

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	The natural history of tinnitus in adults: a cross sectional and longitudinal analysis
<b>AUTHORS</b>	Dawes, Piers; Newall, John; Stockdale, David; Baguley, David

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Roberta W Scherer Johns Hopkins Bloomberg School of Public Health United States
<b>REVIEW RETURNED</b>	24-Jun-2020

<b>GENERAL COMMENTS</b>	<p>Review for “The natural history of tinnitus in adults: a cross sectional and longitudinal analysis” by Newall et al.</p> <p>By analyzing the natural history of tinnitus using UK Biobank data, the author provide important information about the progression and resolution of tinnitus among adults. Given the difficulty in defining tinnitus, use of such a large data resource promises to provide insight into the natural course of the tinnitus condition. I found some issues with the manuscript however, as itemized below.</p> <ol style="list-style-type: none"><li>1. Please define all abbreviations at first use (e.g., SRT)</li><li>2. Please be careful with the use of incidence and prevalence in the introduction. Many of the cited studies provide prevalence, and not incidence or provide both. It is not correct to label the table as only providing incidence (page 4, line 19). It would also be helpful to describe clearly which results presented in Table 2 represent prevalence. Some lines do indicate incidence but it is not clear if these are the only reports of incidence.</li><li>3. At what years were the hearing and tinnitus measures initially obtained? From the description that the interval is 2-7 years and the first year of collection is 2006 and the last year of retest is 2013, then it would appear these measures were taken very soon after initiation (2013-2006 = 7).</li><li>4. Please provide the range of possible values for the Townsend and Eysenck instruments – it would be helpful in understanding the values presented in Table 2. That is, are these middle values or at either end of the scale. Some benchmarks would also be useful –e.g., what is considered a threshold for neuroticism?</li><li>5. How were the various responses to the work and music noise questions interpreted? Were all ‘yes’ responses considered exposure? How was ‘do not know’ and ‘prefer not to answer’ handled? How is 85 dB related to the yes responses?</li><li>6. I do not understand the relevance of the information contained with the paragraph describing ‘Patient and public involvement’ to the work presented here. Please clarify or omit.</li></ol>
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	<p>7. A flow chart would be quite helpful here, especially given the various 'N's" used in the analyses. At times it is not clear which populations are being compared. Also, in the analyses, it appears that a number of records were dropped, possibly due to missing values, but this seems like a lot of missing values. For example, the first analysis (tinnitus vs no tinnitus) has an N of 80,380 but looking at Table 2, the number should be twice that (168,348). The next analysis, bothersome tinnitus vs not bothersome has an N of 21,690, but there is a total of 29,861 persons with tinnitus. Please clarify if these differences are due to missing values or some other reason. Some justification or explanation should be included as to the difference in numbers across all the analyses when compared to Table 2.</p> <p>8. Please describe who is included in the 'resolved tinnitus" population presented in Table 4. One assumes this would include the 820 with tinnitus at baseline with responses at follow-up, but the N is 565.</p> <p>9. Thank you for including the STROBE checklist.</p>
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<b>REVIEWER</b>	Sho Kanzaki Keio University, Tokyo, Japan
<b>REVIEW RETURNED</b>	24-Jul-2020

<b>GENERAL COMMENTS</b>	I am wondering why the neuroticism scores are not associated with people who bothersome tinnitus. Worsening tinnitus is usually an exacerbation of sleep deprivation and depression.
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<b>REVIEWER</b>	Pawel Jastreboff JHDF, Inc. USA
<b>REVIEW RETURNED</b>	05-Aug-2020

