PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Association between hypertension and hearing impairment in health check-ups among Japanese workers: a cross-sectional study
AUTHORS	Umesawa, Mitsumasa; Sairenchi, Toshimi; Haruyama, Yasuo; Nagao, Masanori; Kobashi, Gen

VERSION 1 - REVIEW

REVIEWER	Christopher Spankovich University of Mississippi Medical Center United States of America
REVIEW RETURNED	26-Dec-2018

GENERAL COMMENTS	The authors present on the association between hypertension and hearing loss in Japanese workers. In general the design and analysis are appropriate and data presented in an adequate fashion. The primary limitation is the lack of novel findings or further insight into the hypertension/hearing relationship. Please see further comments below stratified by section: Abstract Page 2 Line 38-40, the sentence starting with "Likewise..." is unclear in its description. Is the parentheses indicating "or" Strengths and Limitations The first statement should end in "consistent" not "consisted". Introduction Page 5 Line 15-20, reference for the WHO fact sheet is missing Page 5 Line 43, refer to as person with diabetes not diabetic patient Page 6, last paragraph; Please reference data showing higher hypertension in Japan vs West Methods Please expand on the hearing testing methods. Was this performed in a sound treated room, what type of audiometer, transducers, calibration standards, etc. Page 9: I am not sure all 3 models are necessary, as all show relationship, you could probably take this down to 1 or 2 z(age/sex adjusted and full-adjusted) Results: Organize table 1 by continuous and categorical variables All abbreviations should be spelled out in legend, each table should be able to stand alone

	Discussion: The lack of relationship between HI and hypertension in the more severe hearing loss group was likely due to smaller sample size.

REVIEWER	Hsern Ern Tan
	1. Ear Science Institute Australia, Perth, Western Australia 2. Sir Charles Gairdner Hospital, Perth, Western Australia
REVIEW RETURNED	05-Jan-2019

GENERAL COMMENTS	General comments
	* Summary of paper
	* The authors seek to examine the relationship between hypertension (HTN) and hearing impairment (HI) in a predominantly male, industrial workers from a single institution. Their hypothesis was that HI and HTN were linked, but literature thus far had been inconsistent. They have concluded moderate HI and HTN were linked.
	* Literature review discussion
	* The authors concisely summarise current literature linking HI and HTN
	* Another recent study to have also examined this relationship is Tan et al. (2018) "Associations between cardiovascular disease and its risk factors with hearing loss"
	* Methods discussion
	* Elaboration on what audiometric tools were used to record "hearing tests", and other objective measures such as blood tests (does this refer to full blood picture? lipid profile? what was measured in blood tests?)
	* Reference to recognised or standardised definitions of mild, moderate and severe HI may be useful
	* One weakness is the inability to adjust for other confounding HI risk factors such as workplace noise exposure (given the majority of the study population is in a Fujitsu factory, is machinery noise impactful?) and other known determinants of HI such as family history of HI (presumably from medical history). Is there any data on family history or noise exposure as confounding risk factors? If not, perhaps acknowledging this as a weakness of the dataset would be appropriate or elaborating it more clearly on page 13. I understand 66 subjects were excluded due to working in 'noisy environments' perhaps more detail into this would add value.
	* The term "average" hearing threshold was sometimes confusing, for example 4FAHL (4 frequency average hearing loss) is more commonly used. I understand the limitations of only 1kHz and 4kHz thresholds being measured.
	* Results interpretation
	* It was good to the proposed etiologic mechanisms or microvascular disease, proposed in several papers on this topic
	* perhaps the authors could offer their thoughts on why severe HI was not linked to HTN
	* a popular theme in some papers was the difference between low frequency and high frequency hearing loss. Did the data lend any insight into low (1kHz) vs high (4Khz) frequency HI?
	* acknowledgement of the 4 main weakness - observational study, limited threshold measurement, other workplace noise exposure, limited population
	* it would be interesting to see if there is a graduated association, i.e. higher systolic BP = worsened or more severe HTN. This

