Serum vitamin D concentration is lower in patients with tinnitus: a meta-analysis of observational studies

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Systematic Review

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Serum vitamin D concentration is lower in patients with tinnitus: a meta-analysis of observational studies

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Abstract

Background: Tinnitus is a highly prevalent and frequently disabling condition, such that the identification of possible causal mechanisms would yield significant clinical and social benefits. Since vitamin D (Vit D) is involved in the pathogenesis of several ear disturbances, we review here the current scientific literature addressing the relationship between Vit D status and tinnitus.

Methods: An electronic search was conducted in PubMed, Scopus and Web of Science with the keywords "tinnitus" and "Vitamin D" or "Vit D" or "25OH-D" or "cholecalciferol" or "ergocalciferol" or "hydroxycholecalciferol", without date (i.e., up to November 10, 2022) or language restrictions, in accordance with a protocol based on the transparent reporting of systematic reviews and meta-analysis (PRISMA) 2020 checklist, for identifying studies which assayed serum Vit D concentration in patients with or without tinnitus.

Results: Three observational, case-control studies encompassing four cohorts and totaling 468 patients with (n=268) or without tinnitus (n=200) were included in this meta-analysis. Pooled analysis with quality effects models evidenced significantly reduced serum Vit D levels in patients with tinnitus compared to those without (weighted mean difference [WMD], -6.2 ng/mL; 95%CI, -10.3 to -2.1 ng/mL; I^2, 56%). Serum Vit D was found to be 22% lower in patients with tinnitus compared to those without.

Conclusions: Lower serum Vit D levels may be associated with tinnitus, thus paving the way to plan future trials aimed at exploring whether Vit D supplementation may aid in preventing and/or improving tinnitus.

Keywords: Vitamin D; 25OH-D; cholecalciferol; ergocalciferol; hydroxycholecalciferol; tinnitus

Introduction

Tinnitus, a term deriving from the Latin word “tinnire” (i.e., “to ring”) is conventionally defined as perception of a particular sound (like ringing, buzzing, roaring, clicking, hissing, humming, whooshing, throbbing, etc.) in the lack of vibration of an external elastic body, which can be perceived as subjective or objective (i.e., can be heard by an outside observer), pulsatile (e.g., most often heart rhythmic) or not [1,2]. According to recent data, the different forms of tinnitus have a dramatically high burden in the general population, with annual incidence in adults ranging between 1-14% (2% with severe forms) and prevalence of 10% in young adults, increasing to 14% in middle-aged adults, and peaking at 24% in older adults (around 2.3% with severe phenotype), respectively [3]. The burden of this condition has also consistently increased during the coronavirus disease 2019 (COVID-19) pandemic [4], due to direct viral injury of sensorineural hearing apparatus [5], compounded by a considerable onset of COVID-19-realted psychosocial conditions in the general population (e.g., stress, anxiety and depression) that may have worsened a pre-existing tinnitus [6]. This epidemiologic data portrays the picture of a serious public health issue, since the consequences on the daily quality of life of the people affected by permanent (e.g., long-lasting or even chronic) tinnitus may be devastating, encompassing hyperacusis, concentration and communication derangements, annoyance, irritability, depression, anxiety, sleep disturbances, insomnia [7], up to development of suicidal thoughts needing urgent psychiatric intervention [8].

The pathogenesis of tinnitus is complex and often multifactorial, recognizing pathologies of the outer ear (excessive earwax, tympanic membrane injuries or infections), middle ear (i.e., acute or chronic infections, otosclerosis, injuries due to heavy noise exposure, ototoxic drugs usage, middle ear tumors such as glomus tympanicum, muscle spasms, Eustachian tube dysfunction), inner ear (Meniere disease, cochlear injuries, age-related hearing loss or presbycusis), acoustic nerve pathologies (vestibular schwannoma,

acoustic neuroma, conflict with itracranial arteries), as well as a kaleidoscope of other causal factors, some located in the nearby tissues (e.g., disorders or malformations of blood vessels, ostemalacia, Paget's disease, cerebellopontine-angle tumors, temporomandibular joint disorder), others relatively far from the hearing apparatus such as hyperactivity of auditory brain neurons, multiple sclerosis, idiopathic intracranial hypertension, dural blood vessels abnormalities, head and/or neck injuries, musculoskeletal cervical imbalance, anemia, hypertiroidism and hypertension, along with somatoform or phobic disorders [9-11]. Notably, although it is important to remember that tinnitus is always a symptom of an underlying pathology and not a disease in itself, the clinical cause(s) or the triggering factor(s) often remain frequently conjectural or even completely unidentifiable [12].

