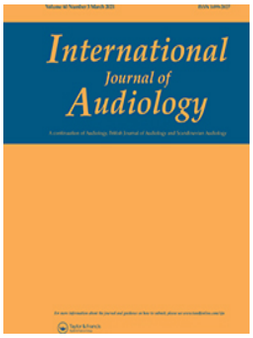

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One year on: an updated systematic review of SARS-CoV-2, COVID-19 and audio-vestibular symptoms

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REVIEW ARTICLE

One year on: an updated systematic review of SARS-CoV-2, COVID-19 and audio-vestibular symptoms

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ABSTRACT

Objective: The aim was to systematically review the literature to December 2020, in order to provide a timely summary of evidence on SARS-CoV-2, COVID-19 and audio-vestibular symptoms.

Design: The protocol was registered in the International Prospective Register of Systematic Reviews. The methods were developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines. Risk of bias was assessed using the National Institutes of Heath quality assessment tools.

Study sample: After rejecting 850 records, 28 case reports/series and 28 cross-sectional studies met the inclusion criteria.

Results: There are multiple reports of hearing loss (e.g. sudden sensorineural), tinnitus and rotatory vertigo in adults having a wide range of COVID-19 symptom severity. The pooled estimate of prevalence based primarily on retrospective recall of symptoms, was 7.6% (CI: 2.5–15.1), 14.8% (CI: 6.3–26.1) and 7.2% (CI: 0.01–26.4), for hearing loss, tinnitus and rotatory vertigo, respectively. However, these could be an over-estimate because it was not always clear that studies report a change in symptom.

Conclusion: There are multiple reports of audio-vestibular symptoms associated with COVID-19. However, there is a dearth of high-quality studies comparing COVID-19 cases and controls.

Review registration: Prospective Register of Systematic Reviews (PROSPERO); registration number CRD42020227038).

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KEYWORDS
Coronavirus; Covid-19; SARS-CoV-2; hearing loss; tinnitus; vertigo

Introduction

The first clinical description of COVID-19, the disease caused by severe acute respiratory coronavirus 2 (SARS-CoV-2), was published on 24 January 2020 (Huang et al. 2020). One week later, the World Health Organisation (WHO) categorized COVID-19 as a Public Health Emergency of International Concern (WHO 2020a), meaning the virus was a risk to other countries and required a coordinated international response. Then, on 11 March 2020, WHO declared COVID-19 a pandemic (WHO 2020b). At the time of writing, there have been 116 million reported cases and more than 2.6 million deaths (WHO 2020a).

The symptoms and severity of COVID-19 vary from asymptomatic to severe or fatal (Guan et al. 2020). The UK National Institute for Health and Care Excellence (NICE; National Institute for Health and Care Excellence 2020) has provided a set of definitions for three phases of signs and symptoms: (i) acute, persisting for up to 4 weeks; (ii) ongoing, from 4 to 12 weeks; and (iii) post-COVID syndrome, continuing for more than 12 weeks (the latter two phases are often grouped together and referred to as 'long COVID'). According to NICE, common symptoms of long COVID include dizziness, tinnitus and otalgia.

It is well known that some viral infections may cause hearing loss (Young 2020). For instance, sequelae of cytomegalovirus, rubella and measles can include sensorineural hearing loss (Cohen et al. 2014). COVID-19 is reportedly associated with several neurological manifestations, including Guillain Barre Syndrome (GBS; Sedaghat and Karimi 2020), which has been found to be associated with auditory neuropathy spectrum disorder (Wong 1997). We were the first to publish a systematic review of coronavirus and audio-vestibular symptoms (Almufarrij et al. 2020; available online 12 June 2020). We searched the literature to May 2020 and identified seven studies (five case reports and two cross-sectional designs) reporting hearing loss, tinnitus and vertigo. Saniasiaya (2021) and Maharaj et al. (2020) conducted searches in July 2020 and reported similar, but not identical, findings to us. We have continued to monitor the literature closely and were aware that the number of studies reporting audio-vestibular symptoms had increased considerably (in excess of 50) since our first review. Given the importance of providing timely evidence for decision-making purposes, we conducted a new search of the literature in December 2020 with the aim of providing an updated systematic review.

Method

The protocol for this review was registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42020227038). The review methods were

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Supplemental data for this article can be accessed here.

described according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Moher et al. 2009). The protocol was similar to the one used in our earlier review (Almufarrij et al. 2020), but with modifications to:

- Eligibility criteria: audio-vestibular symptoms initiated or exacerbated as a result of Middle East Respiratory Syndrome (MERS) or Severe Acute Respiratory Syndrome (SARS) were excluded;
- Information sources: two additional databases were included (Embase and Web of Science) but preprint sources and clinical trial registries were not searched; and
- Search strategy: a more exhaustive search strategy was used to capture a wide range of audio-vestibular symptoms including vertigo.

Eligibility criteria

The inclusion criteria were similar to our previous review (Almufarrij et al. 2020). Participants were those who developed audio-vestibular symptoms (or experienced exacerbation of pre-existing symptoms) following contraction of SARS-CoV-2. Studies of symptoms that could solely be attributed to anxiety were excluded. There were no restrictions in terms of participant age or the diagnostic tool used to detect SARS-CoV-2. Studies that involved probable (i.e., medically confirmed, symptom-based) and suspected (i.e., medically unconfirmed, symptom-based) COVID-19 participants were also included. The review's primary outcome of interest was a change in hearing status. Secondary outcomes included vertigo, tinnitus and hyperacusis. All types of study design were included.

