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Prevalence of Olfactory Dysfunction with the Omicron Variant of SARS-CoV-2: A Systematic Review and Meta-analysis

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Abstract

The omicron variant is thought to cause less olfactory dysfunction than previous variants of SARS-CoV-2, but the reported prevalence differs greatly between populations and studies. Our systematic review and meta-analysis provide information about regional differences in prevalence as well as an estimate of the global prevalence of olfactory dysfunction based on 41 studies reporting on nearly 600,000 patients infected with the omicron variant. Our estimate of the omicron-induced prevalence of olfactory dysfunction in populations of European ancestry is 11.6%, while it is significantly lower in all other populations, at 2.9-5.4%. When ethnic differences and population sizes are taken into account, the global prevalence of omicron-induced hyposmia in adults is estimated at 5.2%. Omicron's effect on olfaction is 3-4fold lower than that of the alpha or delta variant, according to previous meta-analyses and our analysis of studies that directly compared prevalence of olfactory dysfunction between omicron and previous variants. The profile of prevalence differences between ethnicities mirrors the results of a recent genome-wide association study that implicated a gene locus encoding an odorant-metabolizing enzyme, UDP glycosyltransferase, to be linked to the extent of COVID-related loss of smell. Our analysis is consistent with the hypothesis that this enzyme contributes to the observed population differences.

KEY WORDS: omicron; SARS-CoV-2; COVID-19; anosmia; loss of smell; prevalence; ethnicity; host factor; UGT2A1; UDP glycosyltransferase

1. Introduction

The omicron variant has been reported to cause less anosmia than the preceding SARS-CoV-2 virus variants [1-3]. The prevalence of olfactory dysfunction varies greatly between studies, and the global prevalence of anosmia caused by omicron has not yet been estimated. The number of confirmed COVID-19 cases reported to the World Health Organization (WHO) by November 30, 2022 was 639 million (WHO Coronavirus (COVID-19) Dashboard, https://covid19.who.int/), but the true number of cases is believed to be much higher, at about 3.4 billion in October 2021 [4]. A total of 6 billion cases – after the global spread of the more infectious omicron variant – has been estimated in October 2022 [5]. Since the prevalence of olfactory dysfunction differs between virus variants [1-3,6,7], it is important for estimates of the current global and regional prevalence of olfactory dysfunction to take properties of different virus variants into account. It has been argued that, even though omicron may cause a lower prevalence of olfactory dysfunction, the increased infectivity may produce equivalency or even a net gain in the cases of hyposmia or anosmia, because a much larger number of people will become infected with the omicron variant [8,9].

It is possible that host factors also contribute to the population differences in COVID's olfactory dysfunction [6,10-12]. Such host factors, besides age and gender, are apparently not due to differences in expression levels or in genetic variation of the virus entry proteins, ACE2 and TMPRSS2, as was initially assumed [10,11,13], but rather may be due to genetic variation and the frequency of risk alleles of an odorant-metabolizing enzyme, a glycosyltransferase that is encoded by the UGT2A1/A2 locus [12]. This enzyme is abundantly expressed in sustentacular

support cells of the olfactory epithelium of vertebrates [14,15], including humans [16-19].

Here, we conducted a systematic review and meta-analysis of the literature on olfactory dysfunction caused by the omicron variant. In this review, we focused on loss of smell rather than loss of taste. Loss of taste is thought to be, in part, due to loss of smell [20], and therefore we grouped the diverse reports on “loss of smell”, “loss of smell and taste”, and “loss of smell or taste” in one single category. Furthermore, because the large majority of reports use patients’ subjective recall to identify new olfactory dysfunction, we restricted our analysis to studies that used subjective methodology (the patient’s recollection of changes in smell), rather than objective psychophysical testing, which depends on cultural context and therefore requires population-specific validation [21]. Objective psychophysical testing also benefits from a pre-pandemic or pre-infection base level for each individual for proper interpretation of the results, because of the large fraction of people with pre-existing olfactory dysfunction in the normal population when measured by this method (28.8% [22]). Since people with an acute COVID infection typically quarantine during the acute phase, it is impractical to be objectively tested by ear, nose and throat specialists, and since chemosensory loss often lasts only about a week [23,24], smell and taste may have recovered before they can be tested quantitatively by experts [20].

We generated estimates of the global prevalence of omicron-induced olfactory dysfunction, as well as regional prevalence, which apparently is determined at least in part by genetics (prevailing ethnicity) within populations. Similarities between the results of our analysis and those of a recent genome-wide association study [12] point to differences in the frequency of the risk allele for an odorant-

metabolizing enzyme as a contributing factor, resulting in population differences in the prevalence of olfactory dysfunction.

2. Methods

2.1 Search Strategy

For our systematic review of the literature, we adhered to the guidelines set forth by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [25]. Reports of studies that estimate the prevalence of olfactory dysfunction were identified through a search of two databases, PubMed, as well as the iCite NIH COVID portal (https://icite.od.nih.gov/covid19/search/). The COVID portal was included in order to capture preprints in addition to peer-reviewed articles. The following search strategy was formulated using the keywords “omicron” and “smell”, as well as “omicron” and “anosmia.” Reference lists from the eligible articles were examined to identify additional relevant studies. Duplicates were removed, but the first date of publication, in case of preprints, was recorded, even when the peer-reviewed version of the paper, when available, was compiled in our list of references. All titles were screened, and when potentially relevant, the abstract was evaluated to decide whether the paper should be short-listed for full-text reading. The full text of all short-listed records was reviewed to determine whether they were eligible according to our inclusion and exclusion criteria, and then were used to produce the final selection of studies for inclusion in subsequent analyses (Fig. 1).

2.2 Inclusion/Exclusion Criteria

Studies which were deemed eligible for the systematic review met all of the following inclusion criteria: (1) studies reporting on infections of humans with the omicron variant (B.1.1.529) and any of the omicron subvariants, BA.1, BA.2, BA.1.1, BA.2.2, BA.5; (2) studies on adults or adolescents (when a small number of children was included, this was considered acceptable), but studies that focused entirely on children (e.g. [26]) were not included, because it is known that children with COVID have a significantly lower prevalence of olfactory dysfunction than adults with COVID [27]; (3) evidence of infection with SARS-CoV-2; genomic proof of variant type was not deemed necessary when it was known that the vast majority of infections during the period and in the region of data collection were omicron cases rather than cases caused by another virus variant; (4) olfactory dysfunction was monitored through subjective recall, and all members of the cohort were specifically asked about changes in smell, changes in smell or taste, or changes in smell and taste; review of medical records for entries about loss of smell, but without universal and specific questioning of patients, was not acceptable (e.g. [28]); (5) the olfactory dysfunction occurred during the acute phase of infection – long-term studies inquiring about changes of smell persisting for weeks or months after the infection were not included. Papers written in languages other than English were not excluded, but would not have been encountered unless they had an English title. Comparison with variants other than omicron was not a required inclusion criterion.

2.3 Quality Assessment and Publication Bias

Risk of bias in cohort studies was assessed using a modified Newcastle-Ottawa scale (adapted Cochrane's risk of bias tool [29]). This scale attempts to assess accuracy of measurements, as well as whether the cohort is representative of the community. Duration of follow-up is not relevant for the current review and analysis. It does assess study design and cohort size, as well as information about convenience samples and response rates, when applicable. In addition, we explored the magnitude of the potential bias caused by survey-type studies that rely on the initiative and motivation of respondents [8,30-32] by comparing the results of traditional-design studies with those of survey-type studies. In addition, we generated funnel plots to assess potential publication bias [33].

2.4 Data Extraction

The relevant data of each study were extracted by using pre-designed tables, including the first date of publication, first author name, country, geographic region, the cohort size, the number of cases, and the percentage calculated from the number of cases per cohort. When applicable, the comparator virus variant was also noted, along with its cohort size, number of cases with olfactory dysfunction, and the percentage, as well as the name(s) of the previous variant or variants causing the infection. When the comparator virus variant was not disclosed, it was retrieved as G614 vs D614 [34]. Additional information about cohorts such as age, gender, and ethnic composition was recorded when studies provided this information.