would add strength to this hypothesis that HI and HTN are linked. For example, this graded association was demonstrated in Tan et al. (2018) paper, linking higher Framingham risk score with worsened hearing outcomes.
* Summary
* a short summary, I feel commenting on the clinical relevance to the reader would make for a more in depth paper.
* Writing language style
* some minor grammatical mistakes but overall clear and concise
* Figures and tables
* clear and following the STROBE checklist
* Review conclusion
* a well written paper, that has some limitations due to the data set being single institution, heavily skewed to males and an absence of more standard measurements (e.g. 4 frequency HL, and specific systolic BP measurements).
* interesting things to explore would be:
* thoughts on low vs high frequency HI
* impact of severity of HTN on severity of HI
* The overall message is clear and it reads well

Specific comments
* pg 5 line 18 - needs reference
* pg 5 line 57 - grammar
* pg 6 line 20 - please reference for showing Japan HTN > western population HTN
* pg 7 line 52 - which blood tests
* pg 9 line 43 - grammar
* pg 13 line 17 - references to other studies

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: Christopher Spankovich

Institution and Country: University of Mississippi Medical Center, United States of America

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

The authors present on the association between hypertension and hearing loss in Japanese workers. In general the design and analysis are appropriate and data presented in an adequate fashion. The primary limitation is the lack of novel findings or further insight into the hypertension/hearing relationship. Please see further comments below stratified by section:

Abstract

Page 2 Line 38-40, the sentence starting with "Likewise..." is unclear in its description. Is the parentheses indicating "or"

Response: We have replaced "likewise" with "also", and have replaced the parentheses with "or". (Page 2, line 38)

Strengths and Limitations

The first statement should end in "consistent" not "consisted".

Response: We corrected this statement and asked a professional native English-speaking science editor to check the text. (Page 4, line 12)

Introduction

Page 5 Line 15-20, reference for the WHO fact sheet is missing

Response: We added information regarding this reference. (Page 5, line 13-18)

Page 5 Line 43, refer to as person with diabetes not diabetic patient

Response: We have modified the text in accord with the reviewer's suggestion. (Page 5, lines 38–43)

Page 6, last paragraph; Please reference data showing higher hypertension in Japan vs West

Response: We added information regarding reference 17. Reference 17 showed country-specific prevalence of hypertension in adults 20 years or older in a figure, not in a table. Thus, we were unable to show the precise prevalence data. (Page 6, lines 31–35)

Methods

Please expand on the hearing testing methods. Was this performed in a sound treated room, what type of audiometer, transducers, calibration standards, etc.

Response:

We agree with the reviewer that the specific hearing test methodology could affect the research results. Unfortunately we were unable to provide additional information about the hearing testing methods, because the study was based on data from annual health check-ups that were conducted at various health check-up agencies. Of course, hearing tests were conducted under silent conditions, it is likely that not all tests were carried out in a sound-treated room. For example, an ordinary room in a quiet environment near the examination room may be used for hearing test. In Japan, the accuracy management of medical examinations is left to each health check-up agency.

We have included discussion of these points in the Strengths and limitations section of the revised manuscript. (Page 14, lines 40–49)

Page 9: I am not sure all 3 models are necessary, as all show relationship, you could probably take this down to 1 or 2 z(age/sex adjusted and full-adjusted)

Response: We reduced the number of models as reviewer suggested. (Table 2 and 3. Page 9, lines 17–31)

Results: Organize table 1 by continuous and categorical variables

All abbreviations should be spelled out in legend, each table should be able to stand alone

Response: We corrected Table 1 in accord with the reviewer's suggestions.

We also corrected the footnotes of the tables to spell out the abbreviations. (Table 1, 2 and 3)

Discussion: The lack of relationship between HI and hypertension in the more severe hearing loss group was likely due to smaller sample size.

