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The association between subjective tinnitus and cognitive performance: protocol for systematic review and meta-analysis

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SCHOLARONE™
Manuscripts

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3 1 **The association between subjective tinnitus and cognitive performance:**
4 **protocol for systematic review and meta-analysis**
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8 4 Nathan A Clarke ^{1,2}, Michael Akeroyd ¹, Helen Henshaw ² & Derek J Hoare ²
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44 **and tables)**
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31 **ABSTRACT**

32 **Introduction:**

33 Subjective tinnitus is very common and has a number of comorbid associations including depression,
34 sleep disturbance and concentration difficulties. Concentration difficulties may be observable in
35 people with tinnitus through poorer behavioural performance in tasks thought to measure specific
36 cognitive domains such as attention and memory (i.e. cognitive performance). Several reviews have
37 discussed the association between tinnitus and cognition, however, none to date have investigated the
38 association between tinnitus and cognitive performance through meta-analysis. Furthermore, there has
39 been little overlap between sets of studies that have been included in previous reviews, potentially
40 contributing to the typically mixed findings that are reported.

41 **Methods and analysis:**

42 This systematic review aims to comprehensively review the literature and quantitatively synthesize
43 relevant data to determine associations between subjective tinnitus and cognitive performance.
44 Methods are reported according to Preferred Reporting Items for Systematic Reviews and Meta-
45 Analyses Protocols (PRISMA-P). All study designs will be eligible for inclusion with no date
46 restrictions on searches. Studies eligible for inclusion must contain adult participants (≥ 18 years) with
47 self-reported, subjective tinnitus and a behavioural measure of cognitive performance. Meta-analysis
48 will be reported via correlation for the association between tinnitus and cognitive performance.

49 **Ethics and dissemination:**

50 No ethical issues are foreseen. Findings will be reported in a student thesis, at national and
51 international ENT/audiology conferences and by peer-reviewed publication.

52 **Systematic review registration number:**

53 PROSPERO 2018 CRD42018085528.

55 **Strengths and limitations of this study**

- 56 • This systematic review and meta-analysis protocol poses a clearly formulated research
57 question and methodology to investigate a common clinical complaint of tinnitus patients;
58 peer-reviewed evidence to date will be synthesised.
- 59 • Grey literature and dissertation abstracts will not be included

61 **Introduction**

62 Subjective tinnitus is the experience of sound in the ears or head in the absence of an external source
63 and is commonly considered a symptom of damage within the auditory system.¹ Most individuals
64 who experience tinnitus do not find it bothersome but a significant proportion are disturbed by it,
65 often reporting a variety of adverse comorbid associations including anxiety, depression, disturbed
66 sleep, or concentration difficulties.²⁻⁴ Concentration difficulties can be conceptualised as failures of

67 cognitive performance in various domains such as attention and memory^{5,6} and previous research has
 68 implicated tinnitus as impacting cognitive domains including executive functions, attention and
 69 working memory.⁷⁻⁹ Investigating the potential impact of tinnitus on cognitive performance is further
 70 complicated by the strong associations that tinnitus shares with depression and anxiety, which can
 71 independently negatively impact cognitive performance.^{4,10,11}

72 Several reviews have explored the relationship between tinnitus and cognition.¹²⁻¹⁵ We note
 73 that all of these are narrative reviews; no review has quantitatively synthesised the literature
 74 specifically concerning tinnitus and behaviourally measured cognitive performance. An overview of
 75 previous reviews and their methodologies is provided in Table 1.

76 *Table 1. Overview of previous reviews investigating cognition and tinnitus*

Study	Databases searched	Example search strategy provided	Number of records retrieved during database search	Number of studies included in review	Synthesis of association between cognition and tinnitus
Trevis et al. (2017)	PsycINFO, MedLine	(1) tinnitus AND psych* (all fields), (2) tinnitus AND mood (all fields), (3) tinnitus AND depress* (all fields), (4) tinnitus AND anx* OR stress (all fields)	725	35	Meta-analysis of 'psychological functioning' in tinnitus participants. Narrative review of association between 'cognitive functioning' (n = 16); i.e. behavioural cognitive task performance and chronic tinnitus, awareness and severity
Mohamad et al. (2016)	PubMed	(((((tinnitus[Title]) AND cogniti*[Title])) OR ((tinnitus[Title]) AND attention[Title])) OR ((tinnitus[Title]) AND memory[Title]))	65	9	Narrative review of 'behavioral research' addressing the impact of tinnitus and its severity of various aspects of cognitive performance in domains of working memory and attention.
Tegg-Quinn et al. (2016)	PubMed, MedLine, CINAHL, SCOPUS, EMBASE	(tinnitus) and (cognition OR memory OR attention OR concentration OR cognitive function OR mental activity) NOT (infant OR child OR adolescent OR paediatric OR animal OR balance OR hyperacusis OR implant OR pharmaceutical OR drugs)	2236	18	Narrative review of behavioural cognitive tasks, electrophysiological correlates of cognition and self-reported cognitive function measures.
Andersson and McKenna (2006)	Not reported	Not reported	Not reported	Not reported	Narrative review of 'cognitive deficits' (i.e. behavioural cognitive tasks), 'cognitive bias' and 'conscious appraisal of tinnitus'.