<b>GENERAL COMMENTS</b>	<p>This is interesting manuscript addressing prevalence of tinnitus in specific, large sub-population in UK and factors associated with tinnitus as experience and of bothersome. There are a minor points clarification of which will be helpful.</p> <p>The manuscript would benefit from adding short explanation assuring that statistical assumption for performing described analyses were met.</p> <p>Results that use of hearing aids apparently had no impact on tinnitus is contrary to common practice where hearing aids frequently are used as a first approach. One possibility is that it is not just amplification but use amplification as a part of specific sound therapy is important. I have excellent results with using combination instruments and hearing aids in treatment patients with Tinnitus Retraining Therapy. This issue deserves broader and in depth discussion.</p> <p>Lack of information about whether subject underwent some (and which type) of treatment severely restrict possibility of assessing the spontaneous recovery. The authors mention this but I believe it should be stronger.</p> <p>I found the following statement intriguing  " Among the 820 people who reported tinnitus at baseline and completed responses at follow-up, 150 reported no tinnitus at follow-up (including 63 who claimed never to have had tinnitus);</p>
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	<p>18.3% of people reporting tinnitus at baseline did not report tinnitus at follow-up.”</p> <p>It rises question regarding validity of subjects reports. It seems that 58% (63/150) of people who reported that their tinnitus disappeared during the time from baseline evaluation to followup claimed that they never have had tinnitus! This issue should be addressed in the Discussion.</p> <p>As customary for my reviews I am disclosing my identity to the authors.</p> <p>Best regards,</p> <p>Pawel J. Jastreboff, Ph.D., Sc.D., M.B.A.</p>
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### VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

By analyzing the natural history of tinnitus using UK Biobank data, the author provide important information about the progression and resolution of tinnitus among adults. Given the difficulty in defining tinnitus, use of such a large data resource promises to provide insight into the natural course of the tinnitus condition. I found some issues with the manuscript however, as itemized below.

1. Please define all abbreviations at first use (e.g., SRT)

**Amended as requested.**

2. Please be careful with the use of incidence and prevalence in the introduction. Many of the cited studies provide prevalence, and not incidence or provide both. It is not correct to label the table as only providing incidence (page 4, line 19). It would also be helpful to describe clearly which results presented in Table 2 represent prevalence. Some lines do indicate incidence but it is not clear if these are the only reports of incidence.

**Amended table to show specifically incidence and prevalence and amended description in text to clarify prevalence/incidence.**

3. At what years were the hearing and tinnitus measures initially obtained? From the description that the interval is 2-7 years and the first year of collection is 2006 and the last year of retest is 2013, then it would appear these measures were taken very soon after initiation (2013-2006 = 7).

**That is correct; the first year of data collection was 2006 and continued to 2010. Subsamples were invited to participate in follow-up studies in 2012 and 2013 when the test battery was repeated. Because baseline data collection ran over 5 years, the retest interval ranges from 2-7 years. We have provided the dates of baseline and repeat assessment in the methods section.**

4. Please provide the range of possible values for the Townsend and Eysenck instruments – it would be helpful in understanding the values presented in Table 2. That is, are these middle values or at either end of the scale. Some benchmarks would also be useful –e.g., what is considered a threshold for neuroticism?

**Added national mean and local maxima and minima for Townsend scores; clarified that Townsend scores are standardised to have a mean of 0 and a standard deviation of 1.**

**We have clarified that the neuroticism score represents the number of neurotic traits present. No threshold for neuroticism vs no neuroticism exists for this scale to our knowledge.**

5. How were the various responses to the work and music noise questions interpreted? Were all 'yes' responses considered exposure? How was 'do not know' and 'prefer not to answer' handled? How is 85 dB related to the yes responses?

**We have clarified that work/music exposure was identified on the basis of any reported exposure. 'Do not know' and 'prefer not to answer' responses were treated as missing data.**

**We clarified that the yes response (indicating exposure to noise where one must 'shout to be heard') corresponds to an approximate noise level of >85dB level is based on guidance from the UK's Health and Safety Executive.**

6. I do not understand the relevance of the information contained with the paragraph describing 'Patient and public involvement' to the work presented here. Please clarify or omit.

**A section on public involvement is required for this specific journal. The paragraph aims to detail how the public were involved in development of the study utilising a standard form.**

7. A flow chart would be quite helpful here, especially given the various 'N's' used in the analyses. At times it is not clear which populations are being compared. Also, in the analyses, it appears that a number of records were dropped, possibly due to missing values, but this seems like a lot of missing values. For example, the first analysis (tinnitus vs no tinnitus) has an N of 80,380 but looking at Table 2, the number should be twice that (168,348). The next analysis, bothersome tinnitus vs not bothersome has an N of 21,690, but there is a total of 29,861 persons with tinnitus. Please clarify if these differences are due to missing values or some other reason. Some justification or explanation should be included as to the difference in numbers across all the analyses when compared to Table 2.