Response: We added a discussion of this issue in the revised Discussion section. (Page 12, line 56 to Page 13, line 8)

Reviewer: 2

Reviewer Name: Hsern Ern Tan

Institution and Country: 1. Ear Science Institute Australia, Perth, Western Australia, 2. Sir Charles Gairdner Hospital, Perth, Western Australia

 Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

Comments on a paper submitted to BMJ Open (Manuscipt ID: bmjopen-2018-028392)

General comments

●Summary of paper

  ○The authors seek to examine the relationship between hypertension (HTN) and hearing impairment (HI) in a predominantly male, industrial workers from a single institution. Their hypothesis was that HI and HTN were linked, but literature thus far had been inconsistent. They have concluded moderate HI and HTN were linked.

●Literature review discussion

  ○The authors concisely summarise current literature linking HI and HTN

  ○Another recent study to have also examined this relationship is Tan et al. (2018) "Associations between cardiovascular disease and its risk factors with hearing loss"

Response: We appreciate the reviewer bringing our attention to this relevant recent study.

We have included this information in the revised manuscript. (Page 5, lines 50–57 and Page 6, lines 19–27)

●Methods discussion

  ○Elaboration on what audiometric tools were used to record "hearing tests", and other objective measures such as blood tests (does this refer to full blood picture? lipid profile? what was measured in blood tests?)

Response: We revised the manuscript to include information regarding medical history and blood tests. (Page 7, lines 49–52 and lines 56–59)

Regarding the hearing tests, we were not able to report all of the details because the surveys were conducted in multiple agencies over several years, and the accuracy management of survey is left to each health check-up agency in Japan. We have provided discussion of this issue as a limitation in the revised manuscript. (Page 14, lines 40–50)

  ○Reference to recognised or standardised definitions of mild, moderate and severe HI may be useful

 Response: We referenced a guideline in the revised manuscript, and have corrected our definition of mild HI as 26–40 dB according to this reference[18].

○One weakness is the inability to adjust for other confounding HI risk factors such as workplace noise exposure (given the majority of the study population is in a Fujitsu factory, is machinery noise impactful?) and other known determinants of HI such as family history of HI (presumably from medical history). Is there any data on family history or noise exposure as confounding risk factors? If not, perhaps acknowledging this as a weakness of the dataset would be appropriate or elaborating it more clearly on page 13. I understand 66 subjects were excluded due to working in 'noisy environments' perhaps more detail into this would add value.

Response:

 In Japan, work environment measurement, including magnitude of noise, is mandatory. If the magnitude is above a certain level, the workers there must undergo detailed hearing tests. Fujitsu is an information and communication technologies company. Few of the company's operations involve substantial noise exposure because of automation.

Although family history is an important risk factor, we unfortunately did not have access to family history information. We added a discussion of this issue as a limitation in the revised manuscript. (Page 14, lines 50–52)

 We found that 66 subjects who worked in a noisy environment exhibited a higher prevalence of HI compared with subjects who did not work in a noisy environment. The prevalence of total hearing impairment was 13.6% among these 66 subjects, while it was only 7.3% among the other 13,475 subjects. We added this information to the revised Methods section. (Page 7, lines 26–33)

○The term "average" hearing threshold was sometimes confusing, for example 4FAHL (4 frequency average hearing loss) is more commonly used. I understand the limitations of only 1kHz and 4kHz thresholds being measured.

Response: To avoid confusion, we changed "average" to "mean" (modified throughout the manuscript).

We agree with the reviewer regarding this methodological limitation in the current study.

●Results interpretation

○It was good to the proposed etiologic mechanisms or microvascular disease, proposed in several papers on this topic

Response: Unfortunately, no previous human studies have examined the mechanism proposed in the current study. However, we have referenced a paper showing that blood flow in the inner ear decreases in hypertensive rats compared with normotensive rats (Reference 23). (Page 14, lines 19–22)

○perhaps the authors could offer their thoughts on why severe HI was not linked to HTN

Response: We speculate that HTN may have affected severe HI because of the number of events, as suggested by another reviewer. We have added this information to the revised Discussion. (Page 12, line 56 to Page 13, line 8)

○A popular theme in some papers was the difference between low frequency and high frequency hearing loss. Did the data lend any insight into low (1kHz) vs high (4Khz) frequency HI?