2.5 Subgroup Analyses and Comparisons

The global prevalence of olfactory dysfunction due to omicron infection was calculated by taking ethnic differences and population sizes into account, and this

prevalence was compared with the global and regional prevalence due to previous variants, using information from studies that reported such data (24 out of 41 studies). Because of ethnic differences between populations, the prevalence for each major ethnicity (European ancestry, African, East Asian, South Asian, Latino) was estimated separately and weighted by population size to calculate an estimate of the current global hyposmia prevalence due to omicron. This was necessary to prevent bias due to the fact that the majority of available studies and those with the largest cohorts have focused on people with European ancestry.

2.6 Data Synthesis

The primary purpose of the meta-analysis was to produce a more precise and reliable estimate of the effect of the omicron variant on olfactory dysfunction, and to compare this estimate with previous estimates that were made pre-omicron (results from previous meta-analyses) as well as preparing a direct comparison by compiling the data from those studies which provided internal comparative data on other virus variants.

2.7 Statistical Analyses

Pooled analyses were performed for olfactory dysfunction prevalence and risk ratio (RR). The heterogeneity among studies was evaluated by Cochran's Q test and the I^2 index [35,36]. The random-effect models were used to conservatively diminish the heterogeneity between the studies [36]. A continuity correction of 0.5 was applied to studies with zero cells [37]. Subgroup pooled analyses were conducted by ethnicity and study type. Meta-regression analyses were performed to test the association between prevalence and key variables [37], including the UGT2A1 risk allele

frequency [12] and the study type [38]. The risk of publication bias was evaluated using funnel plots and Egger's test [39]. The significance level was set to 0.05. All the meta-analyses were performed using the Stata SE 16.0 software (StataCorp, TX, USA).

3. Results

3.1 Properties of Studies

We found 41 studies, published between November 27, 2021 and November 27, 2022, that met our inclusion criteria. Collectively, these studies reported the olfactory status of 590,415 patients infected with the omicron virus (Table 1). These studies were conducted in 20 countries on six continents (Fig. 2). Twenty-two studies were from populations primarily of European ancestry [8,32,40-59], eight studies on East Asians [60-67], three studies on South Asians [68-70], three studies on Latinos [71-73], four studies on populations in Africa [74-77], and one study from West Asia (Turkey [78]). The location of studies, with the prevalence indicated by the color intensity, and the cohort size indicated by the size of the circles, shows that Western countries report the highest prevalence, while studies from East Asia and Africa report the lowest prevalence (Fig. 2). We found that five studies were of low quality, 25 of moderate quality, and eleven of high quality according to the modified Newcastle-Ottawa scale [29]. Twenty-four of the 41 studies also reported the olfactory status caused by one or more of the previous SARS-CoV-2 virus variants, mostly of the delta variant (Table 2).

3.2 Global Prevalence of Olfactory Dysfunction

When we combine all eligible studies in the Forest Plot (Fig. 3), we derive an estimate of the global prevalence of olfactory dysfunction due to the omicron variant as being 7.8% of adults infected with this variant. However, this estimate obscures that ethnicity is a major factor. Our meta-analysis of the studies reporting on populations of European ancestry, which are the majority of studies and the ones with the largest cohort sizes, shows that the pooled prevalence of olfactory dysfunction is 11.6% (Fig. 4). On the other hand, populations of non-European ancestry have a much lower prevalence, ranging from 2.9% to 5.4%, as detailed below (Fig. 4). When ethnic differences between populations and the current population sizes are weighted appropriately (Fig. 4), the global prevalence of olfactory dysfunction due to the omicron variant reduces to 5.2% of omicron-infected adults, as detailed below.

When we compared the prevalence of olfactory dysfunction due to omicron with that of previous variants (mostly delta), we find a 2-fold to 5-fold lower prevalence with omicron, based on the 24 studies that provided a direct comparison (Table 2; Fig. 5A). The overall reduction for omicron vs. previous variants is 0.323 (confidence intervals (CI): 0.300, 0.348). This difference is statistically significant with a p-value of <0.001. When compared with previous meta-analyses reporting on multiple SARS-CoV-2 variants up to August 15, 2020 (prevalence: 43.0%, 104 studies with 38,198 patients [23]) and up to November 10, 2020 (prevalence: 38.2%, 107 studies with 32,142 patients [79]), the prevalence of olfactory dysfunction due to omicron likewise is 3.5 to 4-fold lower. The funnel plot (Fig. 6) indicates the lack of publication bias among the included studies.

3.3 Geographic/Ethnic Differences

The studies compiled in Figs. 2 and 4 suggest that geography or ethnicity is a relevant variable. While the number of studies and their cohorts are small for some of the geographic regions/ethnicities, there are a robust number of studies and cohort sizes for Western countries (with mostly people of European ancestry, n=22 studies, with 582,642 people in all cohorts), for East Asians (n=8 studies, with 1,906 people in all cohorts), and Latinos (n=3 studies, with 4,199 people in all cohorts). The data are sparse for South Asians (n=3 studies, with 413 people in all cohorts), and populations on the African continent (n=4 studies, with 844 people in all cohorts). A comparison of the subgroups indicates that omicron causes a hyposmia prevalence of 2.9% in East Asia (CI = 1.4%-4.3%), 3.4% in populations in Africa (CI =0.4%-6.3%), 3.8% in South Asia (CI = 1.9%-9.6%),5.4% in Hispanics (CI = 4.7%-6.1%), and 11.6% in people of European ancestry (Western countries, CI = 10.2%-13.1%) (Fig. 4; Fig. 5A). Since these data are derived from people infected with the same virus variant, the population difference must be primarily due to host factors rather than virus factors, as detailed in the Discussion.

3.4 Global Prevalence considering Ethnic Differences and Population Sizes

Taking into account the omicron-caused prevalence of hyposmia for the different major ethnicities, and the total population size of these major ethnicities (obtained from the WHO website: https://www.worldometers.info/geography/7-continents/), and using the estimated numbers of COVID cases from the Institute for Health Metrics and Evaluation [5], we can estimate the number of adults in different ethnic populations that can be expected to experience olfactory dysfunction due to omicron

infection (Table 3). Since children make up approximately 25% of the world population, we subtracted 25% from each of the population sizes to account for children – which are not included in our review, because there are too few studies reporting on omicron-infected children, and children with COVID are known to have much less olfactory dysfunction than adults [27]. Assuming a COVID infection of 95% of most populations [5], we calculated for European ancestry a total number of 106.7 million adults with hyposmia out of 0.97 billion (11.6% prevalence), 18.9 million adults with hyposmia out of 370 million Hispanics (5.4% prevalence), 48.6 million with hyposmia out of 1.35 billion South Asians (3.8% prevalence), 31.3 million with hyposmia out of 920 million Africans (3.4% prevalence), and 38.6 million with hyposmia out of 2.1 billion East Asians (2.9% prevalence), for a total of 222.3 million people, as summarized in Table 3. The estimates for East Asians are based on the current "Zero-COVID" policy in China, affecting 1.4 billion people, of whom only 10 million have become infected so far (WHO Coronavirus Disease (COVID-19) Dashboard, https://covid19.who.int/region/wpro/country/cn), and therefore, 1.4 billion East Asians were excluded from the projection. The estimated numbers for East Asia will be substantially higher with the abandonment of the "Zero-COVID" policy in China.

3.5 Ethnic Profiles: Omicron's Hyposmia vs. UGT2A1 Risk Allele Frequency

Initially, it was thought that differences in expression levels or in genetic variation of the virus entry proteins, ACE2 and TMPRSS2, may be host factors that contribute to population differences in COVID's olfactory dysfunction [10,11]. However, this hypothesis turned out to be incorrect [13], and it is now thought that the host factor most likely is an odorant-metabolizing enzyme, a glycosyltransferase that is encoded

by the UGT2A1/A2 locus, based on a recent genome-wide association study showing significant ethnic differences in the frequency of the risk allele at this locus [12].