Reliable epidemiologic evidence has been recently provided that lower serum vitamin D (Vit D) levels may be associated with hearing impairment and/or sensory-neural hearing loss [13,14], and balance disorders [15], thus persuading us to conduct a systematic literature search and meta-analysis to explore whether an epidemiologic association may exist between low serum Vit D status and tinnitus.

Materials and Methods

PRISMA Guidelines

This systematic literature review and meta-analysis was conducted following a protocol based on the transparent reporting of systematic reviews and meta-analysis (PRISMA) 2020 checklist (Suppl. File 1).

Search strategy

We conducted an electronic search in Medline (using the PubMed interface), Scopus and Web of Science (WoS), with the keywords "tinnitus" and "Vitamin D" or "Vit D" or "25OH-D" or "cholecalciferol" or "ergocalciferol" or "hydroxycholecalciferol", without date (i.e., up to November 10, 2022) or language restrictions. Title, abstract and full text of

all documents that we could first identify based on the aforementioned search criteria were systematically screened by two authors (R.N. and G.L.), and those reporting the results of studies which investigated serum Vit D levels in patients with or without tinnitus were finally included in our analysis. The reference list of all pertinent articles was also hand-searched by means of forward and backward citation tracking, for retrieving additional and potentially eligible documents.

Statistical analysis

We carried out a meta-analysis of pertinent studies for estimating the weighted mean difference (WMD) and its 95% confidence interval (95% CI) of serum Vit D levels in subjects with or without tinnitus. The pooled analysis was conducted using both the quality and the random effects models; this latter approach was used for adjusting for possible heterogeneity, which was calculated with χ^2 test and I^2 statistics, whilst the risk of publication bias was assessed with funnel plots. The statistical analysis was performed using MetaXL, software Version 5.3 (EpiGear International Pty Ltd., Sunrise Beach, Australia). This study was conducted in accordance with the declaration of Helsinki and within the terms of local legislations. The investigation was exempted from ethical committee approval as it is not locally required for pooled analyses, nor received any funding.

Results

Study identification and selection

After excluding replicate publications among the three scientific search platforms, a total of 72 articles were originally detected using the predefined criteria and by hand-searching the reference lists, 69 of which ought to be eliminated because they did not present a comparison of serum Vit D levels in patients with or without tinnitus (n=29), did not assessed tinnitus (n=16) or Vit D status (n=5), lacked a control group of subjects

without tinnitus (n=3), were review articles (n=11), editorial material (n=3) or case reports (n=2). A final number of 3 studies (all observational, case-control), with four cohorts and totaling 468 patients with (n=268) or without tinnitus (n=200) were finally included in our meta-analysis [16-18]. The main characteristics of these studies are summarized in Table 1.

Meta-analysis

In all three studies and four cohorts, the serum value of Vit D was found to be lower in patients with tinnitus than in those without. The pooled analysis performed using the quality effects models confirmed a significantly negative WMD of Vit D concentration in patients with tinnitus compared to those without (WMD, -6.2 ng/mL; 95%CI, -10.3 to -2.1 ng/mL; I^2, 56%)m, though such difference was largely determined by the study of Nowaczewska et al. [18], expressing the largest sample size (n=300).

Overall, the serum Vit D concentration was found to be 22% lower in patients with tinnitus compared to those without. A slightly lower but still significant difference was also found using the random effects model (WMD, -4.6 ng/mL; 95%CI, -8.0 to -1.21 ng/mL). The funnel plot, as shown in figure 2, did not reveal a substantial publication bias.

Discussion

One of the first studies that underpinned a potential association between Vit D deficiency and impairment of sensory-neural hearing system was published by Gerald B. Brookes, in 1983 [19]. Briefly, this author described the case of ten patients with bilateral cochlear deafness, who were also found to be Vit D deficient. Two years later, the same author reported other 27 patients affected by bilateral deafness and concomitant Vit D deficiency [20]. Notably, since cochlea demineralization resulting in serious morphological changes and impaired neurosensoral hearing transmission was identified as the underlying cause, Vit D replacement therapy was initiated, yielding to hearing improvement in 50% of patients in whom the treatment response become available. In the same year Gerald B.