Information sources

The following databases were systematically searched to identify relevant studies: PubMed, Cochrane Library, Embase and Web of Science. Grey literature was explored using Google Scholar to identify studies not indexed in the databases (the first 100 hits were screened for inclusion). Reference lists and citation tracking were screened to identify any additional relevant studies.

Search strategy

The search strategies were developed by an experienced medical information specialist in consultation with the review team. The strategies were pilot-tested and refined through an iterative process. The list of search terms consisted of both free text and controlled terms (i.e., Medical Subject Headings). The strategies were built on the previous searches in the National Library of Medicine's PubMed database and the Cochrane Library (Wiley version), and included Embase (Ovid platform) and Web of Science databases.

Strategies utilised a combination of controlled vocabulary (e.g., 'Coronavirus Infections', 'Hearing Loss', 'Vestibular Diseases') and keywords (e.g., 'COVID-19', 'SSNHL', 'sensory neuropathy'). Vocabulary and syntax were adjusted across the databases. There were no language or date restrictions on any of the searches, but where possible, animal-only records were removed from the results. The search strategies are reported in Supplementary Material 1.

Data management and selection process

The records were exported to a reference management software (EndNote) to remove duplications. Next, the records were transferred to an Excel spreadsheet for eligibility screening and, where necessary, manual removal of duplicated entries. Both the title and abstract were independently screened by both authors. A full text inspection was carried out on all records that passed the initial screen by both authors independently. Where there was disagreement (<5%), this was resolved through discussion.

Data collection process and data items

Data were extracted by IA and verified by KJM, as done in our earlier review (Almufarrij et al. 2020). The following data were extracted using a pre-developed extraction form: author(s), date of publication, study design, participant characteristics, reported audio-vestibular symptoms and any relevant data. A graphic extraction tool, Web Plot Digitiser, was used to extract all graphical format data (when necessary).

Risk of bias in individual studies

The quality of the methodology in each eligible study was assessed independently by both authors. The National Institutes of Health's (NIH) quality assessment tools were used because of the availability of risk-of-bias checklists for different study designs (NIH National Heart, Lung and Blood Institute 2014). The quality rating of each study was categorised as: poor (i.e., questionable results or substantial details missing), fair (i.e., results deemed to be unbiased despite missing details) or good (i.e. unbiased and fully described).

Data synthesis and missing data

Audio-vestibular symptoms in case reports/series were narratively synthesised. Multiple meta-analyses were conducted to pool the prevalence of each of the audio-vestibular symptoms reported in cross-sectional studies. The estimates and 95% confidence interval (CI) for each study were calculated using a double arcsine transformation (Freeman and Tukey 1950; Barendregt et al. 2013). The pooled estimates and 95% CI were aggregated using the inverse-variance method (DerSimonian and Laird 1986) following the recommendations of the Cochrane Handbook (Higgins and Green 2008). If the statistical heterogeneity was high ($I^2 > 61\%$), a random-effect model was used to pool the data; otherwise, a fixed-effect model was used. Egger's (Egger et al. 1997) and Begg's (Begg and Mazumdar 1994) tests were performed to assess publication bias. Missing data were inferred from other available data. The analyses were computed using MedCalc® (Version 19.6.4).

Results

Search and selection of studies

The screening process is shown in the PRISMA flow chart (Figure 1). Searching the databases, Google Scholar and other relevant COVID-19 reviews resulted in 1600 retrieved records. After removing duplicates, the titles and abstracts of the remaining 933 records were screened for inclusion. Of these, 76 met the eligibility criteria. The full text of the 76 studies were inspected, and 45 were determined eligible for inclusion. Two of the eligible