The ethnicity profile (East Asians, Africans, South Asians, Hispanics, and people with European ancestry) for both, the risk allele frequency as well as the hyposmia prevalence, is shown in Fig. 7. Our comparison of the major ethnicities for omicron's hyposmia prevalence reveals a remarkably similar ethnic profile when compared with the pattern described [12] for the frequency of the risk allele in the UGT2A1 locus (Fig. 7). We used meta regression to test whether the risk allele in the UGT2A1 locus predicted omicron's hyposmia prevalence and we found that there is an association between a population's risk allele frequency and omicron's hyposmia prevalence. The coefficient is positive, which means that the hyposmia prevalence is higher when the risk allele frequency is higher, consistent with the genome-wide association analysis [12]. This supports the idea that the odorant-metabolizing enzyme, the UDP glycosyltransferase, is involved as a host factor in the suceptibility to SARS-CoV-2 induced olfactory dysfunction.

3.6 Comparison of survey-type studies and traditional-design studies

It has been cautioned that survey-type studies (that invite people to respond to questionnaires, often posted on the internet) may have a bias, because people with more severe conditions tend to be more motivated to respond [8,30-32,38]. Therefore, we estimated the magnitude of such a potential bias by comparing survey-type studies with traditional-design studies, for the same ethnicity (people with European ancestry). We did that for both omicron-caused hyposmia as well as hyposmia caused by previous SARS-CoV-2 variants, separately (Fig. 8A,B). We find that, with omicron, the survey-based studies result in a pooled estimate of the

hyposmia prevalence of 14.2% (CI: 9.7%-18.7%), which is higher than the 10.7% (CI: 9.0%-12.4%) with traditional studies (Fig. 8A). However, a meta regression analysis shows that there is no statistically significant difference between these two prevalences (p=0.466). With the previous variants, mostly delta, the survey-based studies result in a pooled estimate of the hyposmia prevalence of 45.4% (CI: 22.1%-68.8%), which is higher than the 32.7% (CI: 27.0%-38.4%) with traditional studies (Fig. 8B). A meta regression analysis again shows that there is no statistically significant difference between these two prevalences (p=0.358).

4. Discussion

4.1 Global Prevalence of Olfactory Dysfunction with Omicron

We estimate the global prevalence of omicron-induced olfactory dysfunction in adults to be 5.2%. This estimate takes into account ethnic differences and population sizes and is based on the notion that, with the exception of China, 95% of the population has been or will be exposed to SARS-CoV-2 [5]. Our estimate of 5.2% prevalence translates into 222.3 million adults who can be predicted to experience omicron-induced olfactory dysfunction (Table 3). Our review and meta-analysis confirm that the olfactory dysfunction after omicron infection is about 3-4fold lower than with previous variants, with a similar and consistent reduction in all ethnicities (Fig. 5B).

Our analysis reveals substantial ethnic differences in the prevalence of omicron-induced olfactory dysfunction: The estimation of omicron's current olfactory dysfunction in Western countries with 11.6% prevalence is well supported, and the

estimates for Hispanics and East Asians, with 4,199 and 1,906 people in the cohorts, respectively, are also fairly well attested, but there is less certainty about the prevalence in South Asians (3.8%), and African populations (3.4%).

4.2 Why is Omicron's Effect on Olfaction Different than that of Previous Variants?

Two main reasons have been proposed to explain this phenomenon, and they are not mutually exclusive. The mutations in the spike protein make the omicron variant more hydrophobic [80] which may reduce the solubility of the virus in the mucus, diminishing its ability to reach the olfactory epithelium [2,81]. Second, due to reduced furin cleavage, the omicron variant prefers an endosomal route via cathepsin for entering host cells rather than a surface membrane fusion via the protease TMPRSS2 [82]. Sustentacular cells and Bowman gland cells are the cells in the olfactory epithelium which most abundantly express not only ACE2, but also TMPRSS2 [83,84] and for this reason these support cells were the prime target of previous SARS-CoV-2 variants for host cell entry via the route using cell surface membrane fusion enabled by TMPRSS2 [85]. Since the support cells – similar to many other host cells – have evolved more potent defense mechanisms for the endosomal route of infection [81,86], for example, the antiviral IFITM2 gene is the most highly upregulated gene in support cells at 3 days after infection [87], this may lead to a lower efficiency in omicron infection of the support cells of the olfactory epithelium, and therefore reduced olfactory dysfunction [88].

4.3 Ethnic Differences in UGT2A1 Risk Allele Frequency: Implications

The similarity in the ethnic profiles between omicron's prevalence of hyposmia and the frequency of the UGT2A1 risk allele (Fig. 7) suggests that the UGT2A1-encoded

glycosyltransferase is the host factor, or one of the major host factors, that determines the risk of olfactory dysfunction due to SARS-CoV-2 infection. How does the UDP glycosyltransferase affect the sense of smell? This is an evolutionary highly conserved enzyme in olfaction, not only from rodents to human [15,17], but also in invertebrates [14]. It is thought to modulate the concentration of odorant molecules and terminate odorant signal transduction [16,89]. It contributes to the biotransformation of odorant molecules, prevents saturation of the odorant receptors, modifies the perceived quality of odorants [15,89], and thereby plays a major role in olfactory sensitivity. Polymorphisms in the enzyme may account for inter-individual variability in olfactory perception [15]. Furthermore, UDP glycosyltransferases are expressed differentially with aging [89] which could explain the increased olfactory dysfunction seen in young adults (but less in children or older people [23,27]), and expression of UDP glycosyltransferase also differs between genders [90], which may explain the higher female susceptibility to olfactory dysfunction [23].

What does the genetic/ethnic difference in the risk allele frequency in the host (with the most extreme values in East Asians vs European ancestry) tell us about olfactory dysfunction? The risk allele at the UGT2A1 locus causes more olfactory dysfunction [12], which may explain why Europeans are more susceptible to loss of smell, but the mechanism still is unclear. Nevertheless, the new data point to the sustentacular cell as the site of pathogenesis, and this reveals where we need to look for answers to better understand how SARS-CoV-2 attacks the olfactory system.

4.4 Technical Considerations of Methodology

For reasons explained in the introduction, we had to rely on studies reporting the results of subjective testing or patient recall for the monitoring of olfactory

dysfunction. In fact, we found only a single study that reported omicron-induced hyposmia based on psychophysical testing [63], while there were 41 studies that reported on subjective recall (Table 1). However, it is still debated whether subjective recall or psychophysical testing is the most valid approach to assess COVID-related chemosensory dysfunction [20,29].

Most of the studies we compiled were scored as moderate or high quality according to the modified Newcastle-Ottawa scale (Table 1), and omission of studies scoring low for quality did not change our results and conclusions. There was no evidence for publication bias in the analysis of the funnel plot (Fig. 6).

Because people who are more impacted by their condition may be more likely to respond in an internet-based survey [8,30-32,38], this could lead to bias in survey-type studies. Therefore, we compared survey-type studies with traditional representative sampling studies that use direct and immediate questioning of each member of the eligible cohort, rather than inviting eligible individuals online and collecting responses on internet-provided questionnaires. Such study designs rely on equitable participation of individuals suffering from loss of smell and those with no such loss. We found that although survey-type studies reported higher prevalence of hyposmia than traditional study designs, there was no evidence for heterogeneity between the two study types (Fig. 8A,B). The issue of potential bias in survey-type studies deserves further scrutiny and should be examined in the future with more studies and larger cohorts.

4.5 Limitations of our Review

Most studies compiled in our review did not stratify by age group, but age is a relevant factor [12,23,91]. Likewise, most studies did not report on gender of the

cohort and gender of the cases, yet gender also is a relevant factor [12,23]. There were few studies on Africans and South Asians, and those studies had small cohorts – additional data are needed to conduct a more reliable subgroup analysis and achieve higher certainty for the prevalence of hyposmia in these populations.

Many studies did not specify change in smell vs change in taste, and reported them as either change or loss of smell *and* taste, or change or loss of smell *or* taste. Additional studies are needed to better distinguish effects of omicron on smell and taste.

We did not attempt to resolve whether omicron sub-variants have different effects on olfactory dysfunction – there are too few studies yet that report effects of subvariants on loss of smell [49,51,57].

Some cohorts of the studies were ethnically mixed, but the exact ethnic composition of the cohort was reported in only a few studies (e.g. [49]), and none of the studies reported the prevalence of olfactory dysfunction separately for distinct ethnicities. This should be done in the future to verify differences between ethnicities, and this may also “sharpen” the ethnic distinctions which may be blurred by ethnically mixed cohorts. For example, the large fraction of Asians in the cohort of Weil et al. [49] may explain the relatively low overall prevalence of hyposmia in their study. Although ethnic patterns are emerging, more detailed analyses in future studies may allow to assign a more precise prevalence of olfactory dysfunction to each major ethnicity.

