PEER REVIEW HISTORY

ARTICLE DETAILS

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

VERSION 1 – REVIEW

REVIEWER	Mariusz Dąbrowski University of Rzeszów, Faculty of Medicine, Institute of Nursing and Health Sciences; Poland
REVIEW RETURNED	16-Jan-2018

GENERAL COMMENTS	Dear Authors, You performed interesting study and you found relationship between impaired hearing function and proteinuria in a dipstick test. Your findings are surely worth to be published. However, your manuscript is not free from some issues: 1. The abstract is not fully informative, because the reader cannot find any information about other tests performed in the study population, and that multivariate adjustment was performed. Thus, abstract should be reorganized to include these important informations. 2. You cite only paper by GA Gates et al. with regards to association between CVD risk factors and hearing (reference #14). There are several newer papers in this field, e.g.: ■ de Moraes Marchiori L.L.et al. Hypertension as a factor associated with hearing loss. Braz J Otorrinolaringol 2006; 72: 533-540. ■ Narlawar U.W.et al. Hypertension and hearing impairment in workers of iron and steel industry. Indian J Physiol Pharmacol 2006; 50: 60-66. ■ Esparza C.M. et al. Systemic high blood pressure and inner ear dysfunction: A preliminary study. Clin Otolaryngol 2007; 32: 173-178. ■ Torre III P.et al. The association between cardiovascular disease and cochlear function in older adults. J Speech Lang Hear Res 2005; 48: 473-481. ■ Evans M.B. et al. Dyslipidemia and auditory function. Otol Neurotol 2005; 27: 609-614. ■ Chang N-Cet al. Hyperlipidemia in noise-induced hearing loss. Otolaryngol Head Neck Surg 2007; 137: 603-606. ■ Suzuki K., Kaneko M., Murai K. Influence of serum lipids on auditory function. Laryngoscope 2000; 110: 1736-1738. ■ Dabrowski M, Mielnik-Niedzielska G, Nowakowski A. Impact of different modifiable factors on hearing function in type 1 and type 2 diabetic subjects. A preliminary study

	Ann. Agric. Environ. Med., 2013; 20: 773-778. ■ Bainbridge K.E., Cheng Y.J., Cowie C.C. Potential mediators of diabetes-related hearing impairment in the U.S. population. National Health and Nutrition Examination Survey 1999–2004. Diabetes Care 2010; 33: 811-816. Surely, not all of them should be cited. 3. Language. Although language of the manuscript is of acceptable quality, you should check you paper thoroughly to correct some syntax and grammar errors. In summary, your work is valuable and your paper is worth to be published, however, suggested corrections should be implemented.

REVIEWER	Simeon Pierre choukem Faculty of Health Sciences, University of Buea, and Douala General Hospital, Douala, Cameroon
REVIEW RETURNED	23-Jan-2018

GENERAL COMMENTS	Reviewer's report Title: Association between dipstick proteinuria and hearing impairment health in health check-ups among Japanese workers: a cross-sectional study General comments In this study, the authors have sought the potential association between proteinuria and hearing impairment using data from annual check-up in Japanese workers. Though the association found in this study adds to the findings of previous studies and raise questions regarding the underlying mechanisms, the general feeling is that they have done a lot of analyses that dilute the main aim, and the reader finds it difficult to get the main message. Such a study would be better understood if they clearly describe their multivariate models and keep simple and focussed, without trying to display all potential interconnections between variables. It is especially important data/tests not initially intended for research may not be rigorously collected/performed; also the likelihood of chance findings is high. There is an absolute need to review and correct the language. Authors should delete 'prevalence' wherever they have written "associated with the prevalence of…". If they keep the term, they should add 'higher' Abstract - It is not clear which variable is the outcome. You write that hearing impairment was the outcome variable, but the way results are presented suggest that proteinuria was also an outcome variable. You do not describe the procedure for dipstick (what stream of what urine did you test?). - The last sentence of the conclusion is too speculative. The association is not strong enough to suggest that "urine test is effective to detect hearing impairment." Was multivariate analysis done so as to account for potential confounders? Strengths and limitations - Page 6, line 25: delete "was" Introduction - Page 7, 1st paragraph: I suggest you delete the statements on dementia, because they aren't relevant to the study. - Page 7, line 40: delete the second 'in'