Response:

The results of the present study revealed that subjects with HTN had a higher prevalence of hearing impairment for both lower and higher frequencies, compared with subjects without hypertension.

This result is in accord with the findings of a previous study in Korea[12], but differs from the findings of a study in Mexico, which showed an association between hypertension and higher hearing thresholds in 8 kHz[15] and a study in Australia that reported an association between hypertension and best ear low-frequency average (dB)[11].

Therefore, we assumed that a possible association exists between hypertension and hearing impairment among Asians.

We have added a discussion of this issue in the revised Discussion. (Page 13, lines 19–40)

○Acknowledgement of the 4 main weakness - observational study, limited threshold measurement, other workplace noise exposure, limited population

Response: We provided a discussion of the potential limitation related to the measurement and study population in the revised Discussion section. (Page 14, lines 31–40, and Page 14, line 51 to Page 15, line 13)

○It would be interesting to see if there is a graduated association, i.e. higher systolic BP = worsened or more severe HTN. This would add strength to this hypothesis that HI and HTN are linked. For example, this graded association was demonstrated in Tan et al. (2018) paper, linking higher Framingham risk score with worsened hearing outcomes.

Response: In accord with the reviewer's suggestion, we attempted to examine the association between HTN and HI according to the grade of HTN in two patterns.

1. Grade of HTN: normal, mild HTN ($140 \leq SBP < 160$ and/or $90 \leq DBP < 100$), severe HTN ($160 \leq SBP$ and/or $100 \leq DBP$) and medicated HTN.

The prevalence rates of total HI were 6.9% in the normal group, 8.0% in the mild HTN group, 7.0% in the severe HTN group and 9.2% in the medicated HTN group ($P = 0.21$, $P = 0.94$ and $P < 0.01$). For HI in the 1 kHz condition, the prevalence rates were 3.0%, 5.0%, 2.2% and 4.1%, respectively ($P < 0.01$, $P = 0.58$ and $P = 0.01$). For HI in the 4 kHz condition, the prevalence rates were 5.5%, 5.8%, 5.1% and 7.5%, respectively ($P = 0.75$, $P = 0.78$ and $P < 0.01$). For the severity of HI, the prevalence rates of mean mild HI were 18.2%, 20.6%, 17.7% and 20.0%, respectively ($P = 0.08$, $P = 0.87$ and $P = 0.08$). The prevalence rates of mean moderate to severe HI were 1.1%, 1.4%, 0.3% and 1.6%, respectively ($P = 0.57$, $P = 0.29$ and $P = 0.10$).

2. Grade of HTN: normal, mild HTN ($140 \leq SBP < 160$ and/or $90 \leq DBP < 100$), severe and medicated HTN ($160 \leq SBP$ and/or $100 \leq DBP$ and/or medicated)

The prevalence rates of total HI were 6.9% in normal group, 8.0% in the mild HTN group and 9.0% in the severe and medicated HTN group ($P = 0.21$ and $P < 0.01$). For HI in the 1 kHz condition, the prevalence rates were 3.0%, 5.0% and 4.0%, respectively ($P < 0.01$ and $P < 0.01$). For HI in the 4 kHz condition, the prevalence rates were 5.5%, 5.8% and 7.3%, respectively ($P = 0.76$ and $P < 0.01$). For the severity of HI, the prevalence rates of mean mild HI were 18.2%, 20.6% and 19.8%, respectively ($P = 0.08$ and $P = 0.11$). The prevalence rates of mean moderate to severe HI were 1.1%, 1.4% and 1.5%, respectively ($P = 0.58$ and $P = 0.21$).