4.6 Future Directions

Although we have a clue that the UGT2A1 locus, and therefore the UDP glycosyltransferase, is involved in the ethnic differences in COVID-related olfactory

dysfunction [12], the mechanism still is unclear. Nevertheless, the sustentacular support cell in the olfactory epithelium appears to play a major role. This helps to direct focus on this cell type and its key roles in the processing of odorants and fundamental workings of the sense of smell [81]. A better understanding of the molecular mechanisms of loss of smell in COVID may inform about new therapies to help with persistent loss of smell, beyond the current olfactory training that is not effective for more than half of cases [92].

While some studies indicate that a previous SARS-CoV-2 infection may reduce the likelihood of olfactory dysfunction in a subsequent COVID infection [52], it is known that a previous COVID infection with an earlier variant does not necessarily prevent a second loss of smell when the same individual becomes infected with a subsequent SARS-CoV-2 variant [93,94]. It also does not seem that vaccinations reliably prevent the occurrence of loss of smell in break-through infections [8,53,71,95].

If omicron infects about 6 billion people worldwide, what does a global prevalence of 5.2% olfactory dysfunction (222.3 million cases world-wide) mean for trends in global cases of olfactory dysfunction? Our ethnicity-adjusted projections suggest that olfactory dysfunction will decline globally despite the higher infectivity of the omicron variant, contrary to previous predictions [8,9]. It is not yet known whether there will be *persistent* loss of smell after omicron infection. Will it be similar to previous variants – with about 5% persistent loss of smell among those who experience olfactory dysfunction [9]? Does a smaller number of cases of olfactory dysfunction with omicron also reduce the percentage of those who will have a persistent loss of smell? We don't know yet about persistent loss of smell due to omicron, since it has been only about one year since the first cases of omicron

infection. Much is still to be learned about the effects of omicron (and previous and future) variants of SARS-CoV-2 on olfaction.

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Author Contributions

Both authors contributed to the data collection, analysis, and writing of the manuscript.

Conflict of interest

The authors declare no conflict of interest.

Data Availability Statement

All data referenced in this study are publicly available.

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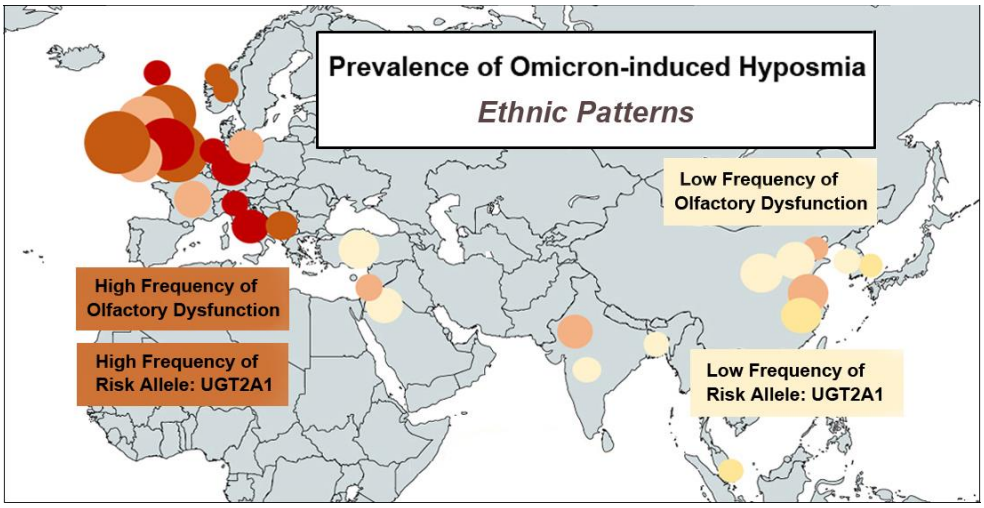
Figures and Legends



Graphical Abstract

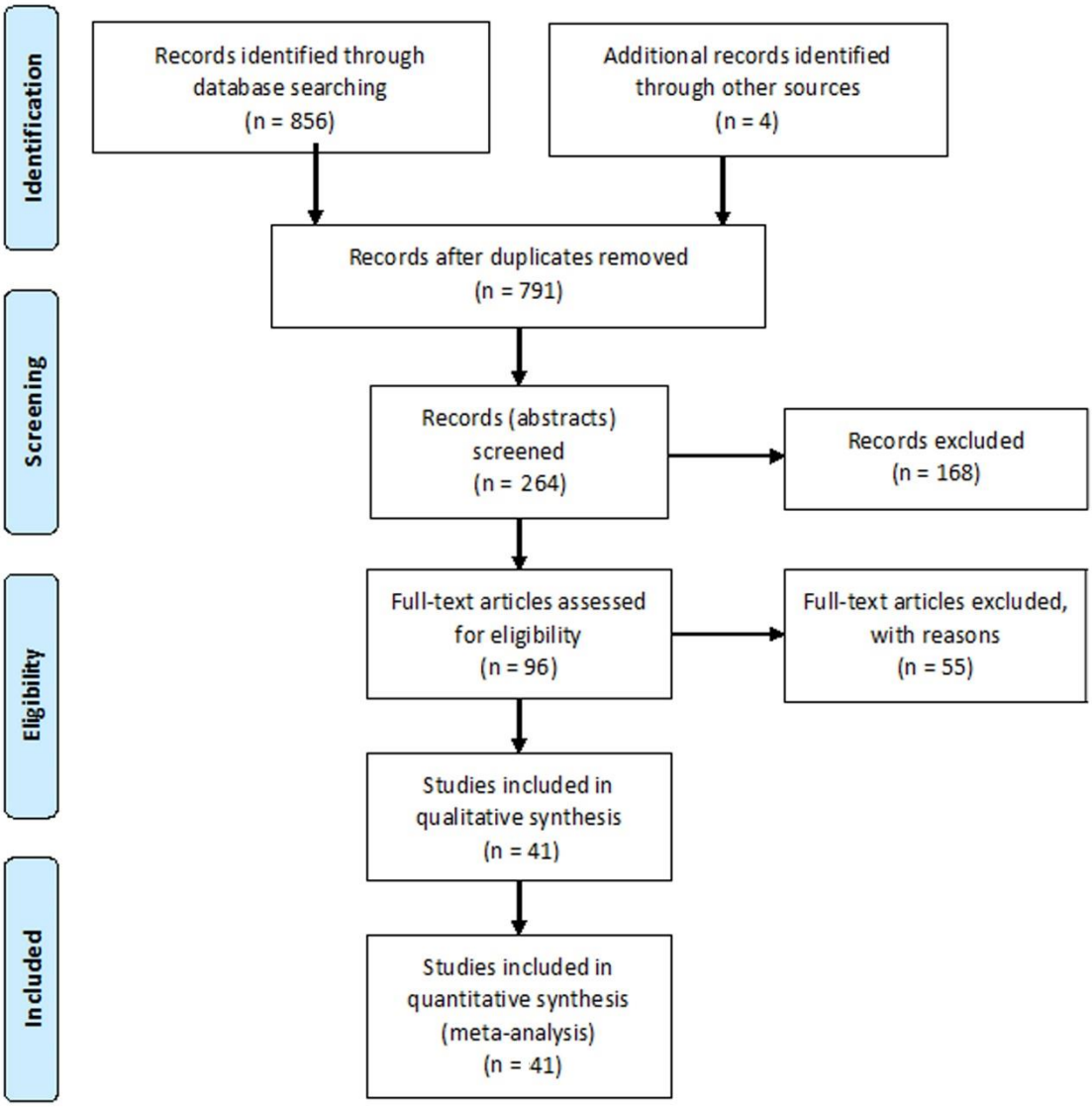


Figure 1. Flowchart illustrating the Literature Search, Systematic Review and Meta-analysis according to the PRISMA guidelines.