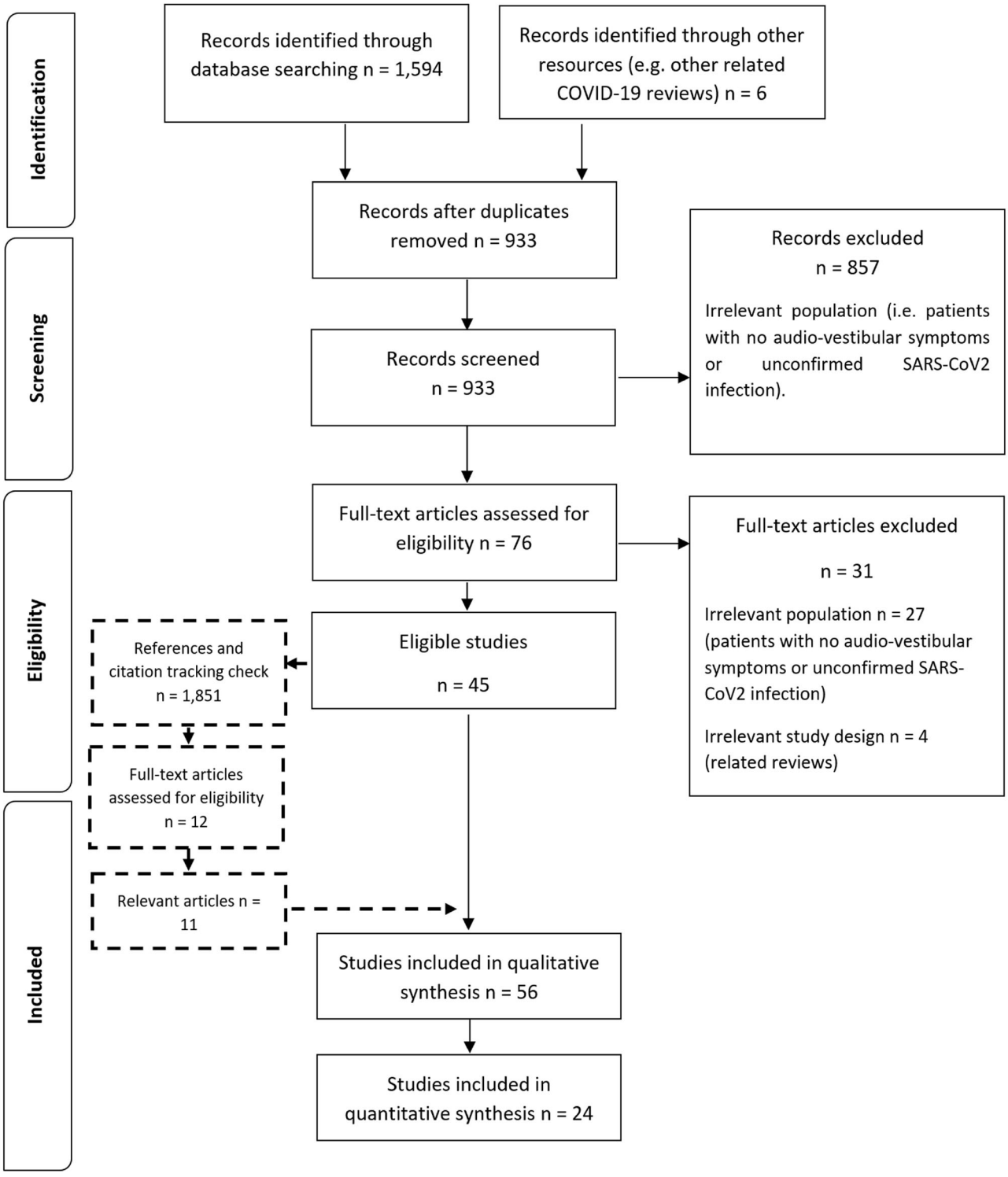

Figure 1. A PRISMA flow chart of the selection process.

studies were non-English (i.e., Russian and Italian) but had an English abstract. The full text was translated and included in this review. Screening the reference lists and tracking the citations of all eligible studies led to the identification of 1851 additional records. After screening, 11 were deemed eligible for inclusion. Thus, in total, 56 studies (including seven identified in our previous review; Almufarrij et al. 2020) were included in this review.

Characteristics of the included studies

Table 1 lists the studies and the symptoms each reported. Half of the studies ($N = 28$) were either case reports or case series. All but six of these studies were published in 2020. The six exceptions were published in 2021 (Brzycki et al. 2021; Chern et al. 2021; Chirakkal et al. 2021; Kamal et al. 2021; Salepci et al. 2021;

Table 1. Summary of studies included in the review.

Case study/series ($n = 28$)	Overall quality rating consensus	Cross-sectional ($n = 28$)	Overall quality rating consensus
Abdel Rhman and Abdel Wahid (2020) [HL, T]	Fair	Beukes et al. (2020) [HL, T]	Good
Brzycki et al. (2021) [HL]	Fair	Carfì et al. (2020) [V]	Fair
Chern et al. (2021) [HL, V]	Fair	Cirulli et al. (2020) [T]	Fair
Chirakkal et al. (2021) [HL, T]	Fair	Daikhes et al. (2020) [HL, T, O]	Fair
Cui et al. (2020) [T, O]	Fair	Davis et al. (2020) [HL, T, V, O]	Fair
Degen et al. (2020) [HL, T]	Fair	Dror et al. (2020)	Fair
Fadakar et al. (2020) [V]	Fair	Elibol (2020) [HL, T, O]	Fair
Fidan (2020) [HL, T, O]	Fair	Freni et al. (2020) [HL, T, O]	Fair
García-Romo et al. (2020) [V]	Fair	Goërtz et al. (2020) [O]	Fair
Goh et al. (2020) [O]	Fair	Iltaf et al. (2020) [V]	Fair
Han et al. (2020) [V]	Fair	Kamal et al. (2021) [T]	Fair
Jacob et al. (2020) [HL]	Poor	Karimi et al. (2020) [HL]	Fair
Karimi-Galougahi et al. (2020a) [HL, T, V]	Fair	Khalaf et al. (2020) [V]	Fair
Karimi-Galougahi et al. (2020b) [HL, O]	Fair	Klopfenstein et al. (2020) [HL, T]	Fair
Kilic et al. (2020) [HL]	Good	Lechien et al. (2020) [T, V, O]	Fair
Koumpa et al. (2020) [HL, T]	Fair	Liang et al. (2020) [T]	Fair
Lamounier et al. (2020) [HL, T]	Good	Membrilla et al. (2020) [O]	Fair
Lang et al. (2020) [HL, T]	Fair	Micarelli et al. (2020) [T, V, O]	Fair
Liu et al. (2020) [V]	Fair	Moradian et al. (2020) [O]	Fair
Maharaj and Hari (2020) [T, V]	Good	Munro et al. (2020) [HL, T, V]	Fair
Malayala and Raza (2020) [V]	Good	Mustafa (2020) [HL]	Poor
Miri and Ajallouеyan (2020) [O]	Fair	Özçelik Korkmaz et al. (2020) [HL, T, V]	Fair
Mohan et al. (2020) [HL, O]	Fair	Rocha-Filho and Magalhães, (2020) [O]	Fair
Sriwijitalai and Wiwanitkitb (2020) [HL]	Poor	Salahuddin et al. (2020) [V]	Fair
Sun et al. (2020) [HL, T]	Poor	Salepci et al. (2021) [HL, V, O]	Fair
Takahashi et al. (2020) [HL]	Poor	Savtale et al. (2021) [HL, T]	Fair
Vanaparthy et al. (2020) [V]	Fair	Stavem et al. (2020) [O]	Fair
Ye and Xianyang (2020) [O]	Fair	Viola et al. (2020) [T, V]	Fair

The symptoms reported in each study is shown in brackets. HL: hearing loss; T: tinnitus; V: vertigo; O: other.