	- Page 7, last line: replace ‘administered’ by ‘performed’ - Page 8, line 9: replace “is” in “if dipstick is associated…” by “were” Methods - Page 9, lines 50-55: It is not understood why moderate HI is defined twice. Then, what was defined as mild? What was defined as severe? - Page 10, lines 10-18: was HbA1c tested for all participants or only for those with diabetes? - Page 10, statistical analysis, 1st line: replace ‘cardiovascular risk factors’ by ‘variables’. The variables referred to as cardiovascular factors aren’t actually cardiovascular risk factors. Instead, it is their abnormal levels that are cardiovascular risk factors. This notion should be corrected else were in the manuscript. - Page 10, statistical analysis: the 1st sentence is extremely long (9 lines). Authors should subdivide it to 2-4 sentences for better understanding. - Page 10, statistical analysis: authors should extract all information regarding definitions of variables, and combine them with the definitions of hearing impairment, to form a section ‘definition of variables’ (or whichever appropriate terms). - The statistical analysis section is extremely complicated to the reader. Author should make it much simpler by describing their models (univariate or multivariate, stepwise multivariate…). A major confusion (also raised in the abstract) stems from the fact that some variables (moderate HI, proteinuria, and the so called cardiovascular risk factors) seem to be interchangeably used as dependent and independent variables. - To my opinion, there is no relevance to use “borderline significance”, and this should be deleted. Also, al reference to ‘borderline significance’ in the results should be deleted. - Dipstick proteinuria has a lot of confounders. Authors should describe in what conditions it was performed (what urine (morning or casual)? What stream of the urine? Were other confounders ruled out?) Results - The results are globally too bulky and are not congruent with the main aim of the study. Several comparisons are presented and it is difficult to relate them with the rationale of the study. - 1st paragraph: for better understanding, authors should split it in many sentences. The word ‘including’ brings confusion because the addition of percentages (1.7%+4.5%) is > 5.2%. Obviously some people had HI at both 1Hz and 4Hz; how many? - Absolute need to review and correct the style. There are many redundant words. The word ‘prevalence’ for instance is misused several times. - Page 13: lines 37-38: “…failed to find…” should be replaced by “…did not find…”

VERSION 1 – AUTHOR RESPONSE

Editorial Requirements:
- Please work to improve the quality of English throughout the manuscript, either with the help of a native speaking colleague or with the assistance of a professional copyediting agency.

The manuscript has been edited by a professional native English-speaking proofreader (https://www.edanzediting.co.jp/services/standard.html).

- Please revise the Strengths and Limitations section (after the abstract) to focus on the methodological strengths and limitations of your study rather than summarizing the results.

We checked our manuscript and believe that the Strengths and Limitations section is focused on the methodological strength and limitations.

Reviewer(s)' Comments to Author:

Reviewer: 1
Reviewer Name: Mariusz Dąbrowski
Institution and Country: University of Rzeszów, Faculty of Medicine, Institute of Nursing and Health Sciences; Poland
Please state any competing interests: None declared

Please leave your comments for the authors below

Dear Authors,

You performed interesting study and you found relationship between impaired hearing function and proteinuria in a dipstick test. Your findings are surely worth to be published. However, your manuscript is not free from some issues:
1. The abstract is not fully informative, because the reader cannot find any information about other tests performed in the study population, and that multivariate adjustment was performed. Thus, abstract should be reorganized to include these important informations.

We have revised the manuscript and abstract to include more detail on the kinds of variables that were measured in health checkups. (Page 4)