Brookes also noted that Vit D deficiency was commonplace in patients with otosclerosis, causing impairment of cochlear structure and deafness [21]. Although in none of these articles the association between tinnitus and Vit D status was explored, the evidence that this important vitamin would interplay with hearing fitness had been unraveled. It is hence not surprising that a number of very recent studies have highlighted that Vit D deficiency may have causal associations with and chronic otitis media [22], development of benign paroxysmal positional vertigo [23] and its recurrence [24], as well as with old age deafness and presbycusis [25], all factors that deeply contribute to the pathogenesis of haring impairment and consequent tinnitus.

Although we could only find a limited numbers of observational studies linking serum Vit D with the presence or absence of tinnitus (n=3, with four cohorts, with one including 300 out of 468 individuals), the results emerged from of our meta-analysis reveal that serum Vit D levels are frequently decreased (by around 22%, according to our estimation) in patients with tinnitus compared to those without, thus pointing out a definite role for Vit D metabolism in development and/or amplification of this seriously debilitating hearing disturbance.

One article that was excluded from our analysis because no final data on vitamin D status in patients with tinnitus were presented deserves special mention. Briefly, the authors administered a questionnaire to 34,576 UK adults aged between 40-69 to garner information on their nutritional status. Vitamin D intake was defined as quintiles of dietary patterns, from low to high. In a final regression models including several demographical variables, use of ototoxic therapy, noise exposure, alcohol consumption and cardiovascular disease, subjects in the highest quintile of vitamin D intake did not display a significantly different odds of tinnitus compared to those in the lowest quintile of vitamin D intake (OR, 0.99; 95%CI, 0.88-1.11; p=0.535), whilst a higher intake of vitamin D was found to be associated lower odds of hearing difficulties (1^{st} vs. 5^{th} quintiles of Vit D intake: OR, 0.90;

95%CI, 0.81-1.00; p=0.013) [26]. Yet, serum Vit D was not measured in patients with or without tinnitus, such that it cannot be assessed to what extent Vit D status may have impacted tinnitus development or perception in this study.

We could also identify another interesting study, which did not compare vitamin status in patients with or without tinnitus, but still presented interesting findings [27]. Briefly, the author assessed Vit D status in 35 adult subjects with bilateral tinnitus (age range, 20-50 years), who were supplemented with oral vitamin D (50000 IU/week) for 3 months. After completing the supplementation period, the tinnitus handicap inventory (THI; a self-reported, 25-item questionnaire to assess the severity of perceived tinnitus handicap) substantially decreased by nearly 40%, from 2.50±0.88 to 1.47±0.57 ($p<0.001$).

Based on our findings, we propose that several aspects in Vit D deficiency may actually contribute to enhance the risk of developing or worsening tinnitus, as summarized in table 2.

One of the most obvious mechanisms linking Vit D deficiency to hearing problems encompassed the development of rickets and/or osteomalacia affecting the osteoskeletal system, including skull bones [28]. Thus, besides cochlear demineralization and the resulting neurosensoral hearing transmission impairment which is per se a major cause of tinnitus [19], Vit D-related demineralization of petrous temporal bone may reduce the perception of external (environmental) sounds, enhancing internal resonance and transmission of internal sounds caused by voice, respiration or vascular pulsation among others, thus ultimately triggering tinnitus [29]. This is especially true if one considers that the woven bone of the otic capsule contains a considerably high concentration of calcium [30], such that an impairment of Vit D metabolism may have a profound and unfavorable impact on adequate mineralization of this skeletal district.

Then, Vit D deficiency is associated with an increased risk of developing a vast array of pathologies of the hearing system such as acute and chronic otitis [22], tympanosclerosis

[31], otosclerosis [21], but also predisposes to accelerated deafness and presbycusis [25]. A strict relationship has been recently underpinned between stress, anxiety and depression-like behaviors [32,33], in that patients with low Vit D serum levels were found to be at enhanced risk of developing these psychophysiological disorders. In turn, an increased burden of stress, anxiety and depression could act by directly triggering newly onset tinnitus, or even by amplifying a pre-existing hearing disturbance [7]. Notably, the relationship between tinnitus and depression is especially important, since it follows a bi-directional path, where depression may predispose to development or intensification of tinnitus, whilst onset or aggravation of tinnitus may then worsen depression, thus generating a devastating biological and psychological loop.