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 79 Andersson and McKenna¹² were the first to review the relationship between cognition and
 80 tinnitus, detailing three separate but related lines of cognitive research. The strands of research
 81 included neuropsychological studies involving attention, cognitive bias (concerning selective attention
 82 and memory) and appraisal (i.e. conscious recollection) of tinnitus. Tegg-Quinn et al.¹³ performed a
 83 systematic review of all studies pertaining to the impact of tinnitus upon cognition in adults. The
 84 review described studies that included both behavioural and electrophysiological measures and
 85 concluded that tinnitus impairs cognition through impacting on executive control of attention.
 86 Mohamad et al.¹⁴ performed a narrative review of the behavioural evidence concerning the

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3 87 consequences of tinnitus and its severity on cognition. They concluded that there was suggestive
4 88 evidence for tinnitus being associated with poorer performance in behavioural tasks attempting to
5 89 measure executive attention, selective attention and working memory. Trevis et al.¹⁵ performed a
6 90 systematic review and meta-analysis of psychological functioning in chronic tinnitus. The authors
7 91 predominantly investigated the presence and severity of tinnitus in relation to emotional wellbeing
8 92 through meta-analysis, while cognitive function (i.e. cognitive performance) was described through a
9 93 narrative review. Of the recent reviews that discuss cognition through behavioural performance in
10 94 tinnitus participants, there is a notable lack of overlap in the studies that met criteria for inclusion in
11 95 the final reviews; e.g. Mohamad et al.¹⁴ reviewed nine studies and Trevis et al.¹⁵ reviewed a total of
12 96 thirty-five studies (with sixteen of these concerning cognitive performance), however, only three
13 97 studies were included in both reviews. Therefore, previous work has essentially investigated the
14 98 association between tinnitus and cognitive performance with different datasets. Like any statistical
15 99 technique, meta-analysis is only as robust as the data that is inputted. It is, therefore, essential to
16 100 include as much relevant data as possible - through a comprehensive search strategy - to ensure that
17 101 conclusions are based on all evidence for an effect of tinnitus on specific cognitive domains.

18 102 Tinnitus is a symptom of heterogeneous and often unknown aetiologies. It is, therefore,
19 103 inherently difficult to define and specify within the context of a systematic review. Different inclusion
20 104 criteria and working definitions of tinnitus are likely to significantly influence the records included
21 105 within a review. For example, Trevis et al.¹⁵ defined 'chronic tinnitus' as participants who had
22 106 experienced tinnitus for at least one month. An alternative approach would be to not attempt to
23 107 temporally specify a population, but rather investigate this variable through further quantitative
24 108 analysis if feasible. With regards to domains of cognitive performance, the aforementioned reviews
25 109 have implicated tinnitus as impacting executive attention, although the evidence is not conclusive:
26 110 additional domains of cognitive performance are also potentially associated with tinnitus, including
27 111 selective attention and working memory¹²⁻¹⁵. A promising approach to foster empirically valid insights
28 112 into any association between cognition and subjective tinnitus is through evaluating and categorising
29 113 tests of cognitive performance according to the theoretical constructs that they are thought to
30 114 measure¹⁶. Any associations between categorised measures of cognitive performance and subjective
31 115 tinnitus can then be subjected to meta-analysis in order to understand which cognitive domains are
32 116 associated with tinnitus, as well as the best estimate of any such effect. To summarise, although
33 117 several authors have reviewed associations between tinnitus and cognitive performance assessed
34 118 through behavioural measures, these have been through narrative syntheses, discussing different sets
35 119 of studies derived from different search strategies. A comprehensive, quantitative investigation of the
36 120 association between tinnitus and cognitive performance, building on earlier efforts in this field and
37 121 exploring the underlying theoretical domains of cognition involved, is therefore both necessary and
38 122 timely.

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3 123 The primary aim of this work is to comprehensively review the literature and synthesize
4 124 relevant data to determine the associations between self-reported subjective tinnitus and cognitive task
5 125 performance in adults. If possible, a secondary examination of patient characteristics (e.g. age or
6 126 gender) or commonly used patient-reported outcomes (e.g. depression or anxiety) and their influence
7 127 on any association between subjective tinnitus and cognitive performance will also be conducted.
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13 130 **Methods and Analysis**

14 131 The methodology of this review is reported in accordance with the Preferred Reporting Items for
15 132 Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) checklist¹⁷. Specified roles of named
16 133 authors are identified throughout the review protocol.
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20 21 135 **Eligibility criteria**

22 136 Only published or in-press, peer-reviewed journal articles will be considered. Articles that are not
23 137 written in English or have no English language translation available will be excluded as the review
24 138 team does not have resource available to support translation. No date restriction will be applied.
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28 140 Review inclusion criteria are specified according to Participant, Intervention (or Interest),
29 141 Comparator, Outcome and Setting (PICOS) characteristics.

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33 143 *Participants:* Studies including adults (≥ 18 years) with subjective tinnitus. Studies that include both
34 144 children (< 18 years) and adults will be excluded, unless the adult data are reported separately.

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36 145
37 146 *Intervention/Interest:* Subjective tinnitus (via self-report, tinnitus severity scale, item or established
38 147 tinnitus questionnaires).

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42 149 *Comparator:* A minimum of one established measure of cognitive performance (behavioural or self-
43 150 report).

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46 152 *Outcome measures:* An association between tinnitus and cognitive performance. Where available,
47 153 data for associations between subjective tinnitus and additional potential moderator variables will be
48 154 extracted, such as measures of anxiety or depression.
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52 156 *Study design:* Any type of study design and setting will be considered.
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55 158 **Information Sources and Search strategy**

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3 159 A systematic search strategy will be employed to identify completed, peer-reviewed journal articles
4 160 from the following bibliographic databases: MEDLINE (via Ovid SP), EMBASE (via Ovid SP),
5 161 PsycINFO (via Ovid SP), ASSIA (via ProQuest), CINAHL (via EBSCO Host), Scopus, PubMed, and
6 162 Web of Science (Science and Social Science Citation Index). Searches will be performed during
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8 163 01/02/18 – 01/03/18.