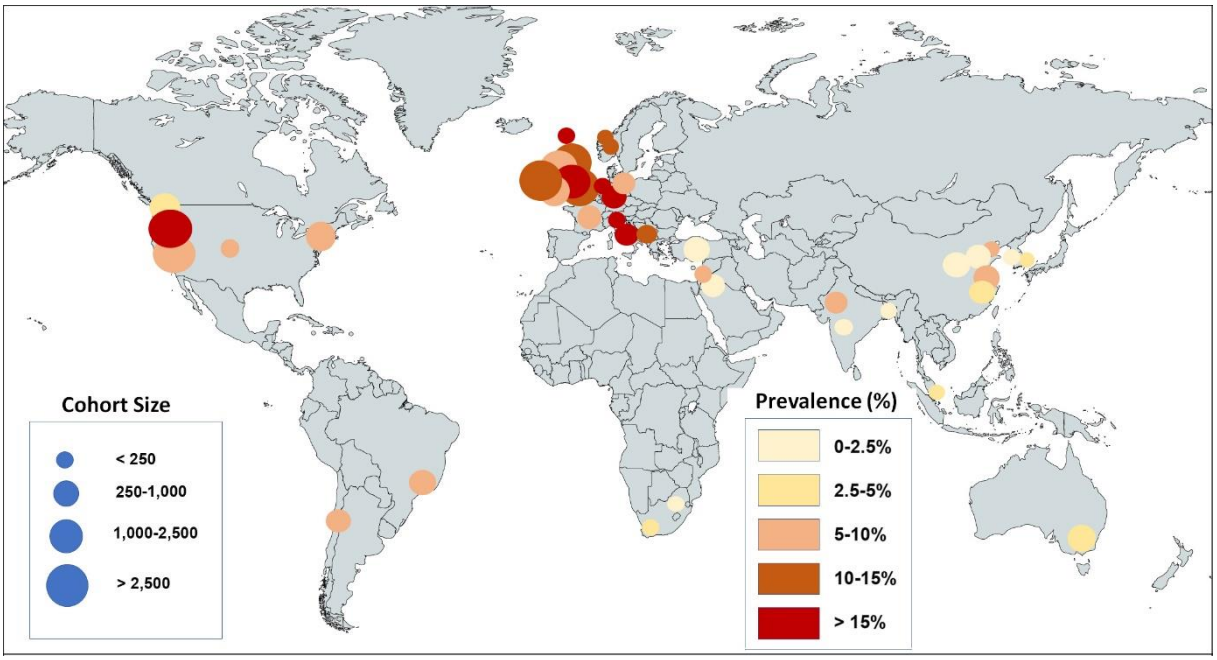


Figure 2. World map showing the location of cohorts included in the systematic review and the prevalence of olfactory dysfunction due to the omicron variant. The size of the circles represents the size of the cohort as indicated in blue; the heat map indicates the prevalence range as shown on the right side. Note that populations of European ancestry have larger prevalences than populations of non-European ancestry.

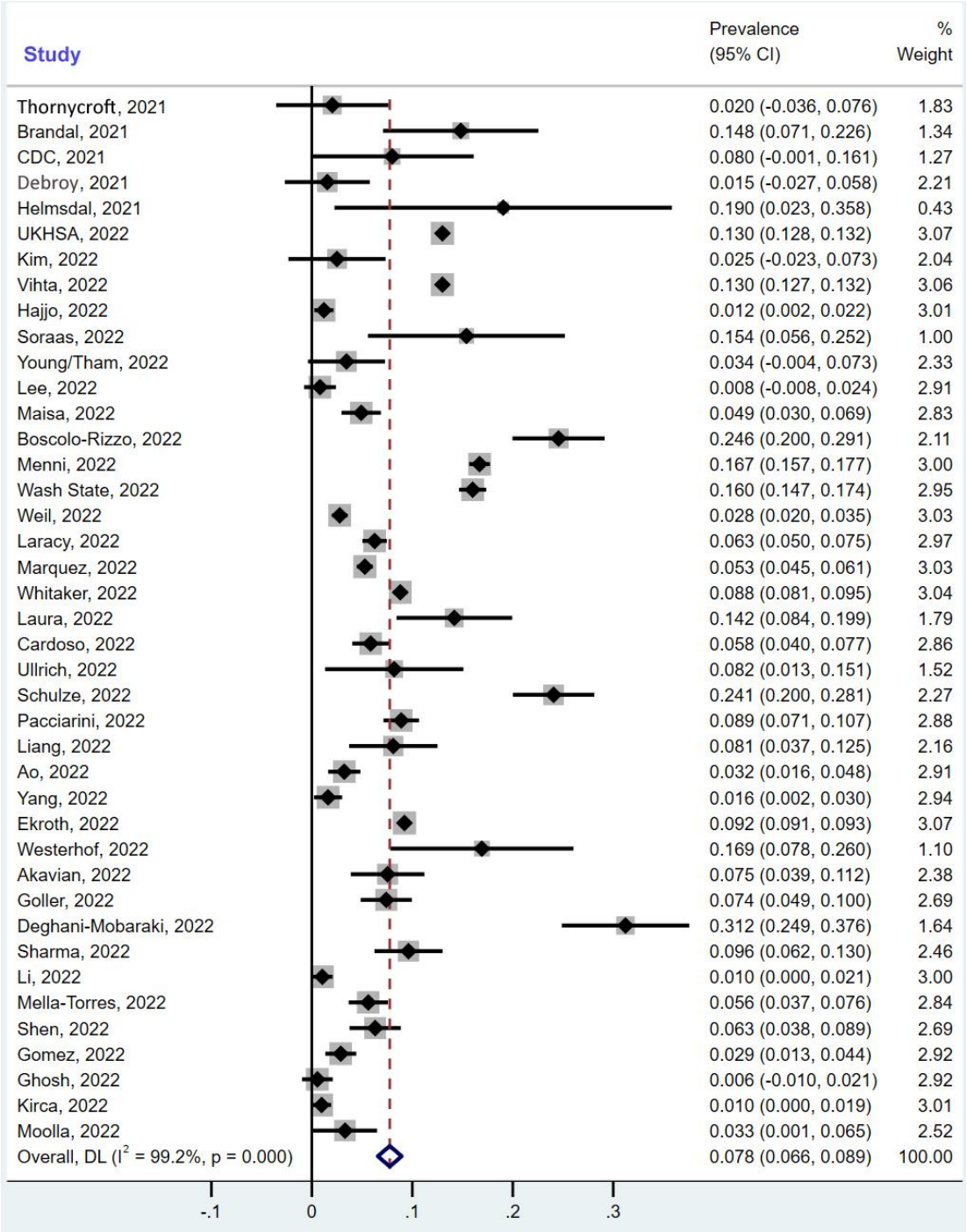


Figure 3. Forest plot of the 41 studies reporting the prevalence of olfactory dysfunction due to the omicron variant. The confidence intervals (CI) and the weight of each study are indicated on the right. The pooled overall global prevalence is 7.8% according to the meta-analysis, but this does not take into account ethnic differences and population sizes as explained in Fig. 4. CI, confidence interval; DL, DerSimonian-Laird method; I^2, I-squared index.