**Table 2 and in the text reference to it has been altered to make the populations clearer.**

**In each instance we have also added comment to delineate the populations included and where cases of exclusion due to missing data have altered N's.**

8. Please describe who is included in the 'resolved tinnitus' population presented in Table 4. One assumes this would include the 820 with tinnitus at baseline with responses at follow-up, but the N is 565.

**In each instance we have now added comment to delineate the populations included (for Tables 4 and 5) where cases of exclusion due to missing data have altered N's.**

9. Thank you for including the STROBE checklist.

**Thank you very much for your review.**

Reviewer: 2

I am wondering why the neuroticism scores are not associated with people who bothersome tinnitus. Worsening tinnitus is usually an exacerbation of sleep deprivation and depression.

**Neuroticism was associated with increased odds of tinnitus and bothersome tinnitus, but not with bothersomeness becoming worse over the study period. We have added further commentary in the discussion to make this clearer.**

Reviewer: 3

This is interesting manuscript addressing prevalence of tinnitus in specific, large sub-population in UK and factors associated with tinnitus as experience and of bothersome. There are a minor points clarification of which will be helpful.

The manuscript would benefit from adding short explanation assuring that statistical assumption for performing described analyses were met.

**We have added a statement as such.**

Results that use of hearing aids apparently had no impact on tinnitus is contrary to common practice where hearing aids frequently are used as a first approach. One possibility is that it is not just amplification but use amplification as a part of specific sound therapy is important. I have excellent results with using combination instruments and hearing aids in treatment patients with Tinnitus Retraining Therapy. This issue deserves broader and in depth discussion.

**We agree, our own clinical experience bears out the potential benefits of hearing aid, and combined hearing aid/sound therapy.**

**We have added a comment to clarify that other known successful therapies and combination therapies (with aids) were not evaluated here.**

**I think a longer discussion of this topic is not warranted due to the broader focus of this particular study, however, perhaps it may be useful to publish a shorter opinion piece focusing on this element of the data. It may be an indication that, for instance, that a hearing aid by itself (without further counselling/therapy) is not enough. Hopefully that now comes across in the paper.**

Lack of information about whether subject underwent some (and which type) of treatment severely restrict possibility of assessing the spontaneous recovery. The authors mention this but I believe it should be stronger.

**We have added a stronger statement regarding the potential impact and confound of this factor.**

I found the following statement intriguing

“ Among the 820 people who reported tinnitus at baseline and completed responses at follow-up, 150 reported no tinnitus at follow-up (including 63 who claimed never to have had tinnitus); 18.3% of people reporting tinnitus at baseline did not report tinnitus at follow-up.”

It rises question regarding validity of subjects reports. It seems that 58% (63/150) of people who reported that their tinnitus disappeared during the time from baseline evaluation to followup claimed that they never have had tinnitus! This issue should be addressed in the Discussion.

We agree that it is concerning that questions used to identify tinnitus phenotypes in this study (which are typical of those used in epidemiological studies, ie self-reported persistent tinnitus) were subject to variation for unknown reasons.

We include mention of the reliability of current self-report measures of tinnitus and identify a need for more consistent/stringent measures of tinnitus, perhaps based on an objective physiological measure.

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	Roberta W. Scherer Johns Hopkins Bloomberg School of Public Health
<b>REVIEW RETURNED</b>	22-Oct-2020

<b>GENERAL COMMENTS</b>	Thank you for allowing me to review this paper. All my previous concerns have been adequately addressed in this revision.
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<b>REVIEWER</b>	Pawel J. Jastreboff Emory University School of Medicine USA
<b>REVIEW RETURNED</b>	02-Nov-2020

<b>GENERAL COMMENTS</b>	I found responses to my questions basically acceptable. I would suggest making statement regarding spontaneous recovery even stronger - as it is not known whether subjects have been receiving treatment(s) I believe it is impossible to make any statement about existence of spontaneous recovery.
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