Noise Exposure as a Risk Factor for Acoustic Neuroma:

A Systematic Review and Meta-analysis

Zuwei Cao[1, 2], Fei Zhao[2,3*], and Helena Mulugeta[4]

1. Center for Rehabilitative Auditory Research, Guizhou Provincial People's Hospital, Guiyang, China;

2. Centre for Speech and Language Therapy and Hearing Sciences, Cardiff School of Sport and Health Sciences, Cardiff Metropolitan University, Cardiff, Wales;

3. Department of Hearing and Speech Science, Xinhua College, Sun Yat-Sen University, Guangzhou, China

4. Children and Young People's Audiology Centre, St Thomas' Hospital, London, England

* *Correspondence:fzhao@cardiffmet.ac.uk; Tel.: +44-07590033326*

Abstract:

Objective: To investigate whether acoustic neuroma is associated with noise.

Design: PubMed, Cochrane, Embase and CINAHL databases were searched. A meta-analysis was performed to calculate odds ratio (OR) and 95% confidence interval (CI) using quality-effect models. *Study sample:* A total of 8 studies with moderate or high quality involving 75,571 participants met the inclusion criteria.

Results: There was no significant relationship between overall noise exposure and acoustic neuroma (OR:1.02, 95% CI: 0.64 - 1.63). However, further subgroup analysis showed that leisure noise exposure (OR: 1.73, 95% CI: 1.10 - 2.73), above five years' exposure (OR: 1.81, 95% CI: 1.14 - 2.85) and continuous exposure (OR:2.77, 95% CI: 1.70 - 4.49) were associated with an increased risk of acoustic neuroma.

Conclusions: These results suggest an elevated risk of acoustic neuroma among individuals who have been exposed to occupational noise when some subgroup analysis are conducted. Leisure noise in particular seems to play a significant role in the development of acoustic neuroma. However, due to the heterogeneity among the included studies, this conclusion should be interpreted with cautions, even though the continuous long-term consequences should not be ignored.

1. Introduction

Acoustic Neuroma (AN) is a benign Schwannoma arising from the Schwann Cells of the Vestibular division of the eighth Cranial Nerve (Gelfand, 2009). They account for approximately 6% of all intracranial tumors (Anderson et al., 2000) with an incidence of 1.1 per 100,000 (Gal et al., 2010; Kshettry et al., 2015).

Several studies have implicated etiological factors in the development of acoustic neuroma such as; genetic factors (Evans et al., 1992), radiation exposure (Lönn et al., 2004) and noise exposure (Fisher et al., 2014). The most established risk factor for bilateral AN is the genetic condition Neurofibromatosis Type 2 (NF2). This disorder is characterized by the development of multiple Schwannomas and Meningiomas (Evans, 2009). However, there is evidence that exposing children to high dose ionizing radiation may also increase the risk of AN later in life (Schneider et al., 2008). In this latter study, the effect of radiation exposure to reduce tonsil and adenoid size was investigated. Such exposure provides a significant radiation dose to the Cerebello-Pontine Angle. An association was identified with 43 out of 3112 participants developing benign AN later in life (43/3112,1.38%).

Although noise exposure is considered a risk factor, the correlation is far less conclusive, mainly because of inconsistencies in data. For example, an early study by Preston-Martin et al. (1989). found that occupational noise exposure was associated with increased risk of AN. Their participant group was men in Los Angeles County, USA. Each participant was interviewed and completed a questionnaire about occupational history and various life experiences of noise, chemical, and radiation exposure. The occupational histories in each case were reviewed to assess the risk of noise exposure with reference to the National Occupational Hazards Survey (Rantanen 1981). The results showed an increased risk of AN with increased duration of noise exposure.

Like Preston-Martin et al. (1989), Hours et al. (2009) investigated the possible associations between AN and exposure to loud noise in leisure and occupational settings. They also found an increased risk of AN with increased noise exposure duration. However, a case-controlled study by Edwards et al. (2007) on full-time employees obtained from the Swedish census between 1975 and 1990 found no increased risk of AN in relation to occupational noise exposure, even after a long period of observation. It is noteworthy that statistically significant associations between leisure-time exposures to loud noise without hearing protection were found in this large sample study.

