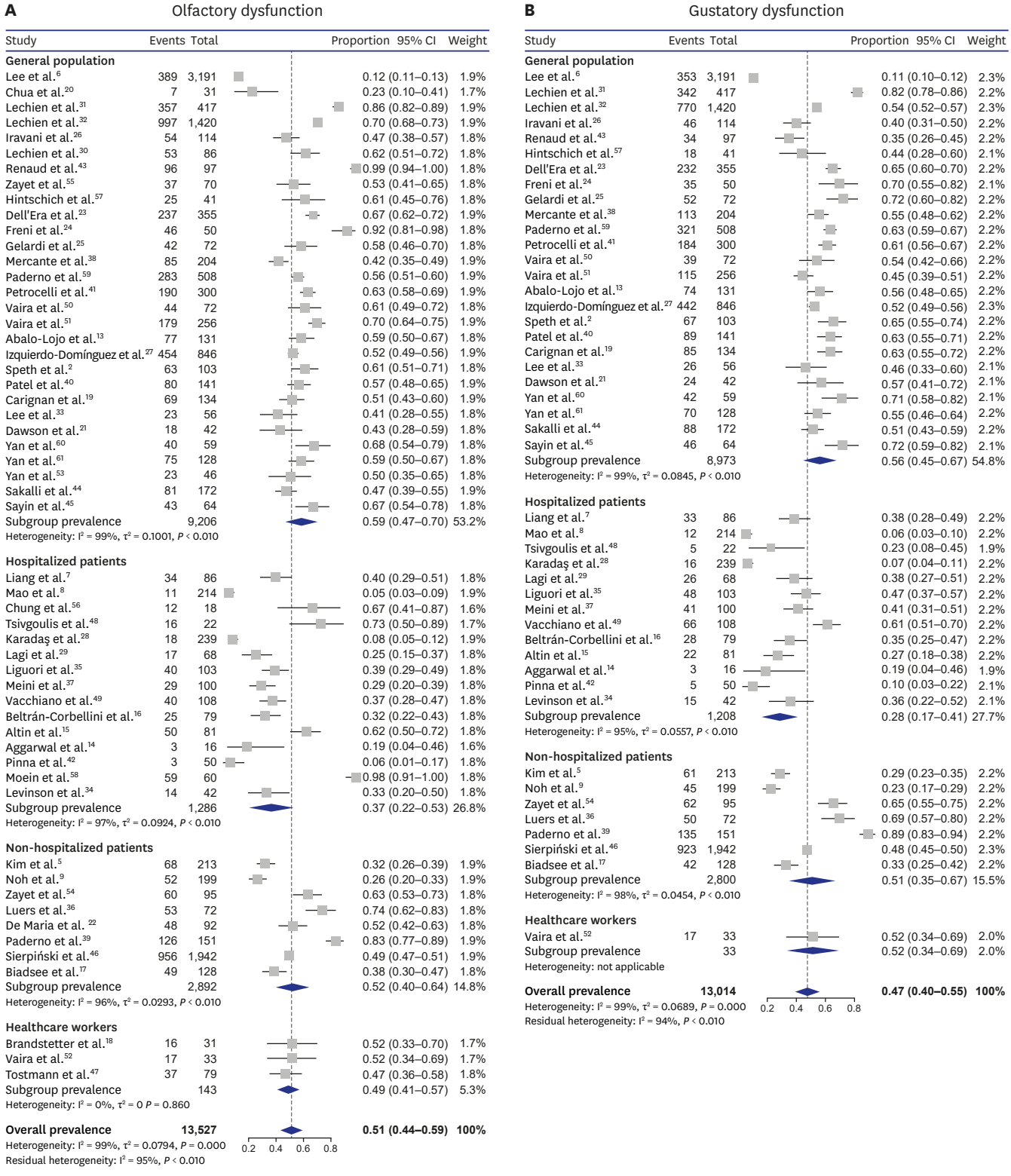

Fig. 7. Subgroup analysis on the characteristics of population. The characteristics of population was classified into general population, hospitalized population, non-hospitalized population, and population of healthcare workers. (**A**) Forest plot meta-analysis of the prevalence of olfactory dysfunction of the four demographics showed 58.7%, 36.7%, 52.3%, and 48.9% pooled subgroup prevalence rates in the random-effect model, respectively (P < 0.001 for subgroup difference). (**B**) Forest plot meta-analysis of the prevalences of gustatory dysfunction of the four demographics showed 56.2%, 28.3%, 51.1%, and 51.5% pooled subgroup prevalence rates in random-effect model, respectively (P < 0.001 for subgroup difference). The diamonds represent pooled prevalence rates with 95% CI, and the estimates of individual studies are represented as squares, with 95% CIs represented as horizontal lines.
CI = confidence interval.

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As we hypothesized, the prevalence rates of olfactory and gustatory dysfunction were different among the four geographical regions. The prevalence of olfactory dysfunction in East Asia was significantly lower than that in Europe or the Middle East and prevalence of gustatory dysfunction in East Asia was significantly lower than that in Europe and North America. In the subgroup analysis on the time of enrollment, there was no significant difference among the three periods. However, considering the spread of the virus occurred regionally and chronologically, the regional factor might be a potential confounding factor. In an ANOVA of the studies from Europe alone, there were significant differences in the prevalence rates of olfactory dysfunction among the three time period groups, indicating that a genetic mutation of virus in the same region may have affected the prevalence of olfactory dysfunction. The prevalence rates of olfactory dysfunction of the all regions were 39.5% for the 1st period, 57.7% for the 2nd period, and 49.0% for the 3rd period, which was a similar tendency compared to that of Europe: 45.2% for the 1st period, 65.4% for the 2nd period, and 59.0% for the 3rd period. Interestingly, olfactory dysfunction increased from the 1st to 2nd period but slightly decreased from the 2nd to 3rd period.