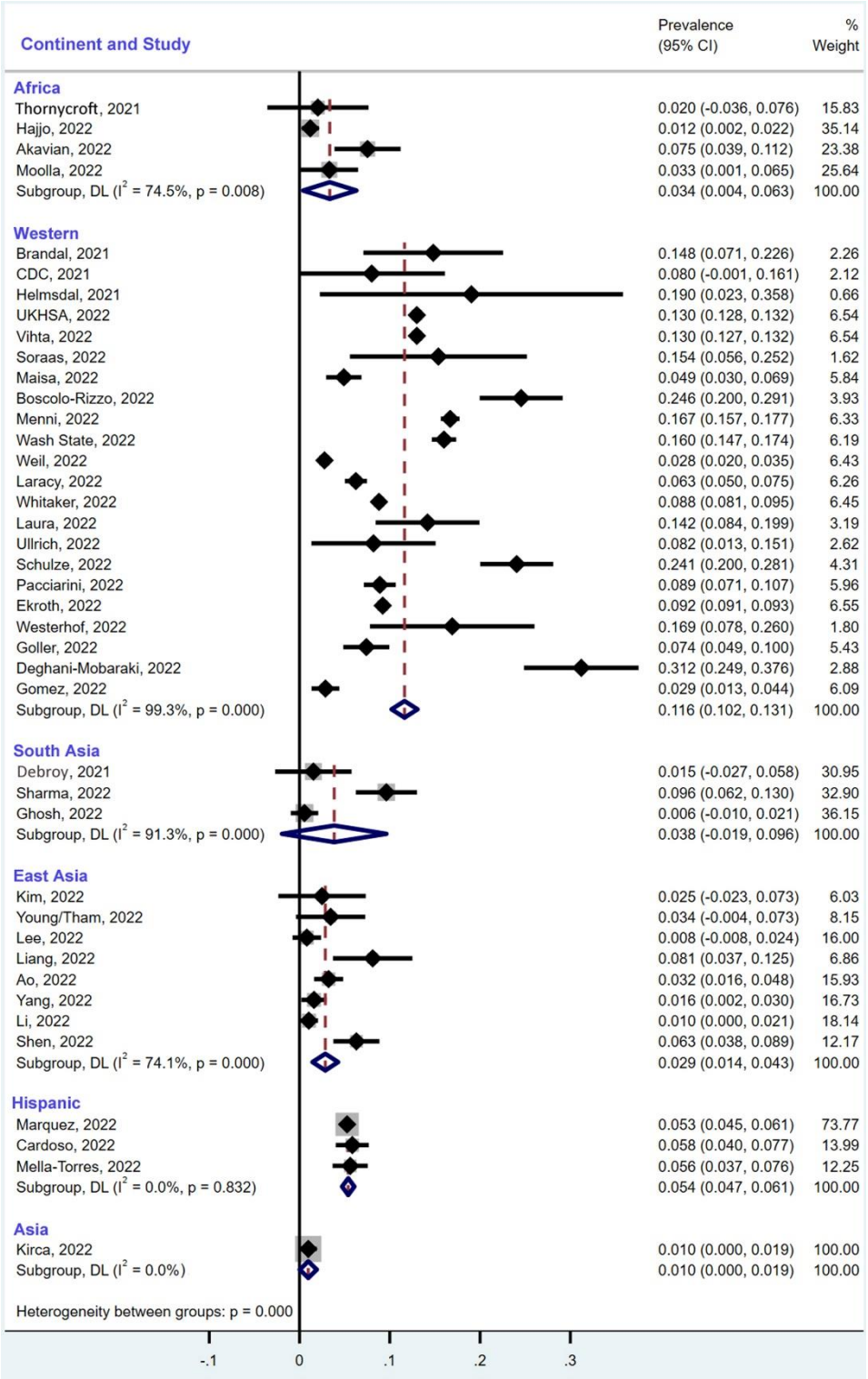


Figure 4. Forest plots of the prevalence of olfactory dysfunction due to omicron by different regions/ethnic populations according to the meta-analysis. Prevalences are 2.9% (CI=1.4%-4.3%) in East Asians, 3.8% (0%-9.6%) in South Asians, 5.4% (4.7%-6.1%) in Hispanics, and 11.6% (10.2%-13.1%) in populations of European ancestry. CI, confidence interval; DL, DerSimonian-Laird method; I^2, I-squared index.

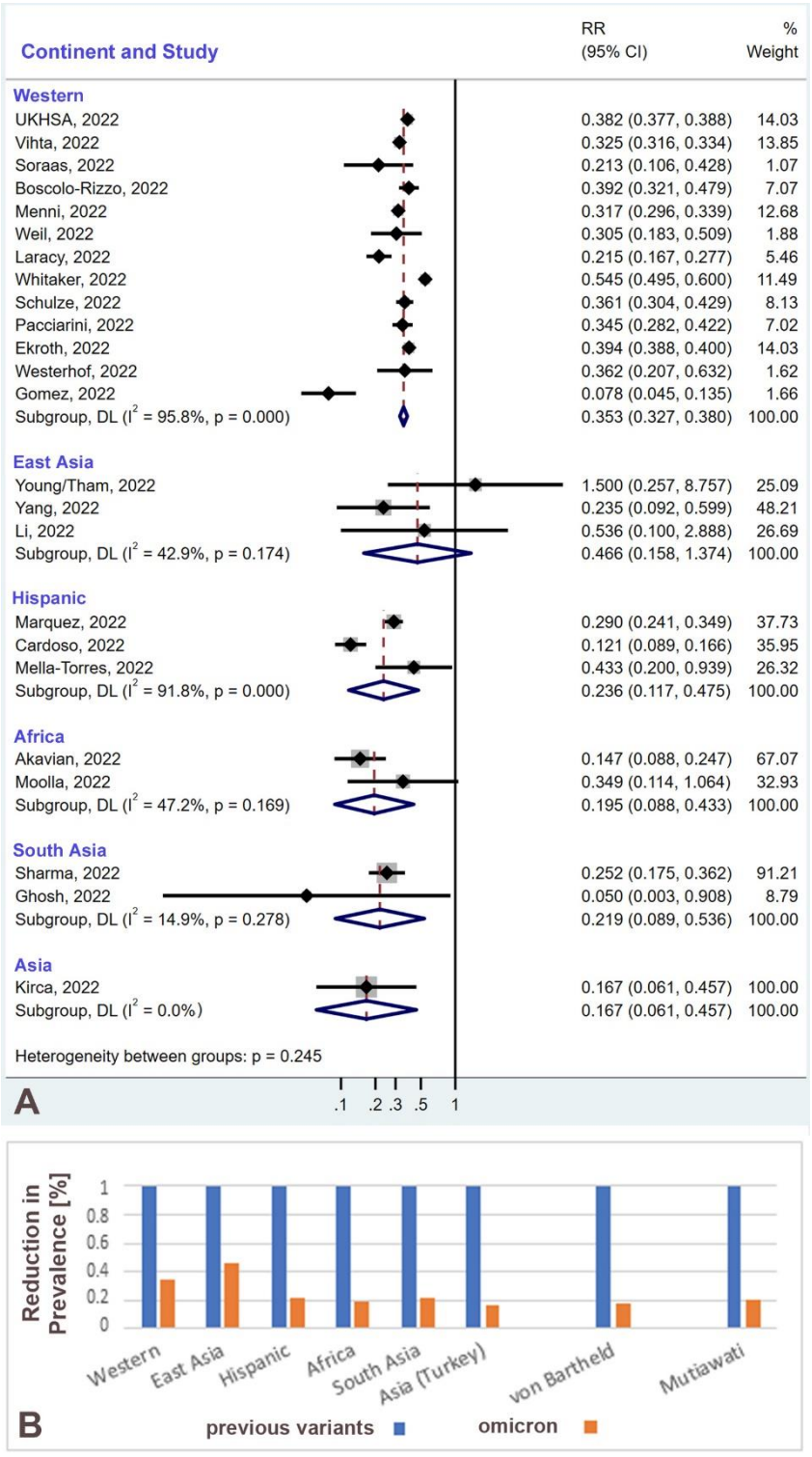


Figure 5. The prevalence of olfactory dysfunction (OD) due to omicron is reduced by 2-fold to 5-fold compared to the previous SARS-CoV-2 variants, regardless of ethnic population and region. (A) The reduction of OD due to omicron in direct comparisons within similar populations and regions during the predominance of mostly the delta

variant (for specifics of the comparator variants, see Table 2). (B) The bar graph summarizes the reduction in prevalence of OD for the direct comparisons from panel A (n=24), and also two indirect comparisons with pooled estimates from previous meta-analyses, von Bartheld et al., 2020 [23], and Mutiawati et al., 2021 [79]. The percent reduction is consistently between 2-fold and 5-fold. CI, confidence interval; DL, DerSimonian-Laird method; I^2, I-squared index, RR, risk ratio.