It should then be considered that Vit D deficiency may be a bystander rather than an active player in the complex pathogenesis of tinnitus. For example, Vit D deficiency is commonplace in patients with extremes of body weight, thus in those with malnutrition [34], as well as in those with overweight or obesity [35]. In turn, tinnitus appears to be more prevalent in overweight/obese patients (e.g., due to pseudotumor cerebri syndrome or other disturbances) [36,37], as well as in those underweight [38] and/or with recent weight loss [39], in whom a reduced fat tissue lining may predispose a major propagation of internal sounds to the cochlea or amplify bone-conduction sounds [40]. Finally, Vit D has been convincingly link to an enhanced risk of developing hypertension [41], since a recent meta-analysis emphasized that hypertensive patients have an increased odds of tinnitus (OR, 1.37; 95%CI: 1.16-1.62) [42].

The results of our meta-analysis may have some potentially useful clinical implications. First, the evidence that tinnitus more frequently and more intensely develops in patients with lower values of serum Vit D should persuade patients and clinicians to routinely assess Vit D status after diagnosing tinnitus, since this will enable to correct potential deficiencies, thus lowering the risk of developing a large number of health

disorders that frequently accompany Vit D deficiency (i.e., osteoporosis, cardiovascular and autoimmune diseases, infections, cancer, metabolic syndrome and diabetes among others) [43,44]. As concerns the specific management of tinnitus, the identification of the underlying cause remains elusive in a large number of patients, whilst the treatment remains mostly symptomatic (i.e., encompassing psychotherapy, psychoactive drugs administration, physical therapy, use of individualized sound stimulation or masking devices, cognitive behavioral or tinnitus retraining therapy) and not completely resolutive in the vast majority of cases even when a possible cause can be identified [45]. Therefore, although large randomized clinical trials on Vit D supplementation in tinnitus patients are still unavailable to the best of our knowledge, the evidence emerged from the recent study of Abdelmawgoud Elsayed [27], that Vit D supplementation was accompanied by a substantial reduction of mental and physical impairment due to idiopathic tinnitus, leads the way to explore the possibility of administering Vit D to patients with tinnitus with concomitantly low serum levels of this important vitamin.

Conclusions

Taken together, the results of our study show that lower serum Vit D levels may be associated with tinnitus, thus paving the way to plan future randomized prospective trials aimed at exploring as to whether Vit D supplementation may aid in preventing and/or reducing tinnitus-related impairment.

Author Contributions: Conceptualization, R.N. and G.L.; methodology, R.N. and G.L.; software, G.L.; formal analysis, R.N., C.M. and G.L.; data curation, G.L. and C.M.; writing—original draft preparation, G.L.; writing—review and editing, R.N., B.M.H. and C.M. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: Not applicable. The investigation was exempted from ethical committee approval as it is not locally required for pooled analyses.

Informed Consent Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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Table 1. Main characteristics of studies reporting serum vitamin D concentration in patients with or without tinnitus.

Authors	Setting	Study design	Sample size	Age and sex	Vitamin D assessement
Acra-Tolari R et al., 2022 [16]	Dominican Republic	Observational, case-control	Postmenopausal women with tinnitus (5) or with history of hearing difficulty without tinnitus (n=39)	Entire cohort: median age, 74 (IQR, 12) years and 100% women	Not described
Fanimolky et al., 2022[a] [17]	Iran	Observational, case-control	Ear cholesteatoma patients with (n=43) or without (n=19) tinnitus	Entire cohort: mean age, 32±1 years and 34% females	ELISA
Fanimolky et al., 2022[b] [17]	Iran	Observational, case-control	Chronic otitis media patients with (n=19) or without (n=43) tinnitus	Entire cohort: mean age, 34±1 years and 34% females	ELISA
Nowaczewska et al., 2021 [18]	Poland	Observational, case-control	Patients with tinnitus (n=201) and matched healthy controls (n=99)	Tinnitus cohort: mean age, 49.9±13.2 years and 54% females; control cohort: mean age, 48.3±17.5 years and 52% females	Not described

ELISA, Enzyme-linked immunosorbent assay; IQR, interquartile range

Table 2. Mechanisms by which low serum vitamin D levels may trigger or aggravate tinnitus.

- Increased risk of tympanosclerosis
- Higher likelihood of developing acute or chronic middle ear pathologies
    - Acute or chronic otitis media
    - Otosclerosis
    - Cochlear demineralization
- Enhanced odds of hypertension
- Increased risk of advancing age deafness and presbycusis
- Major perception of pre-existing tinnitus
    - Demineralization of petrous temporal bone
    - Stress, anxiety and depression

Figure 1. Weighted mean difference (WMD) and 95% confidence interval (95% CI) of serum vitamin D (Vit D) values in patients with or without tinnitus.