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10 164 The search terms to be used in this systematic review were identified using free text,
11 165 controlled vocabularies (i.e. Medical Subject Headings - MeSH and CINAHL Headings), literature
12 166 review, expert opinion, and scrutiny of test search results. The following search strategy will be used
13 167 for PubMed, which will then be adapted for other databases to be searched:

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15 168 (“tinnitus”[MeSH] OR “tinnitus”[tiab] OR “phantom sound*”[tiab] OR “ringing”[tiab] OR
16 169 “buzzing”[tiab]) AND (“cognition”[MeSH] OR “cogniti*”[tiab] OR “memory”[tiab] or
17 170 “attention*”[tiab] OR “executive”[tiab])
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23 172 **Data management**

24 173 NAC will be responsible for data management. Covidence online systematic review software
25 174 (<https://www.covidence.org>) will be used for article screening and data management throughout the
26 175 review. All articles identified through the search process will be recorded digitally and will be
27 176 trackable through the data screening and extraction processes. Articles excluded at the full text
28 177 screening stage will have justification for exclusion noted. Included articles will be assigned a unique
29 178 study identification code, enabling it to be linked to its corresponding full text and data collection
30 179 sheet.
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36 181 **Article selection process**

37 182 NAC, DH, and MA will independently screen titles and abstracts of records retrieved from searches
38 183 such that all records are independently screened by two reviewers. Records that meet the specified
39 184 inclusion criteria will then be taken forward to full text screening, as well as records where there is too
40 185 little information available to make a decision to exclude. All full texts selected will be independently
41 186 screened by two reviewers who will resolve any discrepancies in which records are included. Where
42 187 discrepancies for inclusion are not resolved by the two reviewers, a third reviewer will adjudicate. If
43 188 necessary, study authors will be contacted to request additional information that may help ascertain
44 189 suitability for inclusion.
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51 191 **Data extraction process**

52 192 Data extraction will be performed using a customised form via Covidence. Relevant guidance notes
53 193 will be created and disseminated to review team members by NAC prior to commencement. The data
54 194 form and guidance notes will be piloted by NAC and HH. All included records will be subject to data
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195 extraction. Data from each included record will be extracted independently by two reviewers and the
196 results compared. Any disagreements arising will be resolved through discussion or the involvement
197 of a third reviewer.

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199 **Data items**

200 The data collection form will include various fields corresponding to study type, population, reported
201 effect size, and any other relevant study findings. Study authors will be contacted if there are relevant
202 missing data. Data will be approximated from figures for instances where it can only be estimated,
203 using software such as WebPlotDigitizer (<http://arohatgi.info/WebPlotDigitizer/app/>). Disagreements
204 regarding numerical data extracted from figures will be discussed by investigators and/or resolved by
205 averaging.

206

207 **Risk of bias in individual studies**

208 NAC, HH, and DH (two reviewers per record) will independently assess the risk of bias using
209 relevant items adapted from the Critical Appraisal Skills Programme (CASP) Case Control Checklist
210 (<https://casp-uk.net/casp-tools-checklists/>).

211

212 **Data synthesis**

213 The effect of interest is the association between subjective tinnitus and measures of cognitive
214 performance expressed as correlation. Where possible, results not expressed as correlations (e.g. mean
215 differences between groups) will be calculated as appropriate correlations, such as point-biserial or
216 polyserial correlation coefficients.¹⁸ Bias corrections will be applied to all derived correlation
217 coefficients prior to pooling.¹⁹ Where possible, missing effect sizes will be calculated from reported
218 test statistics such as standard deviations or t-values¹⁸. Narrative synthesis will be undertaken for
219 records where appropriate effect sizes cannot be obtained.

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221 **Assessment of heterogeneity**

222 The ratio of observed variation to within-study variance will be assessed with the Q-statistic, used to
223 test the null hypothesis of homogeneity of effect sizes. The I^2 statistic will provide a further index of
224 heterogeneity across studies. If the apparent heterogeneity across studies exceeds 50%, potential
225 causes of heterogeneity will be explored through subgroup analysis. The Tau-squared statistic will
226 also be used to assess the amount of heterogeneity where a random-effects model is fitted to the data.
227 A Baujat plot will be used as a graphical means of identifying studies that contribute excessively to
228 any observed heterogeneity and also provide insight into potential moderating variables that
229 contribute to heterogeneity across studies²⁰.

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231 **Subgroup analyses**

232 Potential contributors to heterogeneity across studies will be explored through subgroup analysis (i.e.
233 sensitivity analyses, moderator analysis or meta-regression). Variables of potential interest for
234 subgroup analyses include participant age, gender, presence of hearing impairment and presence of
235 anxiety or depression, or study design aspects, such as inclusion of a control group.

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238 **Assessment of reporting bias**

239 The influence of reporting bias through potentially unpublished results (i.e. publication bias) will be
240 explored via funnel plots, rank correlation test and/or Egger's regression test.

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243 **Ethics and dissemination**

244 No ethical issues are foreseen in this systematic review. Reports will be guided by the Preferred
245 Reporting Items for Systematic Reviews and Meta-Analysis guidelines²¹. Various dissemination
246 strategies will be employed, that will likely include: journal article and PhD thesis (NC) made
247 available via an institutional repository, results being reported at national and international academic
248 conferences, and public and patient engagement (e.g. articles written for relevant non-specialist
249 audiences).