In addition, we attempted to examine the association between Framingham risk score (FRS) and prevalence of HI in the revised manuscript.

We divided male participants into three groups according to FRS, as follows: low (−15 to 1), middle (2 to 4), high (5 or more). We set the criteria according to the number of trisections.

We found that the prevalence of HI gradually increased. The prevalence rates of total HI were 4.0% in the low group, 7.1% in the middle group and 11.1% in the high group ($P < 0.01$ and $P < 0.01$). The

prevalence rates of HI in the 1 kHz condition were 2.1%, 2.9% and 4.9%, respectively (P = 0.07 and P < 0.01). The prevalence rates of HI in the 4 kHz condition were 3.0%, 5.9% and 8.9%, respectively (P < 0.01 and P < 0.01). For severity of HI, the prevalence rates of mean mild HI were 16.2%, 18.1% and 21.7%, respectively (P = 0.053 and P < 0.01). The prevalence rates of mean moderate to severe HI were 0.7%, 1.1% and 1.8%, respectively (P = 0.14 and P < 0.01).

We added information regarding the severity of HTN and severity of HI in the revised Results section. (Page 11, lines 15–17)

We also added the information regarding FRS and the prevalence of HI in the revised Discussion section. (Page 13, lines 42–57)

●Summary

○A short summary, I feel commenting on the clinical relevance to the reader would make for a more in depth paper.

Response: Thank you for comment. However, the "instructions for authors" indicated that a short summary entitled "Strengths and limitations of this study" should not include a description of the results of the study.

●Writing language style

○Some minor grammatical mistakes but overall clear and concise

Response: We apologize for the grammatical mistakes in the previous version of our manuscript.

As we made several major corrections in the revised manuscript, we asked a professional native English-speaking science editor to check the whole text.

●Figures and tables

○Clear and following the STROBE checklist

Response: We checked the STROBE checklist.

The figure legends are provided at the end of the revised manuscript.

●Review conclusion

○A well written paper, that has some limitations due to the data set being single institution, heavily skewed to males and an absence of more standard measurements (e.g. 4 frequency HL, and specific systolic BP measurements).

○interesting things to explore would be:

   ■thoughts on low vs high frequency HI

   ■impact of severity of HTN on severity of HI

○The overall message is clear and it reads well

Response:

We have modified the text to discuss the topics suggested by the reviewer.

We added discussion about low vs high frequency HI. (Page 13, lines 19-40)

We also added the results of analysis between severity of HTN and severity of HI. (Page 11, lines 15-17)

We appreciate the reviewer's helpful suggestions.

Specific comments

* pg 5 line 18 - needs reference

Response: We added an appropriate reference for this sentence. (Page 5, line 18)

* pg 5 line 57 – grammar

Response: We corrected this section in accord with the reviewer's comment. (Page 6, lines 6–10)

* pg 6 line 20 - please reference for showing Japan HTN > western population HTN

Response: We added references and corrected the manuscript in accord with the reviewer's comment. (Page 6, lines 31–36)

* pg 7 line 52 - which blood tests

Response: We added more detailed information regarding the blood test procedure. We corrected "tests" to "test". (Page 7, lines 56–59)

* pg 9 line 43 – grammar

Response: We corrected the "Patient and public involvement" section. (Page 9, lines 45–52)

* pg 13 line 17 - references to other studies

Response: In accord with the reviewer's suggestions, we added appropriate references and used the term "peripheral arterial disease" to clarify our intended meaning. (Page 14, lines 8-10)

VERSION 2 – REVIEW

REVIEWER	Hsern Ern Tan
	University of Western Australia, Australia Ear Science Institute Australia, Australia Sir Charles Gairdner Hospital, Australia
REVIEW RETURNED	24-Feb-2019

GENERAL COMMENTS	The previously mentioned comments have been appropriately addressed. Within the limits of the study, the author's findings are sufficiently supported.