2. You cite only paper by GA Gates et al. with regards to association between CVD risk factors and hearing (reference #14). There are several newer papers in this field, e.g.:
■ de Moraes Marchiori L.L.et al. Hypertension as a factor associated with hearing loss. Braz J Otorrinolaringol 2006; 72: 533-540.
■ Narlawar U.W.et al. Hypertension and hearing impairment in workers of iron and steel industry. Indian J Physiol Pharmacol 2006; 50: 60-66.
■ Esparza C.M. et al. Systemic high blood pressure and inner ear dysfunction: A preliminary study. Clin Otolaryngol 2007; 32: 173-178.
■ Torre III P.et al. The association between cardiovascular disease and cochlear function in older adults. J Speech Lang Hear Res 2005; 48: 473-481.
■ Evans M.B. et al. Dyslipidemia and auditory function. Otol Neurotol 2005; 27: 609-614.
■ Chang N-Cet al. Hyperlipidemia in noise-induced hearing loss. Otolaryngol Head Neck Surg 2007; 137: 603-606.
■ Suzuki K., Kaneko M., Murai K. Influence of serum lipids on auditory function. Laryngoscope 2000; 110: 1736-1738.
■ Dabrowski M, Mielnik-Niedzielska G, Nowakowski A. Impact of different modifiable factors on hearing function in type 1 and type 2 diabetic subjects. A preliminary study
Ann. Agric. Environ. Med., 2013; 20: 773-778.

■ Bainbridge K.E., Cheng Y.J., Cowie C.C. Potential mediators of diabetes-related hearing impairment in the U.S. population. National Health and Nutrition Examination Survey 1999–2004. Diabetes Care 2010; 33: 811-816.
Surely, not all of them should be cited.

Many thanks to all the reviewer for their thoughtful comments. We included two papers in the introduction to explain the results of previous studies concerned with association between CVD risk factors and hearing impairment/hearing loss. (Page 7)
We have revised the manuscript, especially the results and discussion, so as not to dilute the association between proteinuria and hearing impairment, in accordance with the suggestion from the other reviewer.

3. Language. Although language of the manuscript is of acceptable quality, you should check you paper thoroughly to correct some syntax and grammar errors.

The manuscript has been edited by a professional native English-speaking proofreader (https://www.edanzediting.co.jp/services/standard.html).

In summary, your work is valuable and your paper is worth to be published, however, suggested corrections should be implemented.

Thank you for the helpful comments, which have allowed us to improve the manuscript.

Reviewer: 2
Reviewer Name: Simeon Pierre choukem
Institution and Country: Faculty of Health Sciences, University of Buea, and Douala General Hospital, Douala, Cameroon
Please state any competing interests: None

Please leave your comments for the authors below
Reviewer's report

Title: Association between dipstick proteinuria and hearing impairment health in health check-ups among Japanese workers: a cross-sectional study

General comments
In this study, the authors have sought the potential association between proteinuria and hearing impairment using data from annual check-up in Japanese workers. Though the association found in this study adds to the findings of previous studies and raise questions regarding the underlying mechanisms, the general feeling is that they have done a lot of analyses that dilute the main aim, and the reader finds it difficult to get the main message. Such a study would be better understood if they clearly describe their multivariate models and keep simple and focussed, without trying to display all potential interconnections between variables. It is especially important data/tests not initially intended for research may not be rigorously collected/performed; also the likelihood of chance findings is high.

We have simplified the results, discussion and tables.

There is an absolute need to review and correct the language.

The manuscript has been edited by a professional native English-speaking proofreader (https://www.edanzediting.co.jp/services/standard.html).

Authors should delete ‘prevalence’ wherever they have written “associated with the prevalence of…”. If they keep the term, they should add ‘higher’

We deleted ‘prevalence’ through manuscript as reviewer suggested.

Abstract
- It is not clear which variable is the outcome. You write that hearing impairment was the outcome variable, but the way results are presented suggest that proteinuria was also an outcome variable. You do not describe the procedure for dipstick (what stream of what urine did you test?).

We noticed that Table 1 in the previous manuscript was confusing to readers. We deleted the table and revised the manuscript to describe proteinuria consistently.
With regard to the dipstick urine check procedure, this was done during annual health checkups, so, we could not specify the timing when urine was taken. This point has been added to the limitations.

- The last sentence of the conclusion is too speculative. The association is not strong enough to suggest that “urine test is effective to detect hearing impairment.” Was multivariate analysis done so as to account for potential confounders?

We revised the conclusion in the abstract as follows: “Dipstick proteinuria was significantly associated with overall moderate hearing impairment, as well as moderate hearing impairment at both 1 kHz and 4 kHz.”. Also, we corrected the conclusion section in the manuscript.

Strengths and limitations
-Page 6, line 25: delete “was”

We have deleted “was” accordingly.

Introduction
-Page 7, 1st paragraph: I suggest you delete the statements on dementia, because they aren’t relevant to the study.

We deleted sentences that were not associated with hearing impairment.