Because the included studies were performed with various evaluation methods and populations, we carried out further subgroup analyses on the evaluation methods and population group to explain the heterogeneity. In subgroup analysis on the evaluation methods, the prevalence rates of olfactory and gustatory dysfunction evaluated by history taking were lower than those by other evaluation methods. In contrast to survey or objective test, simple history taking may have a risk of omitting questions about olfactory and gustatory dysfunction. The chemosensory function of these patients was often regarded as normal, leading to a low prevalence of olfactory and gustatory dysfunction. Therefore, we confirmed the results of the subgroup analysis on the geographical region and the time of enrollment by omitting studies in which history taking was used as the evaluation method, and we found that it still showed a statistical significance. In subgroup analysis on the population group, interestingly, a significant difference was found in the prevalence of gustatory dysfunction depending on population characteristics but not in that of olfactory dysfunction. In a post-hoc analysis, the prevalence of gustatory dysfunction of the hospitalized patients was lower than that of the general population, which may be attributed to the higher rate of the history taking as the evaluation method in hospitalized patients than that in the general population (46.7% vs. 6.9%, respectively).

There are some possible explanations for the regional and chronological differences in olfactory and gustatory dysfunction in COVID-19—first, the ethnic differences in the frequency variants of angiotensin-converting enzyme 2 (ACE2). As previous studies indicate, ACE2 is a possible host receptor of SARS-CoV-2.[64,65] Variants of ACE2 may affect the course of infection, including susceptibility and symptoms depending on the expression level and pattern of ACE2 in different tissues.[66] In a previous study, presence of a difference in variants of ACE2 according to geographical and ethnic factors was demonstrated,[66] and it is assumed that the difference in variants of ACE2 expressed in olfactory epithelial cells according to populations from different geographical regions can influence the prevalence of olfactory and gustatory dysfunction. Second, phylogenetic mutation may contribute to regional and chronological differences. As the prevalence of olfactory dysfunction was significantly different according to time of enrollment in subgroup analysis with the studies from European countries, the ethnic differences may not be sufficient to explain the chronological differences in the prevalence rates of olfactory dysfunction. Recent studies reported that SARS-CoV-2 has rapidly attained mutations as a typical coronavirus, allowing