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251

252 **Summary**

253 A protocol is described for a -systematic review and meta-analysis to determine a best estimate of the
254 association between subjective tinnitus and cognitive performance in adults. To date, no review has
255 comprehensively explored the veracity of an association through application of quantitative analyses
256 of all available peer-reviewed data. The outlined approach will facilitate an understanding of the
257 potential impact of tinnitus upon cognition, underpinned by relevant cognitive theory. An increased
258 understanding of the relationship between subjective tinnitus and cognitive performance will
259 eventually improve tinnitus sub-typing and inform therapeutic methods²²⁻²⁵ for example, it may be
260 possible to deliver cognitive training paradigms in a targeted manner.

261

262 **Acknowledgements**

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8
9 269 NIHR, the NHS, or the Department of Health and Social Care.

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326 NAC is the guarantor of the review (CRD42018085528). NAC led on the development of all sections
327 of the review protocol. DH, HH & MA read, developed and provided feedback for all sections of the
328 review protocol and approved the final manuscript.

329

For peer review only

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 4:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	<input type="checkbox"/>	N/A
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	<input checked="" type="checkbox"/>	<input type="checkbox"/>	53
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	<input checked="" type="checkbox"/>	<input type="checkbox"/>	6-15
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	325
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	<input type="checkbox"/>	<input type="checkbox"/>	N/A
Support					
Sources	5a	Indicate sources of financial or other support for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	266-270
Sponsor	5b	Provide name for the review funder and/or sponsor	<input checked="" type="checkbox"/>	<input type="checkbox"/>	266-270
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input checked="" type="checkbox"/>	<input type="checkbox"/>	266-270
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	<input checked="" type="checkbox"/>	<input type="checkbox"/>	33-40, 62-127
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to	<input checked="" type="checkbox"/>	<input type="checkbox"/>	128-132, 147-159

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
		participants, interventions, comparators, and outcomes (PICO)			
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	141-159
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	<input checked="" type="checkbox"/>	<input type="checkbox"/>	162-165
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	<input checked="" type="checkbox"/>	<input type="checkbox"/>	170-172
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	175-181
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	184-191
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	<input checked="" type="checkbox"/>	<input type="checkbox"/>	194-199
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	<input checked="" type="checkbox"/>	<input type="checkbox"/>	202-207, 235-237
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	<input checked="" type="checkbox"/>	<input type="checkbox"/>	215-221, 234-237
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	<input checked="" type="checkbox"/>	<input type="checkbox"/>	209-212, 239-241
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	<input checked="" type="checkbox"/>	<input type="checkbox"/>	226
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2 , Kendall's tau)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	215-221, 224-229
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-	<input checked="" type="checkbox"/>	<input type="checkbox"/>	233-237

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
		regression)			
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input checked="" type="checkbox"/>	<input type="checkbox"/>	221-222
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	240-242
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	210-212

BMJ Open

The association between subjective tinnitus and cognitive performance: protocol for systematic review and meta-analysis

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Manuscripts



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3 **1 The association between subjective tinnitus and cognitive performance:**
4 **2 protocol for systematic review and meta-analysis**
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9 4 Nathan A. Clarke ^{1,2,3}, Michael A. Akeroyd ^{1,3}, Helen Henshaw ² & Derek J.
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3 30 **ABSTRACT**

4 31 **Introduction:**

5 32 Subjective tinnitus is very common and has a number of comorbid associations including depression,
6 33 sleep disturbance and concentration difficulties. Concentration difficulties may be observable in
7 34 people with tinnitus through poorer behavioural performance in tasks thought to measure specific
8 35 cognitive domains such as attention and memory (i.e. cognitive performance). Several reviews have
9 36 discussed the association between tinnitus and cognition, however, none to date have investigated the
10 37 association between tinnitus and cognitive performance through meta-analysis with reference to an
11 38 established theoretical taxonomy. Furthermore, there has been little overlap between sets of studies
12 39 that have been included in previous reviews, potentially contributing to the typically mixed findings
13 40 that are reported.

14 41 **Methods and analysis:**

15 42 This systematic review aims to comprehensively review the literature using an established theoretical
16 43 taxonomy and quantitatively synthesize relevant data to determine associations between subjective
17 44 tinnitus and cognitive performance. Methods are reported according to Preferred Reporting Items for
18 45 Systematic Reviews and Meta-Analyses Protocols (PRISMA-P). All study designs will be eligible for
19 46 inclusion with no date restrictions on searches. Studies eligible for inclusion must contain adult
20 47 participants (≥ 18 years) with subjective tinnitus and a behavioural measure of cognitive performance.
21 48 Meta-analysis will be reported via correlation for the association between tinnitus and cognitive
22 49 performance.

23 50 **Ethics and dissemination:**

24 51 No ethical issues are foreseen. Findings will be reported in a student thesis, at national and
25 52 international ENT/audiology conferences and by peer-reviewed publication.

26 53 **Systematic review registration number:**

27 54 PROSPERO 2018 CRD42018085528.

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33 60 NIHR, the NHS, or the Department of Health and Social Care.

34 61 Contributors: NAC led on the development of all sections of the review protocol. DJH, HH & MAA
35 62 developed and provided feedback for all sections of the review protocol and approved the final
36 63 manuscript.

37 64 Competing interests: None declared.