- Page 7, line 40: delete the second ‘in’

We have deleted “in” accordingly.

-Page 7, last line: replace ‘administered’ by ‘performed’

We have replaced this accordingly.

-Page 8, line 9: replace “is” in “if dipstick is associated…” by “were”

We have replaced this accordingly.

Methods

-Page 9, lines 50-55: It is not understood why moderate HI is defined twice. Then, what was defined as mild? What was defined as severe?

We revised the manuscript in accordance with your comment about page 10.
We could not define ‘mild’ and ‘severe’ because we only have data for ‘normal’ or ‘abnormal’ for each ear and each frequency. This was already included in the limitations.

-Page 10, lines 10-18: was HbA1c tested for all participants or only for those with diabetes?

We tested for all participants.

-Page 10, statistical analysis, 1st line: replace ‘cardiovascular risk factors’ by ‘variables’. The variables referred to as cardiovascular factors aren’t actually cardiovascular risk factors. Instead, it is their abnormal levels that are cardiovascular risk factors. This notion should be corrected else were in the manuscript.

We have corrected this throughout the manuscript.

- Page 10, statistical analysis: the 1st sentence is extremely long (9 lines). Authors should subdivide it to 2-4 sentences for better understanding.

We deleted this sentence because we deleted Table 1 from the previous manuscript.
Also, we have broken up the first sentence accordingly.

- Page 10, statistical analysis: authors should extract all information regarding definitions of variables, and combine them with the definitions of hearing impairment, to form a section ‘definition of variables’ (or whichever appropriate terms).

We have included a ‘definition of variables’ section in the methods section. (Page 10)

- The statistical analysis section is extremely complicated to the reader. Author should make it much simpler by describing their models (univariate or multivariate, stepwise multivariate…). A major confusion (also raised in the abstract) stems from the fact that some variables (moderate HI, proteinuria, and the so called cardiovascular risk factors) seem to be interchangeably used as dependent and independent variables.

We have revised the manuscript in accordance with your comments to simplify the presentation. With regard to dependent and independent variables, we have deleted the former Table 1 and revised the relevant parts of the manuscript.

- To my opinion, there is no relevance to use “borderline significance”, and this should be deleted. Also, al reference to ‘borderline significance’ in the results should be deleted.

We have corrected these points as suggested.

-Dipstick proteinuria has a lot of confounders. Authors should describe in what conditions it was performed (what urine (morning or casual)? What stream of the urine? Were other confounders ruled out?)

We could not specify the timing when urine was taken. This point has been added to the limitations..

Results
-The results are globally too bulky and are not congruent with the main aim of the study. Several comparisons are presented and it is difficult to relate them with the rationale of the study.

We have corrected the presentation to more clearly show our findings.

-1st paragraph: for better understanding, authors should split it in many sentences. The word 'including' brings confusion because the addition of percentages (1.7%+4.5%) is > 5.2%. Obviously some people had HI at both 1Hz and 4Hz; how many?

We found that 61 subjects had moderate HI at both 1 kHz and 4 kHz. We have corrected the manuscript accordingly.

-Absolute need to review and correct the style. There are many redundant words. The word 'prevalence' for instance is misused several times.

We have revised the manuscript entirely. Also, we asked a professional native English-speaking proofreader to check our manuscript.

-Page 13: lines 37-38: "…failed to find…" should be replaced by "…did not find…"

We have deleted this paragraph.

VERSION 2 – REVIEW

REVIEWER	Mariusz Dąbrowski University of Rzeszów; Faculty of Medicine; Poland
REVIEW RETURNED	04-Mar-2018

GENERAL COMMENTS	Dear Authors, You introduced all the corrections recommended by Reviewers and Editors. The results are presented in clear and understandable way. Moreover, the results you obtained give a new important informations for the practice regarding relationship between kidney and hearing organ function (although we do not know exact mechanisms linking these two abnormalities). Thus, the topic of your paper is not only interesting but also clinically relevant. In current form the article is written in clear, understandable English, and I have no further remarks regarding your paper. Best Regards.

REVIEWER	simeon Pierre Choukem University of Buea Faculty of Health Sciences
REVIEW RETURNED	18-Mar-2018

GENERAL COMMENTS	My queries have been fully adressed