Savtale et al. 2021). Half of the studies ($N = 28$) were either case reports or case series. The remaining 28 studies were cross-sectional studies: two international (Beukes et al. 2020; Davis et al. 2020), one regional (Europe; Lechien et al. 2020) and the remaining specific to a single country. Although all the studies included confirmed COVID-19 participants, some also enrolled negative ($N = 2$; Davis et al. 2020; Cirulli et al. 2020), undiagnosed ($N = 2$; Davis et al. 2020; Cirulli et al. 2020), probable ($N = 4$; Goërtz et al. 2020; Karimi et al. 2020; Membrilla et al. 2020; Micarelli et al. 2020), and suspected ($N = 3$; Beukes et al. 2020; Goërtz et al. 2020; Micarelli et al. 2020) COVID-19 participants. Fifty studies involved adults, and five involved a range of ages that included children (Lechien et al. 2020; Micarelli et al. 2020; Liang et al. 2020; Khalaf et al. 2020; Salahuddin et al. 2020). The remaining study did not provide any details about the participants' demographics (Sriwijitalai and Wiwanitkit 2020). The characteristics and main findings of the case reports/series and the cross-sectional studies are detailed in Supplementary Materials 2 and 3, respectively.

Audio-vestibular symptoms

Hearing loss

Seventeen case reports and one case series reported hearing loss as a potential COVID-19 related symptom ($N = 28$ patients). Of these, nine reported sensorineural hearing loss (Chern et al. 2021; Sriwijitalai and Wiwanitkit 2020; Degen et al. 2020; Abdel Rhman and Abdel Wahid 2020; Karimi-Galougahi et al. 2020a; Kilic et al. 2020; Koumpa et al. 2020; Lamounier et al. 2020; Lang et al. 2020; with two bilateral [Chern et al. 2021; Degen et al. 2020] and six unilateral [Abdel Rhman and Abdel Wahid 2020; Karimi-Galougahi et al. 2020a; Kilic et al. 2020; Koumpa et al. 2020; Lamounier et al. 2020; Lang et al. 2020] of sudden onset; $N = 14$ patients), three reported conductive hearing loss ($N = 9$; Fidan 2020; Karimi-Galougahi et al. 2020b; Chirakkal et al. 2021); and one reported mixed hearing loss ($N = 1$; Mohan et al. 2020). The remaining studies did not provide sufficient details for the review team to identify the type or severity of hearing loss ($N = 4$; Jacob et al. 2020; Sun et al. 2020; Takahashi et al. 2020; Brzycki et al. 2021).

Hearing loss was investigated in 13 cross-sectional studies (Savtale et al. 2021; Davis et al. 2020; Karimi et al. 2020; Khalaf et al. 2020; Daikhes et al. 2020; Dror et al. 2020; Elibol 2020; Freni et al. 2020; Klopfenstein et al. 2020; Munro et al. 2020; Mustafa 2020; Özçelik Korkmaz et al. 2020; Salepci et al. 2021). Of these, three conducted a battery of audiological tests (Daikhes et al. 2020; Dror et al. 2020; Mustafa 2020), and one (Freni et al. 2020) used a validated hearing-specific quality of life questionnaire (the Hearing Handicap Inventory for Adults; Newman et al. 1990). The remaining studies used self-reported questionnaires or retrospectively reviewed medical records. Twelve out of the 13 studies identified hearing loss as a COVID-19 symptom (Savtale et al. 2021; Davis et al. 2020; Karimi et al. 2020; Khalaf et al. 2020; Daikhes et al. 2020; Elibol 2020; Freni et al. 2020; Klopfenstein et al. 2020; Munro et al. 2020; Mustafa 2020; Özçelik Korkmaz et al. 2020; Salepci et al. 2021). One additional study did not directly investigate hearing loss, but, in response to an open-ended question, four of the participants indicated that their hearing status deteriorated after contracting COVID-19 (Beukes et al. 2020).

Two of the three studies that administered a battery of audiological tests did not find a significant difference in audiometric thresholds between COVID-19 cases and controls (Daikhes et al. 2020; Dror et al. 2020). The exception was Mustafa (2020), who reported that the COVID-19 group had significantly poorer hearing thresholds at high frequencies. In addition, the amplitudes of transient evoked otoacoustic emissions in two of these studies were significantly lower for the COVID-19 group (Daikhes et al. 2020; Mustafa 2020).