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68 Strengths and limitations of this study

- 69 • This systematic review and meta-analysis protocol poses a clearly formulated research
70 question and methodology to investigate a common clinical complaint of tinnitus patients;
71 peer-reviewed evidence to date will be synthesised.
- 72 • This protocol details a comprehensive quantitative synthesis and inclusion of potential *a*
73 *priori* moderator variables
- 74 • Synthesis will be clearly structured according to an established cognitive theoretical
75 framework
- 76 • Grey literature and dissertation abstracts will not be included

77 Introduction

78 Tinnitus refers to the common experience of sound in the ears or head in the absence of an external
79 source. It is commonly considered a symptom of damage within the auditory system [1]. Objective
80 tinnitus involves sound with a known, non-central aetiology such as vascular abnormalities; it may be
81 detected by an observer through auscultation. Objective tinnitus may be treated once the source of the
82 aetiology has been identified and is therefore not of primary interest within this review [2]. Subjective
83 tinnitus (hereafter discussed but simply referred to as ‘tinnitus’) involves sound of unknown
84 aetiology. Most individuals who experience tinnitus do not find it bothersome but a significant
85 proportion are disturbed by it, often reporting a variety of adverse comorbid associations including
86 anxiety, depression, disturbed sleep, or concentration difficulties[3–5]. Concentration difficulties can
87 be conceptualised as failures of cognitive performance expressed behaviourally (sometimes called
88 objective cognition[6]) in various domains such as attention and memory[7,8]. Previous research has
89 implicated tinnitus as negatively impacting cognitive performance in domains including executive
90 functions, attention and working memory [9–11].Furthermore, a link between subjective perception of
91 cognitive performance, or subjective cognitive complaints (SCC), has also been suggested [12].
92 Investigating the potential impact of tinnitus on cognitive performance is further complicated by the
93 strong associations that tinnitus shares with depression and anxiety, which can independently
94 negatively impact cognitive performance [5,13,14].

95 Several reviews have explored the relationship between tinnitus and cognition generally
96 [12,15–17]. We note that all of these are narrative reviews; no review has quantitatively synthesised
97 the literature specifically concerning tinnitus and behaviourally measured cognitive performance. An
98 overview of previous reviews and their methodologies is provided in Table 1.

99 *Table 1. Overview of previous reviews investigating cognition and tinnitus*

Study	Databases searched	Example search strategy provided	Number of records retrieved during database search	Number of studies included in review	Synthesis of association between cognition and tinnitus
Trevis et al. (2018)	PsycINFO, MedLine	(1) tinnitus AND psych* (all fields), (2) tinnitus AND mood (all fields), (3) tinnitus AND depress* (all fields), (4) tinnitus AND anx* OR stress (all fields)	725	35	Meta-analysis of 'psychological functioning' in tinnitus participants. Narrative review of association between 'cognitive functioning' (n = 16); i.e. behavioural cognitive task performance and chronic tinnitus. awareness and severity
Mohamad et al. (2016)	PubMed	(((tinnitus[Title]) AND cogniti*[Title])) OR ((tinnitus[Title]) AND attention[Title])) OR ((tinnitus[Title]) AND memory[Title])	65	9	Narrative review of 'behavioural research' addressing the impact of tinnitus and its severity of various aspects of cognitive performance in domains of working memory and attention.
Tegg-Quinn et al. (2016)	PubMed, MedLine, CINAHL, SCOPUS, EMBASE	(tinnitus) and (cognition OR memory OR attention OR concentration OR cognitive function OR mental activity) NOT (infant OR child OR adolescent OR paediatric OR animal OR balance OR hyperacusis OR implant OR pharmaceutical OR drugs)	2236	18	Narrative review of behavioural cognitive tasks, electrophysiological correlates of cognition and self-reported cognitive function measures.
Andersson and McKenna (2006)	MedLine and Psychological Abstracts	Not reported	Not reported	Not reported	Narrative review of 'cognitive deficits' (i.e. behavioural cognitive tasks), 'cognitive bias and 'conscious appraisal of tinnitus'.

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3 102 Andersson and McKenna [15] were the first to review the relationship between cognition and
4 103 tinnitus, detailing three separate but related lines of cognitive research. The strands of research
5 104 included neuropsychological studies involving attention, cognitive bias (concerning selective attention
6 105 and memory) and appraisal (i.e. conscious recollection) of tinnitus. Tegg-Quinn et al. [16] performed
7 106 a systematic review of all studies pertaining to the impact of tinnitus upon cognition in adults. The
8 107 review described studies that included behavioural, electrophysiological and SCC measures. The
9 108 authors concluded that tinnitus impairs cognition by adversely impacting the executive control of
10 109 attention. Mohamad et al. [12] performed a narrative review of the behavioural evidence concerning
11 110 the consequences of tinnitus and its severity on cognition. They concluded that there was suggestive
12 111 evidence for tinnitus being associated with poorer performance in behavioural tasks attempting to
13 112 measure executive attention, selective attention and working memory. This review also examined the
14 113 proposed relationship between cognitive performance and SCC in individuals with tinnitus. They
15 114 reported that their data was insufficient to form conclusions and recommended further investigation of
16 115 the relationship. Trevis et al.[17] performed a systematic review and meta-analysis of psychological
17 116 functioning in chronic tinnitus. The authors predominantly investigated the presence and severity of
18 117 tinnitus in relation to emotional wellbeing through meta-analysis, while cognitive function (i.e.
19 118 cognitive performance) was described through a narrative review. To summarise, the collective
20 119 conclusions of these reviews describe mixed evidence in support of the hypothesis that tinnitus
21 120 adversely impacts cognitive performance and individually included insufficient data to form
22 121 conclusions regarding associations between cognitive performance and SCC in individuals with
23 122 tinnitus. Several distinct cognitive functions have been implicated in this hypothesis. Previous studies
24 123 have suggested that structures relating to auditory attention and efferent structures within the
25 124 subcallosal region are mechanistically involved in the adverse impacts of tinnitus on cognitive
26 125 performance [16]. Functional disruption to large scale neurocognitive networks has also been
27 126 suggested as a mechanism [17,18] ; specifically, a hypoactive cognitive control network and
28 127 hyperactive 'default mode' or 'task-negative' network.