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for tracking its spread.[67,68] The prevalence of S type and L type of SARS-CoV-2 were 3.7% and 96.3% in viral isolates in Wuhan, respectively, yet viral isolates outside of Wuhan were 38.4% S type and 61.3% L type.[68] Furthermore, the mutation may cause regional differences in virus type. For instance, a previous study revealed that the B1 clade is dominant in the West Coast of the United States, while the A2a clade, which seems to have spread through Europe and Italy, is dominant in the East Coast of the United States.[69] In addition to the regional differences, the expanding phylogenetic diversity can induce a chronologic difference in the type of SARS-CoV-2. A previous study revealed the global transition of the SARS-CoV-2 spike protein from the original D614 to the G614 variant.[70] To be specific, through March 1, 2020, the G614 variant was rare outside Europe; however, it increased in frequency worldwide by the end of March.[70] As the virus types and genetic mutations were different regionally and chronologically,[68-70] the influence of SARS-CoV-2 on the olfactory epithelium may have differed according to virus type and genetic mutation. Lastly, heterogeneity in the study designs may have caused different prevalence rates of olfactory and gustatory dysfunction. The study populations and evaluation methods were variable in the individual studies. As shown in the results, evaluation method may lead to different prevalence. To reduce the confounding effect of the evaluation method, we performed a subgroup analysis without the studies in which history taking was used as an evaluation method. However, the other three methods may also have had differences, although statistical significance was not found. In addition, different characteristics of populations might affect the prevalence rate in individual studies.

In conclusion, olfactory and gustatory dysfunction are commonly reported in patients with COVID-19 and noted as significant symptoms; however, the prevalence rates are variable. This meta-analysis revealed that regional and chronological differences in the prevalence rates of olfactory and gustatory dysfunction explain the inter-study heterogeneity.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Quality assessment for the included studies

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Supplementary Fig. 1

Prevalence of chemosensory dysfunction in patients with COVID-19. (**A**) Forest plot meta-analysis of the prevalence rates of olfactory dysfunction in patients with COVID-19 showed a 52.7% (95% CI, 43.7–59.1) pooled prevalence in random-effect model, as represented by the diamond. (**B**) Forest plot meta-analysis of the prevalence rates of gustatory dysfunction in patients with COVID-19 showed a 47.5% (95% CI, 39.7–55.3) pooled prevalence in random-effect model, as represented by the diamond. The estimates of individual studies are represented as squares, with 95% CIs represented as horizontal lines.

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Supplementary Fig. 2

Subgroup analysis on region, excluding studies in which history taking was used as the evaluation method. (**A**) Forest plot meta-analysis of the prevalence rates of olfactory dysfunction of four regions (East Asia, Europe, North America, and Middle East) showed

37.3%, 61.0%, 52.7%, and 59.8% pooled subgroup prevalence in random-effect model, respectively (P = 0.005 for subgroup difference). (**B**) Forest plot meta-analysis of the prevalence rates of gustatory dysfunction of four regions (East Asia, Europe, North America, and Middle East) showed 32.6%, 56.7%, 58.9%, and 47.9% pooled subgroup prevalence in the random-effect model, respectively (P < 0.001 for subgroup difference). The diamonds represent pooled prevalence with 95% CI, and the estimates of individual studies are represented as squares, with 95% CIs represented as horizontal lines.

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Supplementary Fig. 3

Subgroup analysis on the time of enrollment, only including studies in which evaluation method using surveys or validated instruments among the studies conducted in Europe. The time of enrollment was clarified in 29 out of 55 studies. After calculating the median date (mid-date) between beginning and end date of the time of enrollment, the individual studies were categorized into three groups: 1st period (mid-date February 2, 2020 to March 17, 2020), 2nd period (mid-date March 20, 2020 to March 29, 2020), and 3rd period (mid-date March 30, 2020 to April 9, 2020). Forest plot meta-analysis of the prevalence rates of olfactory showed 48.7%, 65.4%, and 58.4% pooled subgroup prevalence in the random-effect model, respectively (P = 0.038 for subgroup difference).

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Supplementary Fig. 4

Funnel plot of the prevalence rates of (**A**) olfactory and (**B**) gustatory dysfunction.

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