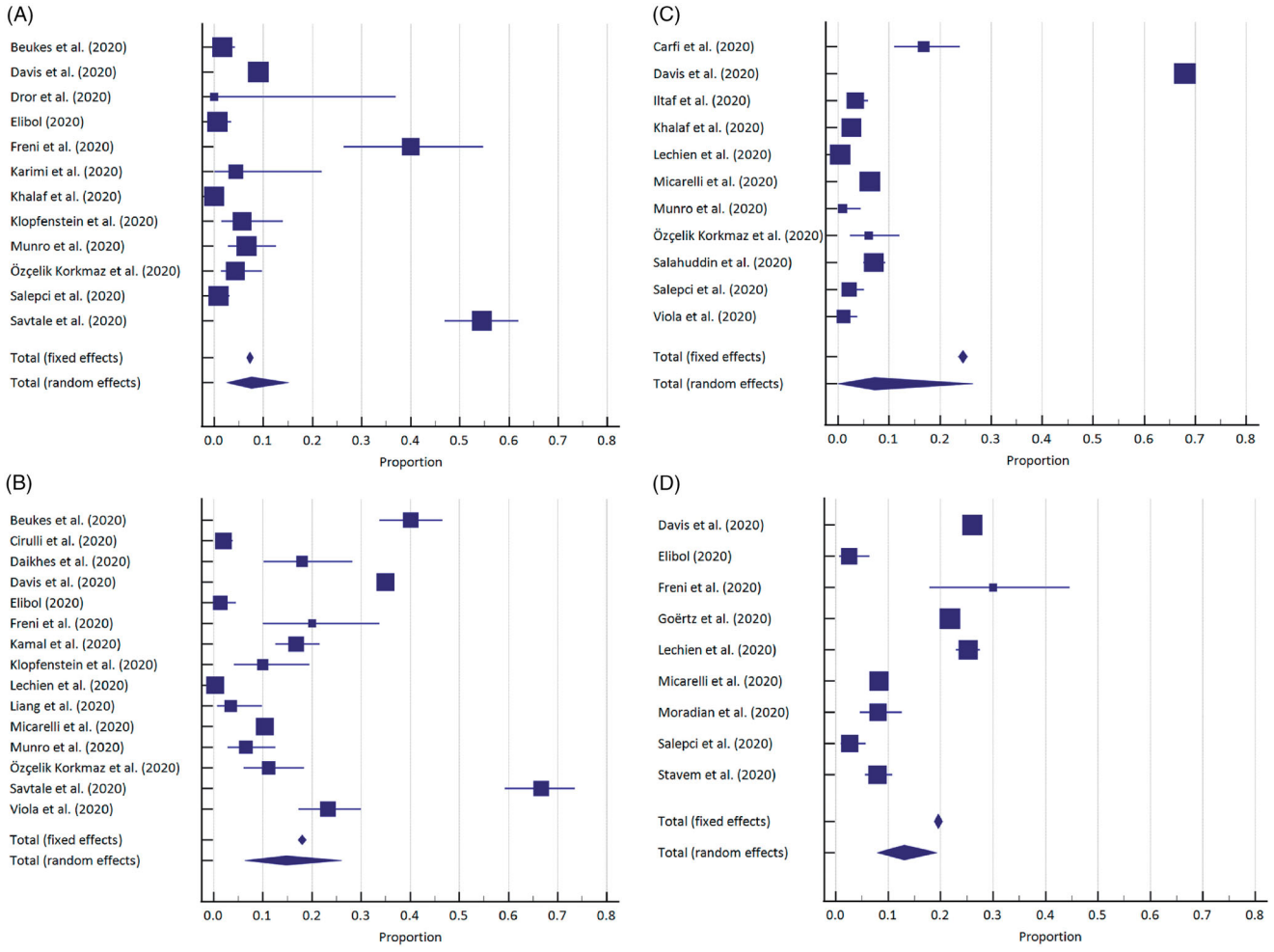

Figure 2. Forest plots for the prevalence of hearing loss (A), tinnitus (B), vertigo (C) and otalgia (D) in confirmed, probable and suspected COVID-19 patients. The pooled estimates and their 95% CI are represented by the centre point and width of the diamonds, respectively. The individual study estimate and its 95% CI are represented by squares and their error bars, respectively.

Figure 2(A) shows the forest plot for the prevalence of hearing loss. The pooled estimate was 7.6% (95% CI: 2.5–15.1%). The estimate was aggregated using both fixed- and random-effect meta-analyses, but only the latter was reported because the heterogeneity was high (I^2 = 97.7%). Two cross-sectional studies could not be included in the meta-analysis because they did not report the number of affected patients. Almost all studies in the meta-analysis employed self-reported questionnaires. On many occasions (Davis et al. 2020; Karimi et al. 2020; Khalaf et al. 2020; Daikhes et al. 2020; Klopfenstein et al. 2020; Mustafa 2020), it was not clear to the review team if studies were referring to new symptoms or pre-existing symptoms. However, the largest outlier (i.e., Savtale et al. 2021) explicitly referred to new symptoms.

Tinnitus

Eleven case reports documented the onset or aggravation of tinnitus (N = 14 patients; Abdel Rhman and Abdel Wahid 2020; Degen et al. 2020; Karimi-Galougahi et al. 2020a; Koumpa et al. 2020; Fidan 2020; Chirakkal et al. 2021; Lamounier et al. 2020; Lang et al. 2020; Sun et al. 2020; Maharaj and Hari 2020; Cui et al. 2020). The characteristics and psychological impacts of tinnitus were only reported in three of these reports. One described the tinnitus as non-pulsatile (Maharaj and Hari 2020), another as white noise (Degen et al. 2020), and the final one matched the tinnitus to 4 kHz and 10 dB sensation level (Chirakkal et al. 2021).

Tinnitus was investigated and identified in 15 cross-sectional studies. Of these, three asked participants to either classify their tinnitus (e.g., intermittent or continuous;Viola et al. 2020); or complete a validated tinnitus questionnaire (Beukes et al. 2020; Freni et al. 2020; e.g., Tinnitus Handicap Inventory; Newman et al. 1990). The tinnitus ranged from intermittent to continuous and, on average, pre-existing tinnitus was more bothersome during the pandemic.

Figure 2(B) shows the forest plot for the prevalence of tinnitus. The pooled estimate was 14.8% (95% CI: 6.3–26.1%). The estimate was aggregated using both fixed- and random-effect meta-analyses, but only the latter was reported because the heterogeneity was high (I^2 = 99.3%). On many occasions (Davis et al. 2020; Cirulli et al. 2020; Micarelli et al. 2020; Daikhes et al. 2020; Elibol 2020; Klopfenstein et al. 2020; Freni et al. 2020; Kamal et al. 2021; Lechien et al. 2020; Viola et al. 2020), it was not clear to the review team if studies were referring to new or pre-existing symptoms. However, the largest outliers (i.e., Savtale et al. 2021) explicitly referred to new or exacerbated tinnitus.