31 128 Of the recent reviews that discuss cognitive performance via behavioural measures in tinnitus
32 129 participants, there is a notable lack of overlap in the studies that met criteria for inclusion in the final
33 130 reviews; e.g. Mohamad et al.[10] reviewed nine studies and Trevis et al.[17] reviewed a total of
34 131 thirty-five studies (with sixteen of these concerning cognitive performance), however, only three
35 132 studies were included in both reviews. Therefore, previous work has essentially investigated the
36 133 association between tinnitus and cognitive performance with different datasets. Schultz et al. [19]
37 134 recently reviewed the evidence for tinnitus impacting neurocognitive profiles following traumatic
38 135 brain injury. They discuss cognitive performance through selective discussion of aforementioned
39 136 reviews - except Andersson and Mckenna [15] – and subsequent implications within a medicolegal
40 137 context. The authors highlight the current lack of and need for empirical investigation of the
41 138 association between tinnitus and cognitive performance through meta-analysis. Like any statistical

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3 139 technique, meta-analysis is only as robust as the data that is inputted. It is, therefore, essential to
4 140 include as much relevant data as possible - through a comprehensive search strategy - to ensure that
5 141 conclusions are based on all evidence for an effect of tinnitus on specific cognitive domains.

7 142 Tinnitus is a symptom of heterogeneous and often unknown aetiologies. It is, therefore,
8 143 inherently difficult to define and specify within the context of a systematic review. Different inclusion
9 144 criteria and working definitions of tinnitus are likely to significantly influence the records included
10 145 within a review. For example, Trevis et al.[17] defined 'chronic tinnitus' as participants who had
11 146 experienced tinnitus for at least one month. An alternative approach would be to not attempt to
12 147 temporally specify a population, but rather investigate this variable through further quantitative
13 148 analysis if feasible. With regards to domains of cognitive performance, the aforementioned reviews
14 149 have implicated tinnitus as impacting executive attention, although the evidence is not conclusive:
15 150 additional domains of cognitive performance are also potentially associated with tinnitus, including
16 151 selective attention, working memory and processing speed [12,15–17]. A promising approach to
17 152 foster empirically valid insights into any association between cognition and tinnitus is through
18 153 evaluating and categorising tests of cognitive performance according to the theoretical constructs that
19 154 they are thought to measure [20]. Webb et al. [21] describe a cross-disciplinary taxonomy for
20 155 categorising cognitive performance measures (CHC-M). It utilises combined Cattell-Horn-Carroll
21 156 (CHC) and Miyake theoretical elements [22,23] and includes a comprehensive taxonomical
22 157 categorisation of cognitive tasks. CHC-M taxonomy will be used to organise synthesis when
23 158 investigating the association between tinnitus and cognitive performance. This approach has several
24 159 benefits: it is informed by the CHC 'three strata' model of cognition, which has been empirically
25 160 validated through decades of research; it incorporates executive functions, a cognitive construct of
26 161 particular clinical interest, facilitating translation to the clinical domain; utilisation of a pre-existing
27 162 taxonomy minimises author bias (as outcome measures are not being subjectively assigned to domains
28 163 of cognitive performance by authors) and enables comparison compared to 'categorisation as usual';
29 164 finally, the taxonomy provides a clear framework around which to structure synthesis of results.
30 165 Associations between categorised measures of cognitive performance and tinnitus may then be
31 166 subjected to meta-analysis of specific cognitive domains in order to understand which are associated
32 167 with tinnitus, as well as the best estimate of any such effect. Given the suggestive nature of the
33 168 evidence provided in previous reviews, we can hypothesise that there will be negative associations
34 169 between tinnitus severity and cognitive performance in the broad stratum domains of executive
35 170 functions, processing speed, and general short-term memory. To summarise, although several authors
36 171 have reviewed the association between tinnitus and cognitive performance assessed through
37 172 behavioural measures, these have been via narrative syntheses. They have discussed different sets of
38 173 studies, derived from different search strategies in the absence of a unifying taxonomy. A
39 174 comprehensive, quantitative investigation of the association between tinnitus and cognitive

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3 175 performance, building on earlier efforts in this field and exploring the underlying theoretical domains
4 176 of cognition involved, is therefore both necessary and timely.

5 177 The primary aim of this work is to comprehensively review the literature and synthesize
6 178 relevant data to determine the associations between tinnitus and cognitive task performance in adults.
7 179 If possible, a secondary examination of patient characteristics (e.g. age or gender) or commonly used
8 180 patient-reported outcomes (e.g. depression or anxiety) and their influence on any association between
9 181 tinnitus and cognitive performance will also be conducted.
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16 184 **Methods and Analysis**

17 185 The methodology of this review is reported in accordance with the Preferred Reporting Items for
18 186 Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) checklist [24]. Specified roles of
19 187 named authors are identified throughout the review protocol.
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24 189 **Eligibility criteria**

25 190 Only published or in-press, peer-reviewed journal articles will be considered. Articles that are not
26 191 written in English or have no English language translation available will be excluded as the review
27 192 team does not have resource available to support translation. No date restriction will be applied.
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31 194 Review inclusion criteria are specified according to Participant, Intervention (or Interest),
32 195 Comparator, Outcome and Setting (PICOS) characteristics.
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36 197 *Participants:* Studies including adults (≥ 18 years) with tinnitus. Studies that include both children
37 198 (< 18 years) and adults will be excluded, unless the adult data are reported separately.
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40 200 *Intervention/Interest:* Tinnitus (via self-report, tinnitus severity scale, item or established tinnitus
41 201 questionnaires).
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45 203 *Comparator:* A minimum of one established measure of cognitive performance (behavioural or self-
46 204 report).
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49 206 *Outcome measures:* An association between tinnitus and cognitive performance. Where available,
50 207 data for associations between tinnitus and additional potential moderator variables will be extracted,
51 208 such as measures of anxiety or depression.
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3 210 *Study design:* Cross-sectional, longitudinal, experimental, quasi-experimental and observational study
4 211 designs will be included (only baseline data will be extracted where multiple timepoint measurements
5 212 are made).