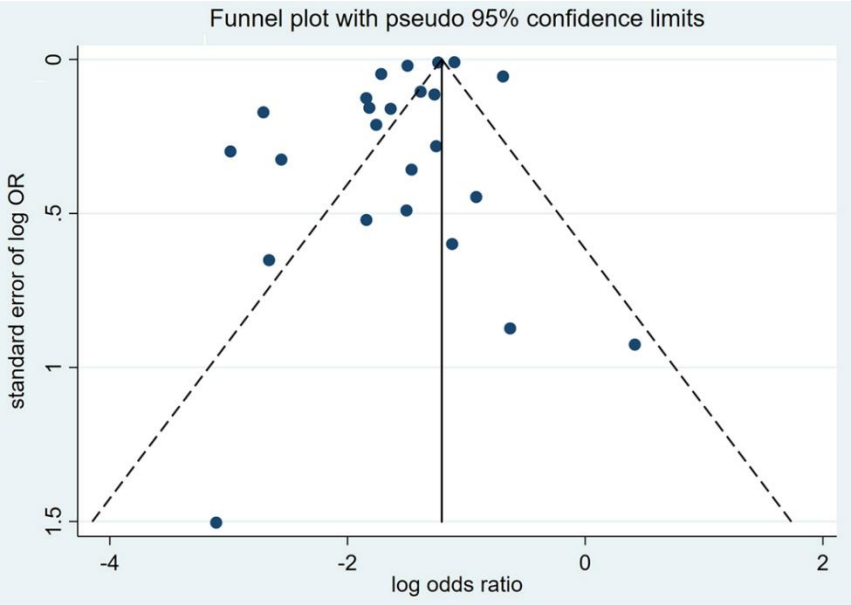


Figure 6. The funnel plot for all 41 eligible studies reporting omicron-induced olfactory dysfunction. This is a scatterplot of prevalences against their standard errors. The vertical solid line is the estimated effect size; the dotted lines are the corresponding pseudo 95% confidence intervals (CIs). They provide insight into the spread of observed effect sizes. The majority of studies are randomly scattered within the CI region, indicating absence of publication bias and heterogeneity (p=0.081).

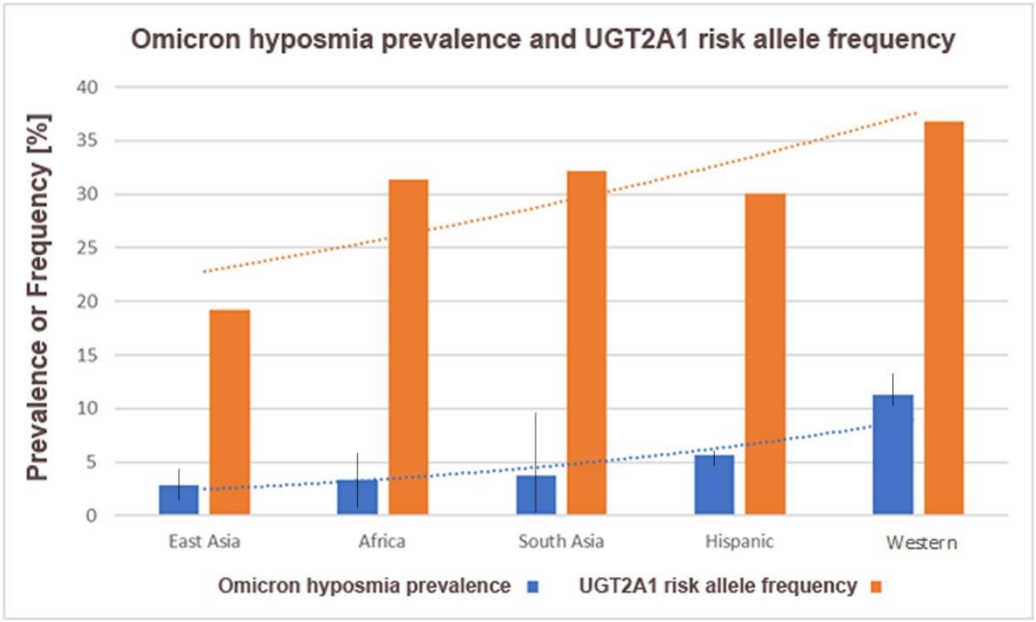


Figure 7. The bar graph shows the differences between ethnicities for omicron's prevalence of olfactory dysfunction (blue bars), compared with the frequency of the risk allele for olfactory dysfunction in the UGT2A1 locus according to Shelton et al., 2022 [12] (orange bars). The error bars indicate 95% confidence intervals. Meta regression shows that there is a positive association between the two parameters (p=0.001): The prevalence of olfactory dysfunction is higher in those ethnic populations that have a higher frequency of the risk allele.The two exponential trend lines show this similarity.

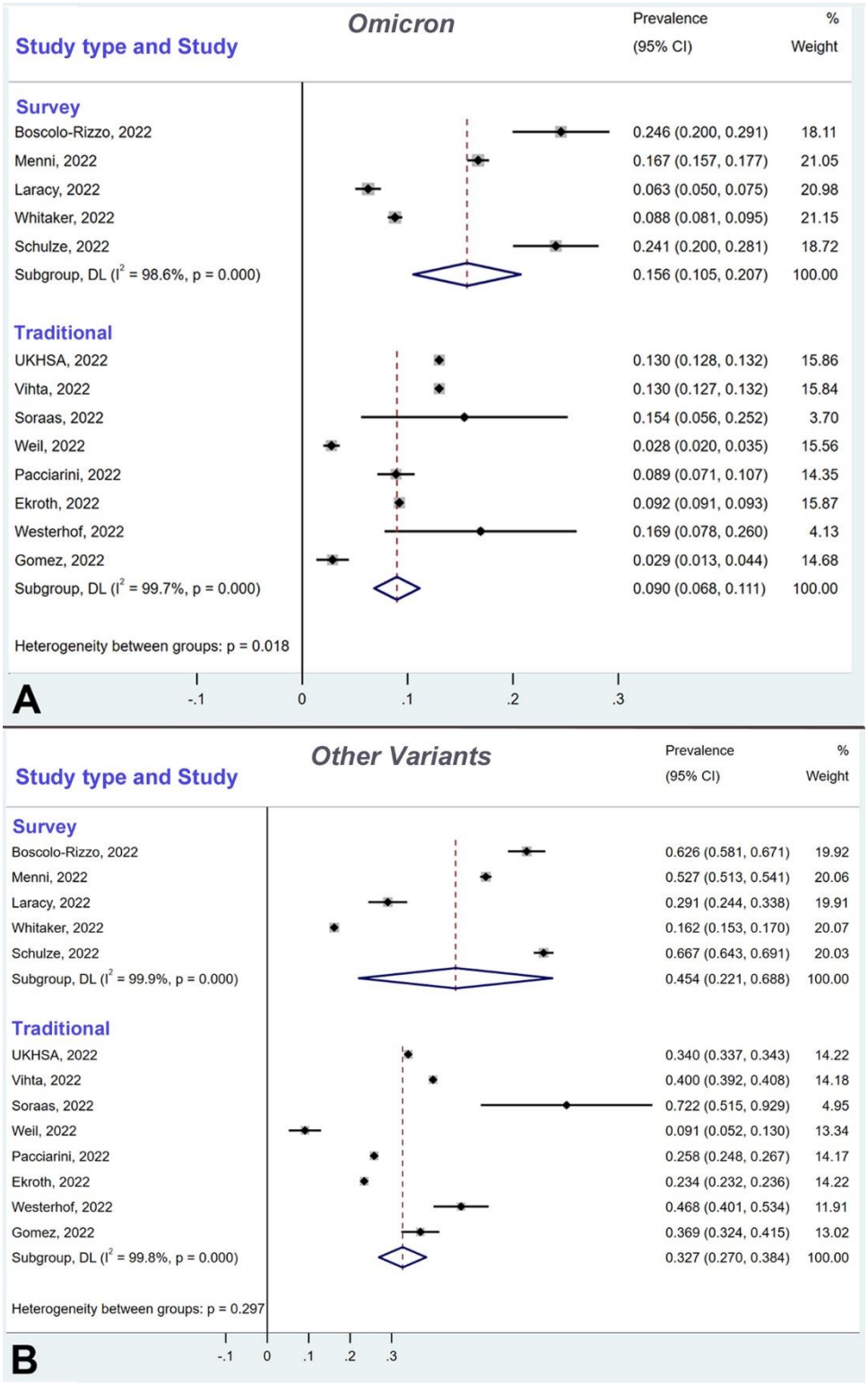


Figure 8. The pooled prevalences of olfactory dysfunction due to omicron (A) and due to other variants (B) in survey-type studies and traditional-design studies for populations of European ancestry. While the pooled estimates are higher in the survey-type studies than in the traditional-design studies,14.2% vs.10.7% for omicron studies (A), and 45.4% vs 32.7% for previous variants (B), meta-regression showed

no heterogeneity between the two study types. Confidence intervals for omicron studies (A) were 9.7%-18.7% for survey-type studies, and 9.0%-12.4% for traditional design studies. Confidence intervals for previous variant studies (B) were 22.1%-68.8% for survey-type studies, and 27.0%-38.4% for traditional design studies.