Vertigo

Nine case reports mentioned rotatory vertigo, which is typical of vestibular dysfunction (N = 10 patients; Chern et al. 2021;

Fadakar et al. 2020; Karimi-Galougahi et al. 2020a; Han et al. 2020; Liu et al. 2020; Malayala and Raza 2020; Maharaj and Hari 2020; Vanaparthy et al. 2020; García-Romo et al. 2020). The tests of vestibular function and the diagnosis were reported in four studies (Fadakar et al. 2020; Maharaj and Hari 2020; Vanaparthy et al. 2020; García-Romo et al. 2020). Of these, one patient was diagnosed with vestibular neuritis (Vanaparthy et al. 2020). One further study reported vestibular neuritis as a final diagnosis without providing details about the tests used (Malayala and Raza 2020).

Rotatory vertigo was investigated and reported in 11 cross-sectional studies. All of the studies used self-reported questionnaires to identify vertigo and mostly did not report specific details about the nature of the vestibular disorder (Davis et al. 2020; Lechien et al. 2020; Carfì et al. 2020; Khalaf et al. 2020; Liang et al. 2020; Micarelli et al. 2020; Salahuddin et al. 2020; Munro et al. 2020; Özçelik Korkmaz et al. 2020; Iltaf et al. 2020; Viola et al. 2020). Four of these studies combined the prevalence of vertigo with dizziness (Davis et al. 2020; Micarelli et al. 2020; Salahuddin et al. 2020; Salepci et al. 2021), although the latter is not necessarily of vestibular origin.

Figure 2(C) shows the forest plot for the prevalence of vertigo (and dizziness, if reported in conjunction with vertigo). The pooled estimate was 7.2% (95% CI: 0.01–26.4%). The estimates were aggregated using both fixed- and random-effect meta-analyses, but only the latter was reported because the heterogeneity was high (I^2 = 99.8%). Once again, all studies in the meta-analysis used self-reported questionnaires. On many occasions (Davis et al. 2020; Carfì et al. 2020; Lechien et al. 2020; Micarelli et al. 2020; Khalaf et al. 2020; Munro et al. 2020; Iltaf et al. 2020; Viola et al. 2020), it was not clear to the review team if the findings were referring to new or pre-existing symptoms. However, the largest outlier (i.e., Davis et al. 2020) combined the prevalence of vertigo with dizziness, which may have inflated the pooled estimate. Indeed, excluding studies that combined these two terms reduced the pooled estimate to 3.4% (95% CI: 1.1–6.9%).

Other ear-related symptoms

Otalgia was reported in five case reports (N = 11; Fidan 2020; Karimi-Galougahi et al. 2020b; Mohan et al. 2020; Ye and Xianyang 2020; Miri and Ajallouеyan 2020). This symptom was also investigated and reported by nine cross-sectional studies (Davis et al. 2020; Lechien et al. 2020; Goërtz et al. 2020; Micarelli et al. 2020; Elibol 2020; Freni et al. 2020; Moradian et al. 2020; Salepci et al. 2021; Stavem et al. 2020). Figure 2(D) shows the forest plot for the prevalence of otalgia in the aforementioned studies. The pooled estimate was 13.1% (95% CI: 7.9–19.3%). The estimates were aggregated using both fixed- and random-effect meta-analyses, but only the latter was reported because the heterogeneity was high (I^2 = 98.3%).

Otitis media was reported in four case reports (often accompanied with otalgia; N = 11 patients; Fidan 2020; Karimi-Galougahi et al. 2020b; Mohan et al. 2020; Ye and Xianyang 2020) and otitis externa in one case study (N = 1 patient; Cui et al. 2020). Retroauricular pain was also reported in one case report (Goh et al. 2020). Other ear-related symptoms were reported in some cross-sectional studies. These symptoms include changes to the ear canal (22%; Davis et al. 2020), ear congestion (19%; Daikhes et al. 2020) and ear fullness (8.6%; Micarelli et al. 2020).

Two more symptoms related to hypersensitivity and overwhelming fear of sounds (i.e., hyperacusis and phonophobia) were investigated and documented in three separate cross-sectional studies. The prevalence of hyperacusis and phonophobia were 35% (Davis et al. 2020) and 27–30% (Membrilla et al. 2020; Rocha-Filho and Magalhães 2020), respectively.

Reporting bias

Because publication bias is well known (de Vries et al. 2018), we investigated this separately for hearing loss, tinnitus, vertigo and otalgia using Egger's and Begg's tests but none were statistically significant.

Quality appraisal

Despite the study designs being of relatively low quality, relative to the accepted hierarchy of evidence in trials (Schünemann et al. 2019), the consensus assessment of bias within each study is shown in the last column of the summary Table 1. In total, five studies were regarded as good, 45 as fair and five as poor. Therefore, despite lacking some details, the majority of studies were deemed to provide unbiased reports of audio-vestibular symptoms. The full assessment checklists of the case reports/series and the cross-sectional studies are reported in Supplementary Materials 4 and 5, respectively.

Discussion

The purpose of this updated systematic review on SARS-CoV-2, COVID-19 and audio-vestibular symptoms was to provide timely evidence for decision-makers. For this update, our search strategies did not include the previously known coronaviruses (i.e., SARS and MERS) because we found no reports of audio-vestibular symptoms associated with these older viruses in our earlier review. Since our first review, the number of studies on COVID-19 and audio-vestibular symptoms has increased from seven to 56. The reporting and methodological qualities have also improved from mostly poor to mostly fair. In addition, the studies are more diverse in terms of design, setting, symptoms and participants. This enabled the review team to conduct meta-analyses to synthesize the prevalence of audio-vestibular symptoms.