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8 214 **Patient and Public Involvement**

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10 215 There was no patient or public involvement in the development of this manuscript.

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13 217 **Information Sources and Search strategy**

14 218 A systematic search strategy will be employed to identify completed, peer-reviewed journal articles
15 219 from the following bibliographic databases: MEDLINE (via Ovid SP), EMBASE (via Ovid SP),
16 220 PsycINFO (via Ovid SP), ASSIA (via ProQuest), CINAHL (via EBSCO Host), Scopus, PubMed, and
17 221 Web of Science (Science and Social Science Citation Index). Initial searches were performed in
18 222 February 2018. Update searches will be conducted shortly before manuscript submission.

19 223 The search terms to be used in this systematic review were identified using free text,
20 224 controlled vocabularies (i.e. Medical Subject Headings - MeSH and CINAHL Headings), literature
21 225 review, opinion of authors and scrutiny of test search results. The following search strategy will be
22 226 used for PubMed, which will then be adapted for other databases to be searched:

23 227 (“tinnitus”[MeSH] OR “tinnitus”[tiab] OR “phantom sound*”[tiab] OR “ringing”[tiab] OR
24 228 “buzzing”[tiab]) AND (“cognition”[MeSH] OR “cogniti*”[tiab] OR “memory”[tiab] or
25 229 “attention*”[tiab] OR “executive”[tiab])

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33 231 **Data management**

34 232 NAC will be responsible for data management. Covidence online systematic review software
35 233 (<https://www.covidence.org>) will be used for article screening and data management throughout the
36 234 review. All articles identified through the search process will be recorded digitally and will be
37 235 trackable through the data screening and extraction processes. Articles excluded at the full text
38 236 screening stage will have justification for exclusion noted. Included articles will be assigned a unique
39 237 study identification code, enabling it to be linked to its corresponding full text and data collection
40 238 sheet.

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43 240 **Article selection process**

44 241 NAC, DJH, and MAA will independently screen titles and abstracts of records retrieved from
45 242 searches such that all records are independently screened by two reviewers. Records that meet the
46 243 specified inclusion criteria will then be taken forward to full text screening, as well as records where
47 244 there is too little information available to make a decision to exclude. All full texts selected will be
48 245 independently screened by two reviewers who will resolve any discrepancies in which records are

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3 246 included. Where discrepancies for inclusion are not resolved by the two reviewers, a third reviewer
4 247 will adjudicate. If necessary, study authors will be contacted to request additional information that
5 248 may help ascertain suitability for inclusion.
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9 250 **Data extraction process**

10 251 Data extraction will be performed using a customised form via Covidence. Relevant guidance notes
11 252 will be created and disseminated to review team members by NAC prior to commencement. The data
12 253 form and guidance notes will be piloted by NAC and HH. All included records will be subject to data
13 254 extraction. Data from each included record will be extracted independently by two reviewers and the
14 255 results compared. Any disagreements arising will be resolved through discussion or the involvement
15 256 of a third reviewer.
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18 258 **Data items**

19 259 The data collection form will include various fields corresponding to study type, population, reported
20 260 effect size, and any other relevant study findings. Study authors will be contacted and if there are
21 261 relevant missing data. This will entail one email reminder, with instances of no response being
22 262 reported as such. Data will be approximated from figures for instances where it can only be estimated,
23 263 using software such as WebPlotDigitizer (<http://arohatgi.info/WebPlotDigitizer/app/>). Disagreements
24 264 regarding numerical data extracted from figures will be discussed by investigators and/or resolved by
25 265 averaging.
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28 267 **Risk of bias in individual studies**

29 268 NAC, HH, and DJH (two reviewers per record) will independently assess the risk of bias using the
30 269 Weight of Evidence (WoE) framework, which allows appraisal of study criteria that is tailored to the
31 270 review question [25,26]. The WoE framework will be customised and used to evaluate
32 271 *Methodological Quality* (WoE A), *Methodological Relevance* (WoE B), and *Topic*
33 272 *Relevance* (WoE C). A rating of low, medium, or high will be assigned for each category in
34 273 accordance with WoE framework criteria. Disagreements regarding bias appraisal will be resolved
35 274 through discussion or the involvement of a third reviewer.
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38 276 **Data synthesis**