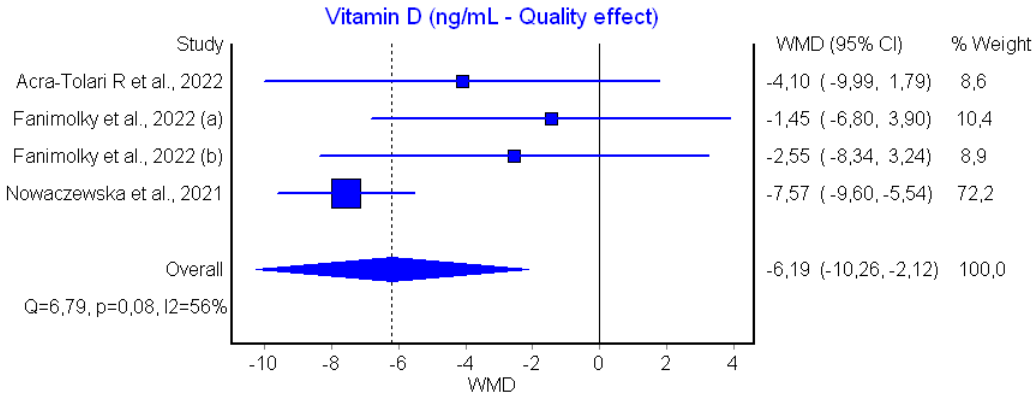
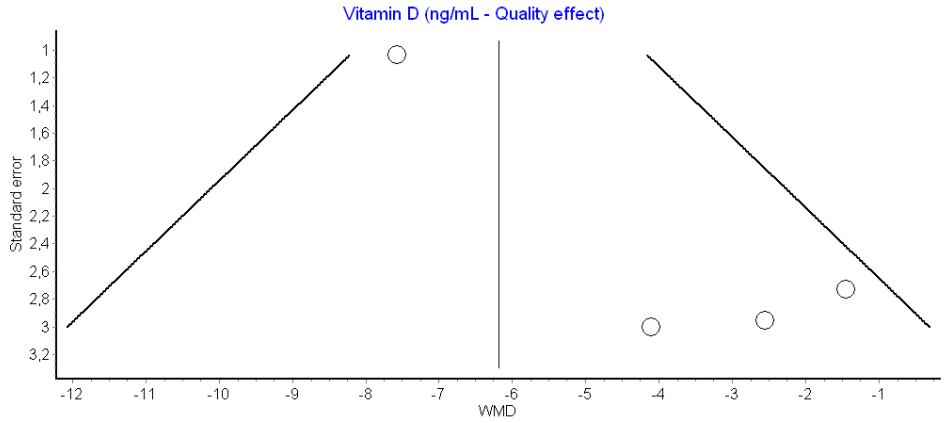


Figure 2. Funnel plot of observational studies reporting serum vitamin D concentration in patients with or without tinnitus.



Supplementary File 1.

PRISMA 2020 Checklist

\	Item #	Checklist item	Location where item is reported
TITLE			Page 1
Title	1	Identify the report as a systematic review.	
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 1-2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 2
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 2
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 2
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 2
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 2
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding	Page 2

\	Item #	Checklist item	Location where item is reported
		sources). Describe any assumptions made about any missing or unclear information.	
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 2
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 2-3
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 2-3
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 3
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 3
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 3
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 3
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 3
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 3
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 3
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 3
Study characteristics	17	Cite each included study and present its characteristics.	Page 3, Table 1
Risk of bias in	18	Present assessments of risk of bias for each included study.	Page 4,

\	Item #	Checklist item	Location where item is reported
studies			Figure 2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 3-4; Table 1
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 3-4
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 4; Figure 1
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 4
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 4
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Page 4, Figure 2
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	N/A
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 4-6
	23b	Discuss any limitations of the evidence included in the review.	Page 4-6
	23c	Discuss any limitations of the review processes used.	Page 4-6
	23d	Discuss implications of the results for practice, policy, and future research.	Page 4-6
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	N/A
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	N/A
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 7
Competing interests	26	Declare any competing interests of review authors.	Page 7
Availability of	27	Report which of the following are publicly available and where	Page 7

\	Item #	Checklist item	Location where item is reported
data, code and other materials		they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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