Hearing loss

This review identified 56 studies, 30 (54%) of which investigated hearing loss and 29 (52%) reported the presence of this symptom, with an estimated prevalence of 7.6%. Nine case reports/series and cross-sectional studies reported sudden sensorineural hearing loss (SSNHL), which was fairly similar in pattern to typical SSNHL (i.e., mostly unilateral and frequently accompanied by tinnitus; Chandrasekhar et al. 2019). Reported cases varied by age (i.e., both young and older adults) and COVID-19 severity (from very mild [i.e., SSNHL was the only symptom] to severe [i.e., required intubation]). Three patients developed SSNHL before being diagnosed with COVID-19 (Chern et al. 2021; Karimi-Galougahi et al. 2020a; Kilic et al. 2020) and two additional patients developed SSNHL after the acute phase (Lamounier et al. 2020; Lang et al. 2020). In these latter cases, SARS-CoV-2 may not be the sole cause of SSNHL. Each year, for example, approximately 5–20 per 100,000 people experience a

SSNHL (Fetterman et al. 1996). Nevertheless, this does not preclude the possibility that SARS-CoV-2 causes SSNHL. While hearing loss of sudden onset is often idiopathic, many aetiologies have been proposed in the literature, including ischaemia, immune-mediated and viral-related inflammation of the cochlea and vestibulocochlear nerve (Chandrasekhar et al. 2019). To determine if there is an association between COVID-19 and SSNHL, some researchers counted the number of SSNHL cases before and during the pandemic (Chari et al. 2020; Mohammed et al. 2020). Mixed results were found, with one reporting a decrease and another reporting an increase (two more cases) of SSNHL.

Reports of conductive and mixed hearing loss are less frequent than sensorineural hearing loss. They are often accompanied with otitis media and otalgia, consistent with acute otitis media. Given that these symptoms were scarce and could reflect normal life circumstances, they may not be directly related to COVID-19.

The pooled prevalence of hearing loss should be interpreted with caution because the majority of studies used self-reported questionnaires or medical records to obtain COVID-19-related symptoms without appropriate audio-vestibular testing. In some instances, these data were collected retrospectively, meaning the data may be affected by recall bias. Also, few studies had a comparator group. Despite these disadvantages, self-report questions can be worded to ask directly about a change in a symptom relative to pre-COVID-19. However, factors such as social distancing and facial masks may have made communication more difficult and contributed to an increase in the self-reported symptom.

We know that older people and those with lower levels of education tend to under-report hearing loss compared to younger people with higher levels of education Kamil et al. (2015). In our review, there was considerable overlap in prevalence between studies that reported clinical data and studies that provided self-reported data. It would, however, have been interesting to compare hearing level with self-reported data within the same sample. This comparison could have been achieved by splitting the sample based on self-reported outcomes (change versus no change) and checking if people who report a change in hearing also had poorer hearing levels. However, no study provided enough information for this comparison.

Despite the possible association between peripheral neuropathies and GBS (Wong 1997), we reviewed a number of GBS and COVID-19 studies (in excess of 10), but none reported symptoms consistent with auditory neuropathy spectrum disorder (e.g., increased difficulty understanding speech in background noise).

Tinnitus

Tinnitus was the most commonly documented audio-vestibular symptom; it was investigated in 26 (46%) studies and all reported it to be present, with an estimated prevalence of 14.8%. Again, the pooled prevalence of tinnitus should be interpreted with caution because in many cases, it was collected using non-validated self-reported questionnaires and with no comparator group. In addition, some studies distributed their questionnaires via national tinnitus associations, which may bias the findings and inflate the pooled estimate of tinnitus (Beukes et al. 2020). Furthermore, tinnitus was not thoroughly investigated in most of the studies, meaning that there is a dearth of knowledge about its onset, duration, severity, characteristics and psychological impact. Most studies reported tinnitus as an early onset symptom, but a few others documented some cases with later acquisition. The tinnitus was reported as generally lasting from a few days to a few weeks, but may also persist. The mean score as measured with the Tinnitus Handicap Inventory indicated slight or no perceived activity limitations or participation restrictions (Freni et al. 2020). The characteristics of tinnitus, when reported, were diverse, ranging from intermittent to continuous, and was sometimes described as pulsatile (Viola et al. 2020). When the impact of the pandemic on people with pre-existing tinnitus was evaluated, the tinnitus was regarded as more bothersome, especially among females and young adults; this could partially be attributed to lifestyle changes (e.g., increased childcare; Beukes et al. 2020).

Tinnitus has a complex bidirectional association with anxiety and stress (Mazurek et al. 2015), both of which were common amongst the general population during this pandemic (Salari et al. 2020). That is, non-auditory factors such as emotional distress could trigger or exacerbate pre-existing tinnitus.