39 277 The effect of interest is the association between tinnitus and measures of cognitive performance
40 278 expressed as correlation. Where possible, results not expressed as correlations (e.g. mean differences
41 279 between groups) will be calculated as appropriate correlations, such as point-biserial or polyserial
42 280 correlation coefficients.[27] Bias corrections will be applied to all derived correlation coefficients
43 281 prior to pooling [28]. Where possible, missing effect sizes will be calculated from reported test
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3 282 statistics such as standard deviations or t-values [27]. Narrative synthesis will be undertaken for
4 283 records where appropriate effect sizes cannot be obtained. If SCC measures assess comparable
5 284 constructs, a separate meta-analysis will be undertaken for the association between tinnitus and SCC.
6
7 285 If not, these studies will be synthesised narratively. Cognitive performance will be collapsed over
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9 286 'broad' factors within the level '2' stratum to enable meta-analysis of the association between tinnitus
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11 287 and cognitive performance these domains. If possible, 'narrow' factors within 'level 3' stratum will be
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13 288 meta-analysed, however, if too few records are included to afford this degree of granulation, then the
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15 289 narrow factors will provide a framework for narrative synthesis.
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292 **Assessment of heterogeneity**

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19 293 The ratio of observed variation to within-study variance will be assessed with the Q-statistic, used to
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21 294 test the null hypothesis of homogeneity of effect sizes. The I^2 statistic will provide a further index of
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23 295 heterogeneity across studies. If the apparent heterogeneity across studies exceeds 50%, potential
24
25 296 causes of heterogeneity will be explored through subgroup analysis. The Tau-squared statistic will
26
27 297 also be used to assess the amount of heterogeneity where a random-effects model is fitted to the data.
28
29 298 A Baujat plot will be used as a graphical means of identifying studies that contribute excessively to
30
31 299 any observed heterogeneity and also provide insight into potential moderating variables that
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33 300 contribute to heterogeneity across studies [29].
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302 **Subgroup analyses**

35 303 Potential contributors to heterogeneity across studies will be explored through subgroup analysis (i.e.
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37 304 sensitivity analyses, moderator analysis or meta-regression). *A priori* variables of interest for
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39 305 subgroup analyses will include tinnitus sample characteristics (duration, laterality, intermittency),
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41 306 study quality and variables known to adversely impact cognitive performance, including sample age,
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43 307 presence of hearing impairment, presence of anxiety or depression, reported medication usage and
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45 308 visual acuity. Additional potential moderating variables may be identified after reviewing the
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47 309 literature and will be documented accordingly.
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312 **Assessment of reporting bias**

49 313 The influence of reporting bias through potentially unpublished results (i.e. publication bias) will be
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51 314 explored via funnel plots, rank correlation test and/or Egger's regression test.
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316 **Ethics and dissemination**

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3 317 No ethical issues are foreseen in this systematic review. Reports will be guided by the Preferred
4 318 Reporting Items for Systematic Reviews and Meta-Analysis guidelines [30]. Various dissemination
5 319 strategies will be employed, that will likely include: journal article and PhD thesis (NAC) made
6 320 available via an institutional repository, results being reported at national and international academic
7 321 conferences, and public and patient engagement (e.g. articles written for relevant non-specialist
8 322 audiences).

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11 325 **Summary**

12 326 A protocol is described for a systematic review and meta-analysis to determine a best estimate of the
13 327 association between tinnitus and cognitive performance in adults. The relationship between tinnitus,
14 328 cognitive performance, and SSC will also be examined. To date, no review has comprehensively
15 329 explored the veracity of an association between tinnitus and cognitive performance through
16 330 application of quantitative analyses of all available peer-reviewed data. The outlined approach will
17 331 facilitate an understanding of the potential impact of tinnitus upon cognitive performance,
18 332 underpinned by relevant cognitive theory. An increased understanding of the relationship between
19 333 tinnitus and cognitive performance will eventually improve tinnitus sub-typing and inform therapeutic
20 334 methods[31–34] for example, it may be possible to deliver cognitive training paradigms in a targeted
21 335 manner.

22 336

23 337 **Acknowledgements**

24 338 Thanks to Oliver Zobay for statistical advice.

25 339

26 340

27 341 **References**

28 342

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422

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 4:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	<input type="checkbox"/>	<input type="checkbox"/>	N/A
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	<input checked="" type="checkbox"/>	<input type="checkbox"/>	55
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	<input checked="" type="checkbox"/>	<input type="checkbox"/>	6-15
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	335
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	<input type="checkbox"/>	<input type="checkbox"/>	N/A
Support					
Sources	5a	Indicate sources of financial or other support for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	330-334
Sponsor	5b	Provide name for the review funder and/or sponsor	<input checked="" type="checkbox"/>	<input type="checkbox"/>	330-334
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	<input checked="" type="checkbox"/>	<input type="checkbox"/>	330-334
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	<input checked="" type="checkbox"/>	<input type="checkbox"/>	33-50, 67-170
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to	<input checked="" type="checkbox"/>	<input type="checkbox"/>	167-170, 183-201

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
		participants, interventions, comparators, and outcomes (PICO)			
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	183-201
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	<input checked="" type="checkbox"/>	<input type="checkbox"/>	207-215
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	<input checked="" type="checkbox"/>	<input type="checkbox"/>	216-218
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	<input checked="" type="checkbox"/>	<input type="checkbox"/>	220-227
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	229-237
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	<input checked="" type="checkbox"/>	<input type="checkbox"/>	239-245
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	<input checked="" type="checkbox"/>	<input type="checkbox"/>	247-254, 292-298
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	<input checked="" type="checkbox"/>	<input type="checkbox"/>	266-278, 292-298
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	<input checked="" type="checkbox"/>	<input type="checkbox"/>	257-263
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	<input checked="" type="checkbox"/>	<input type="checkbox"/>	265-278
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2 , Kendall's tau)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	265-289
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-	<input checked="" type="checkbox"/>	<input type="checkbox"/>	291-298

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
		regression)			
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	<input checked="" type="checkbox"/>	<input type="checkbox"/>	271-278
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	302-303
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	257-263