Tables

Table 1. List of studies reporting the prevalence of olfactory dysfunction caused by the omicron variant.

Date first published	Ref. #	Author/ Publication date (first)	Country	Cohort size	Cases with olf. dysfunct.	%	Quality scores
27 Nov 2021	74	Thornycroft	South Africa	24	0	0%	L
16 Dec 2021	40	Brandal	Norway	81	12	14.8%	M
17 Dec 2021	41	CDC	USA	43	3	7%	M
17 Dec 2021	68	Debroy	India	32	0	0%	L
31 Dec 2021	42	Helmsdal	Denmark	21	4	19%	L
14 Jan 2022	43	UKHSA	UK	182,133	23,677	13%	M
17 Jan 2022	60	Kim	Korea	40	1	2.5%	M
18 Jan 2022	44	Vihta	UK	69,372	9,018	13%	M
25 Jan 2022	75	Hajjo	Jordan	500	6	1.2%	M
27 Jan 2022	45	Soraas	Norway	52	8	15%	M
27 Jan 2022	61	Young/Tham	Singapore	87	3	3.44%	M
10 Feb 2022	62	Lee	Korea	123	1	0.8%	M
12 Feb 2022	46	Maisa	France	468	23	4.9%	H
18 Feb 2022	8	Boscolo-Rizzo	Italy	338	83	24.6%	H
06 Apr 2022	47	Menni	UK	4,990	833	16.7%	H
13 Apr 2022	48	Washington St	USA	2,830	453	16%	L
28 Apr 2022	49	Weil	USA	1,730	48	2.8%	H
04 May 2022	50	Laracy	USA	1,520	95	6.3%	M
23 May 2022	71	Marquez	USA	3,032	160	5.3%	H
23 May 2022	51	Whitaker	UK	6,395	563	8.80%	H
13 Jun 2022	52	Laura	Bosnia	141	20	14.2%	H
24 Jun 2022	72	Cardoso	Brazil	633	37	5.8%	H
25 Jun 2022	53	Ullrich	Germany	61	5	8.2%	M
01 Jul 2022	32	Schulze	Germany	428	103	24.1%	M
12 Jul 2022	54	Pacchiarini	UK, Wales	1,000	89	8.9%	H
02 Aug 2022	63	Liang	China	148	12	8.1%	M
08 Aug 2022	64	Ao	China	465	15	3.2%	M
11 Aug 2022	65	Yang	China	310	5	1.6%	H
17 Aug 2022	55	Ekroth	UK	309,912	28,569	13.4%	H
19 Aug 2022	56	Westerhof	Netherlands	65	11	16.9%	M
03 Sep 2022	76	Akavian	Israel	199	15	9.1%	M
09 Sep 2022	57	Goller	Germany	405	30	7.4%	M
14 Sep 2022	58	Deghani-Mobaraki	Italy	205	64	31.2%	M
23 Sep 2022	69	Sharma	India	291	28	9.6%	L
12 Oct 2022	66	Li	China	384	4	1%	M
21 Oct 2022	73	Mella-Torres	Chile	534	30	5.6%	M
07 Nov 2022	67	Shen	China	349	22	6.3%	H
16 Nov 2022	59	Gomez	Australia	452	13	3.2%	M
18 Nov 2022	70	Ghosh	Bangladesh	90	0	0%	M
24 Nov 2022	78	Kirca	Turkey	411	4	1%	M
24 Nov 2022	77	Moolla	South Africa	121	4	3%	M
				Total: 590,415	**Total: 64,071**		

Footnotes

olf. dysfunct., olfactory dysfunction; Young/Tham, two different first authors on versions 1 and 2 of preprint server; quality scores: L, low, M, moderate, H, high.

Table 2. Compilation of the 24 studies that compare prevalence of olfactory dysfunction due to omicron with that due to delta or other variants.

Region	Ref #	Author	Country	Cohort Size	Percent hyposmia	Cohort Size	Percent hyposmia	Reduction Om./Prev.	Variant Name
				Omicron		Previous Variants			
Africa	76	Akavian	Israel	199	9.1%	119	51.3%	17.5%	G614
Africa	77	Moolla	Africa, Cape Town	121	3.3%	116	9.5%	34.7%	G614
Asia	78	Kirca	Turkey	411	1%	960	5.8%	17.2%	wt
East Asia	61	Young/ Tham	Singapore	87	3.44%	87	2.3%	149.6%	δ
East Asia	65	Yang	China	310	1.6%	422	6.9%	23.2%	β, δ
East Asia	66	Li	China	384	1%	103	2%	50.0%	δ
South Asia	69	Sharma	India, Rajasthan	291	9.6%	762	38.19%	25.1%	δ
South Asia	70	Ghosh	Bangladesh	90	0.0%	40	10.0%	0.0%	δ
Hispanic	71	Marquez	USA, SF	3,032	5.3%	1,533	18.2%	29.1%	δ, prev.
Hispanic	72	Cardoso	Brazil	633	5.8%	5,420	48.2%	12.0%	wt, γ, δ
Hispanic	73	Mella-Torres	Chile	534	5.6%	54	13%	43.1%	δ
Western	43	UKHSA	UK	182,133	13%	87,920	34%	38.2%	δ
Western	44	Vihta	UK	69,372	13%	14,318	40%	32.5%	δ
Western	45	Soraas	Norway	52	15%	18	72.2%	20.8%	δ
Western	8	Boscolo-Rizzo	Italy	338	24.6%	441	62.6%	39.3%	G614
Western	47	Menni	UK	4,990	16.7%	4,990	52.7%	31.7%	δ
Western	49	Weil	USA, WA	1,730	2.8%	209	11.1%	25.2%	δ
Western	50	Laracy	USA, NY	1,520	6.3%	361	29%	21.7%	α, δ
Western	51	Whitaker	UK	6,395	8.8%	6,739	16.2%	54.3%	wt, α, δ
Western	32	Schulze	Germany	428	24.1%	1,497	66.7%	36.1%	G614, α, δ
Western	54	Pacciarini	UK, Wales	1,000	8.9%	8,168	25.8%	34.5%	δ
Western	55	Ekroth	UK	309,912	13.4%	123,529	33.7%	39.8%	δ
Western	56	Westerhof	Netherlands	65	16.9%	216	46.7%	36.2%	G614, α
Western	59	Gomez	Australia	452	3.2%	425	36.9%	8.7%	δ

Footnotes

a, alpha variant; d, delta variant; g, gamma variant; G614, variant with the D to G mutation at position 614; Om., omicron; Prev., previous variants; Ref #, Reference Number; wt, wildtype. Young/Tham, two different first authors on versions 1 and 2 of preprint server;

Table 3. Estimation of the number of adults in different ethnicities expected to experience olfactory dysfunction (OD) with omicron.

	Population	Adults only	COVID Infected Adults *	Pre-valence	Adults with OD	Weight	Prevalence x Weight
	billion	billion	billion	%	million		
Western	1.3	0.97	0.87	11.6	100.9	0.21	2.380
Hispanic	0.5	0.37	0.33	5.4	17.8	0.08	0.420
African	1.3	0.97	0.87	3.4	29.6	0.21	0.698
East Asian	2.8	2.10	0.95**	2.9	27.6	0.22	0.650
South Asian	1.8	1.35	1.22	3.8	46.4	0.29	1.093
Total	7.7	5.76	4.24		222.3		5.241

Footnotes:

* COVID-infected = 90% for all populations except for China (IHME, October 21, 2022 [5])

** China's population of 1.4 billion removed from East Asians because of Zero-COVID policy

Western, populations with mostly European ancestry

Weight = (number of COVID patients in one continent) / (number of total COVID patients)