Vertigo

Vertigo was the least commonly reported audio-vestibular symptom; it was investigated in 20 (36%) studies, with an estimated prevalence of 7.2%. Similar to the previously reported symptoms, caution should be exercised when interpreting the pooled prevalence because the majority of studies relied on self-reported questionnaires and four of the cross-sectional studies combined the prevalence of vertigo with dizziness (Davis et al. 2020; Micarelli et al. 2020; Salahuddin et al. 2020; Salepci et al. 2021), and the latter is not necessarily of vestibular origin. Combining the prevalence of both of these symptoms will increase the pooled estimate because the latter is a common neurological manifestation of COVID-19 (Mao et al. 2020). There was also a concern that some researchers used the terms vertigo and dizziness interchangeably; the latter is a commonly reported symptom in COVID-19 patients. This may have inflated the pooled prevalence estimate. The final diagnosis, as reported in two case reports (Malayala and Raza 2020; Vanaparthy et al. 2020), was vestibular neuritis, an inflammation of the vestibulocochlear nerve. Anxiety and stress can also trigger vertigo attacks (Balaban and Jacob 2001; Chen et al. 2016), and these two factors, as mentioned earlier, are common among the general population during the COVID-19 pandemic (Salari et al. 2020).

Mechanisms

It is possible that SARS-CoV-2 can enter the body via 'air, sea and land' (aerosols, blood and nervous system, respectively). Aerosol spread involves SARS-CoV-2 moving from one cell to another. It is unclear if aerosols in the middle ear can reach the auditory nerve. Some small RNA viruses (enteroviruses) can enter the blood stream via the intestine and be transported around the body. SARS-CoV-2 is a large virus, the quantity in the blood has not been found to be high, and it would still need to find a way to cross the blood brain barrier (perhaps due to an inflammatory response). SARS-CoV-2 could spread throughout the nervous system, perhaps gaining access via the olfactory nerve and bulb. In this case, one might expect an association between loss of taste/smell and audio-vestibular symptoms. Although the pathophysiology of any audio-vestibular disorder

caused by COVID-19 is unknown, some potential mechanisms have been proposed including:

- Cochleitis or neuritis caused by viral involvement of the inner ear or the vestibulocochlear nerve,[1] potentially leading to vertigo, tinnitus and hearing loss (Lang et al. 2020).
- Cross-reactions: Antibodies or T-cells may misidentify inner ear antigens as the virus, leading to accidental damage to the inner ear (Lang et al. 2020).
- Vascular disorders: Cochlea and semicircular canals have no collateral blood supply, meaning that they are largely susceptible to ischaemia (Chandrasekhar et al. 2019). Several cardiovascular manifestations, including a coagulation abnormality, have been reported in COVID-19 patients (Whittaker et al. 2020; Kwenandar et al. 2020; Mao et al. 2020). The sequelae of such manifestations may result in inner ear thrombosis or hypoxia, and could explain, for example, sudden hearing loss.
- Immune-mediated: Sequelae of immune-mediated disorders (e.g., overzealous production of proinflammatory cytokines) may negatively affect the audio-vestibular system (Degen et al. 2020).

Limitations

The quality of almost all studies was regarded as weak because they were uncontrolled and prone to selection and information bias. Despite this weakness, the quality of evidence has improved since our first review. Notably, missing details on audio-vestibular symptoms is no longer a common feature. Many case reports/series provided full audiometric data and this improved the interpretation of these studies. For example, the full audiometric data before, during and after contracting COVID-19 were reported in Lamounier et al. (2020). While some cross-sectional studies used an appropriate study design, others suffered from major flows. For example, Mustafa (2020) and Daikhes et al. (2020) did not report sufficient details about the control group. Comparing unmatched groups of participants (e.g., older adults with otologically normal young adults) may result in a statistically significant difference that is unrelated to COVID-19. Another cross-sectional study involved only those who were asymptomatic in the experimental group, which would diminish detection of any audio-vestibular symptoms (Dror et al. 2020).

The pooled estimates are a combination of confirmed, probable and suspected COVID-19 cases. Our preference would have been to pool the prevalence of confirmed cases only, but it was not possible to extract this information from some of the studies. In addition, hearing health professional would find it helpful to know the prevalence of combinations of symptoms (e.g., hearing loss and tinnitus), but almost no cross-sectional study report the co-occurrence of audio-vestibular symptom.

In around 50% of studies, it was not possible to be sure the authors were reporting a new (or deterioration) symptom. Instead, some of these studies might have asked a state question (e.g., how is your hearing). We already know, for example, that the prevalence of hearing disability and tinnitus within UK adult population is around 11 and 17%, respectively (Dawes et al. 2014). Therefore, we would urge caution when interpreting the pooled prevalence estimate because the proportion may have overestimated the change or deterioration. Studies that measure a change and compare the findings with appropriate controls are urgently required.

The reported quality rating does not speak to the overall evidence quality because, as mentioned earlier, almost all studies used uncontrolled designs and may be subject to confounding, measurement error, and selection and information bias (Hammer et al. 2009). There is a need for high-quality studies that provide a comprehensive assessment of audio-vestibular function in COVID-19 and controls. This should include measures of impairment (pure tone audiometry), hearing difficulty (lab-based speech-in-noise and self-report), and objective measures to identify the location of any dysfunction. Given the reported symptom of fatigue that often persists after the acute phase of COVID-19, measures of listening effort and fatigue might also be appropriate. Our team is currently conducting a comprehensive assessment of auditory function in post-hospitalised COVID cases and controls.

Conclusion

The quality and quantity of studies have increased since our first review in June 2020, with multiple reports of audio-vestibular symptoms associated with COVID-19. However, much of the evidence is based on case reports and surveys (the latter often retrospective, so relying on self-report and recall). There is a dearth of studies reporting a comprehensive assessment of audio-vestibular function in COVID-19 patients and appropriately matched controls.

Note

1. Currently there is little evidence that SARS-CoV-2 is neurotropic. For example, Frontera et al (2021) have shown that neurological disorders in hospitalised COVID-19 cases are primarily a sequelae of severe systemic illness such as admission to an ICU or a result of stroke.

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Disclosure statement

The authors declare no conflict of interest.

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