Author’s response to reviews

Title: Associations of Noise Kurtosis, Genetic Variations in NOX3 and Lifestyle Factors with Noise-induced hearing loss

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Responses to reviewers’ comments

Dear Editor:

Thank you for your kind letter on December 5, 2019. We revised our manuscript based on the reviewers’ comments, and carefully proof-read the manuscript to minimize typographical, grammatical, and bibliographical errors. Here below is our responses to the reviewers’ comments.

To Reviewer #1:
1. The English of the manuscript must be improved before re-submission. In the methods of abstract section, it is appropriate to use the passive voice.
   Response: Thank you very much for reviewing our paper. The active voice has been changed into the passive voice in the methods of abstract section (to see line 28-31).

2. In the methods of abstract section, the relationship between GT genotype and NOX3 should be explained.
   Response: Thank you for your careful review. In this study, three SNPs of NOX3, including rs3749930, rs12665231, rs12195525 in the exon region were tested. The rs12195525 consisted of GT, GG and TT genotypes. We found the GT genotype of NOX3 rs12195525 was associated with noise-induced hearing loss (NIHL) (to see line 37-42 in the abstract).
3. It is suggested to modify the keywords as follows: noise; kurtosis; NOX3; lifestyle; interaction; hearing loss
Response: Thank you for your nice advice. We have modified the keywords as you suggested (to see Line 48).

4. The definition of complex noise needs to be further clarified.
Response: Thank you for your valuable advice. "A complex noise is a non-Gaussian noise consisting of a Gaussian (steady) background noise which is punctuated by a temporally complex series of randomly occurring high-level noise transients." We have added the clarification of complex noise in the introduction (to see line 87-89).

5. Line 78 "law of equal energy" should be replaced with "equal energy hypothesis (EEH)". The hypothesis assumes that regardless of the type of noises, if the equivalent sound levels of noises are the same, the noise-induced hearing losses are equivalent.
Response: Thank you for your valuable advice. We have changed "law of equal energy" into "equal energy hypothesis (EEH)" as you suggested (to see line 83).

6. In the Subjects section, how is the 307 controls selected?
Response: Thank you for your review. The sentence of "The 307 controls with normal hearing, who were matched with gender and age (±3 years), were also selected from the same database." was added (to see line 120-121).

To Reviewer #2:

1. Was the CNE calculated over the working years? The noise measurement using kurtosis is complicated and need some further explanation;
Response 1: Thank you very much for reviewing this paper. The cumulative noise exposure (CNE) was calculated over the working years. CNE, a composite noise exposure index, was used to quantify the noise exposure for each participant. The formula of CNE can be seen in line 154. Where LAeq.8h is the equivalent continuous A-weighted noise exposure level normalized to an 8-hour working day, in decibels, occurring over the time interval Ti in years (working years in the i-th work type); with a total of n different noise levels (i.e. different working tasks/environments) that the participants were exposed to during their employment history (to see line 158-162).

Response 2: The further explanation for kurtosis is as follows: Kurtosis is defined as the ratio of the fourth-order central moment to the squared second-order central moment of a distribution. Kurtosis describes the peakedness of a distribution, which is independent of the overall level and was suggested as a metric of impulsiveness. Kurtosis is proportional to the noise impulse energy. A mean value of the kurtosis, noise environments, was calculated from 8-h noise from the factory. A set of recordings was sampled over the course of the measured subject’s work. The sampling kurtosis of the continuous 40-second time window of the noise signal during the entire shift was calculated using MATLAB software (Natick, MA). We have added some explanations in the introduction (line 86-94) and method (line 167-172).

2. A more detailed rational for choosing beta > 10 as complex noise should be given.
Response: In theory, the kurtosis of Gaussian noise is 3. However, Gaussian noise is rare in real workplaces. Instead, more noise types are close to Gaussian or complex noise. Therefore, it is
appropriate to take 10 of kurtosis as the boundary value of Gaussian noise and complex noise, which was supported by other literatures (to see line 167-172).

3. Was only one 40 s window from each 8 h shift used to calculate the kurtosis?
Response: Thank you for your careful review. In our study, the number of kurtosis which was obtained during the 8-hour work of each worker was 720 (8*3600/40=720), which was calculated sequentially based on a continuous 40s window. We took the average of all kurtosis as the noise kurtosis of this worker. The time period of 40s window gave consideration to the computational efficiency and the dynamic characteristics of complex noise. Our research team has analyzed the correlation between the time length of a window and noise-induced hearing loss (NIHL), and found that a window length of 40s to 1 minute might be most associated with NIHL (not yet published).

4. If so, how was it established that the chosen window was representative? This fact should also be discussed in the limitations of the study in the discussion.
Response: That's a good question. Based on our response to the previous comment, we collected all 40s windows in each work shift, then calculated the average kurtosis, instead of just taking one time window. However, there were still limitations regarding the window time, as the reviewer mentioned, the correlation between window time length and hearing loss needed further study because the types and data of noise sources were not sufficiently abundant in this study (to see line 462-464).

5. First part of Table 1 could be shown as a figure using staples to liven up the paper
Response: Thank you for your advice. We have simplified the Table 1.

6. Line 408 should read 'Thus, the rs12195525 SNP could affecting noise-induced hearing loss by altering NADPH oxidase expression.'
Response: Thank you for your valuable advice. We have modified this sentence as you suggested (to see line 401-402).

7. Some references are old and could be updated
Response: Thank you for your advice. We have updated some references that are old as you suggested.

8. Could add epidemiology references that that show risk factors for NIHL there are several available
Response: Thank you for your advice. We have added the description of risk factors for NIHL in the introduction (to see line 74-80), and added the epidemiology references ([6-8]).

9. Numbering of refs are wrong and must be corrected
Response 8: Thank you for your advice. We checked all the references again, and added several epidemiology references. Finally, we updated the number of references.

10. A more detailed section could be added to the discussion of possible other factors, besides those investigated, that could influence the fact that the control has no hearing loss despite almost the same exposure.
Response: Thank you for your advice. NIHL is caused by an interaction between genetic and environmental factors, the contributing factors of hearing impairment were categorized into occupational noise exposure, non-occupational noise exposure (such as free time noise exposure and firearm activities), individual susceptibility such as sociodemography (age, gender, ethnicity, and education levels), smoking habit, medical problems (hypertension, diabetes mellitus, hypercholesterolemia, and infections), ototoxic drugs, compliance to hearing protection device (HPD) usage, and knowledge and perception regarding noise and HPD. We have added it in the introduction.
(line 74-80), and illustrated it in the limitation of discussion (Line 464-466).

Many grammatical or typographical errors have been revised. All the lines and pages indicated above are in the revised manuscript.

Thank you and all the reviewers for the kind advice.

Sincerely yours,

Tianyu Zhao