Such inconsistent conclusions can only be resolved by a quantitative synthesis of existing data to help address the uncertainty. Until now, only a couple of systematic reviews on risk factors of AN have been published. Although various risk factors (such as chemical exposure, cell phone use, noise exposure) have been reviewed by Corona et al. (2009), methodological limitations and lack of precision in analyzing the findings impose limits to definitive conclusions concerning those risk factors. A recent systematic review with meta-analysis on risk factors of AN has been published by Chen et al. (2016). Unfortunately, there are a couple of weaknesses in this review: a) The risks included other factors besides noise exposure, such as smoking and allergic diseases, but they only dealt with this high heterogeneity by employing a random-effects model, which underestimates the statistical error and makes unjustifiable changes to study weights (Doi & Thalib, 2008). b) They failed to conduct sensitivity and subgroup analyses, which provide a comprehensive understanding of the quality of included data, and test the robustness of the results. In the present systematic review, we conduct an up-to-date meta-analysis of the exposure-response relationship between noise and AN using advanced statistical techniques and take into account the study heterogeneity.

2. Methods

2.1 Search strategy and data sources

PubMed, Cochrane, Embase and CINAHL databases were searched from inception dates to September 17, 2017, using the keywords: (acoustic neuroma OR vestibular schwannoma) AND (noise OR acoustic trauma OR sound OR occupational noise OR environmental exposure OR leisure noise OR noise exposure). There were no restrictions placed on study population by age, language or ethnic background. The retrospective studies, cross-sectional studies, case-control or cohort studies which looked at noise (both leisure or environmental noise and occupational noise included) and its relationship with AN were included. Because all the included articles for meta-analysis were observational studies, this systematic review was conducted following the MOOSE guideline (Stroup et al., 2000). Animal studies were excluded. Case reports or editorials were also excluded as no quantifiable data was present for use in the meta-analysis.

Electronic search results were checked for eligibility. When they were not rejected from title/abstracts, full texts were retrieved. Reference lists and indexes of studies were also scanned for further trials. Existing systematic reviews relevant to this review were also sought to identify additional trials from their reference lists. Authors were contacted if full texts could not be retrieved and if discrepancies occurred within studies. In addition, Audiology textbooks were also manually searched for relevant references. All studies identified by this process were subsequently screened by two independent reviewers.

2.2 Statistical analysis

Meta-analysis was performed on the extracted data with MetaXL 5.3 software (http://www.epigear.com/index_files/metaxl.html). The association of noise exposure with AN was assessed. Different exposure time and intension together with each type of noise source were compared separately. An odds ratio (OR) or relative risk (RR) with a 95%

confidence interval (CI) were calculated. In the present study, the RR was converted to OR using Zhang's format for analysis (Zhang & Yu, 1998).

The quality of individual studies affects the quality of the combined estimates as well as the magnitude of the results, regardless of the use of a fixed- or random-effects model (Doi & Thalib, 2008). Therefore, it is crucial to assess the quality of individual studies included for systematic review with meta-analysis. As a result, a quality-effects model for the meta-analysis was constructed. With this approach, the quality-effects model was able to redistribute the weighting of individual studies in the statistical model/analysis according to their quality. Therefore, high quality studies give greater weight in the analysis, so that more robust results are obtained when analyzing heterogeneous studies. In the present analysis weightings were derived directly from the quality score as well as the study sample size (Table 1).

To assess quality of the case-controlled cohort studies included in this meta-analysis, a modification of the Newcastle-Ottawa Scale (NOS) (Wells et al., 2016) was used. The rating criteria includes definition and selection of case and controls, comparability of the groups, ascertainment of exposure and non-response rate. A 9-point scale was used to assess the quality of the studies, with a score of 0-5 points, 6-7 points, and 8-9 points indicating low, moderate, and high quality, respectively.

To evaluate heterogeneity, sensitivity analysis and subgroup analysis were also conducted. Sensitivity analysis was planned to assess the possible impact on the estimates of the effect of different studies, while subgroup analysis was undertaken according to noise exposure sources (i.e., occupational and leisure noise exposure), noise exposure time and noise exposure patterns. In the present systematic review, occupational noise exposure was defined as contact with potentially hazardous acoustic energy in the workplace, whereas leisure noise exposure included potentially hazardous acoustic energy received by people

involved in daily activities outside the workplace, such as sport related noise exposure (e.g., motor bikes, shooting), listening to music, indulging in nightclubs or doing house work. In addition, the noise exposure time and pattern were categorized as up to or over 5 years, and intermittent or continuous (more than 5 hours a day) (Pourbakht & Yamasoba, 2003), respectively.

3. Results

3.1 Studies retrieved and the summary

The search identified 328 studies on PubMed, 12 on Cochrane, 17 on CINAHL, 59 on Embase. After removing 88 duplicate references, titles and abstracts of these records were screened for inclusion. Full texts of 27 records were read to assess their eligibility. Five studies were excluded as noise was considered a secondary influence factor without the data of the OR results, and subsequently eight studies were included in present systematic review with meta-analysis. Figure 1 shows a flow diagram of the selection process.

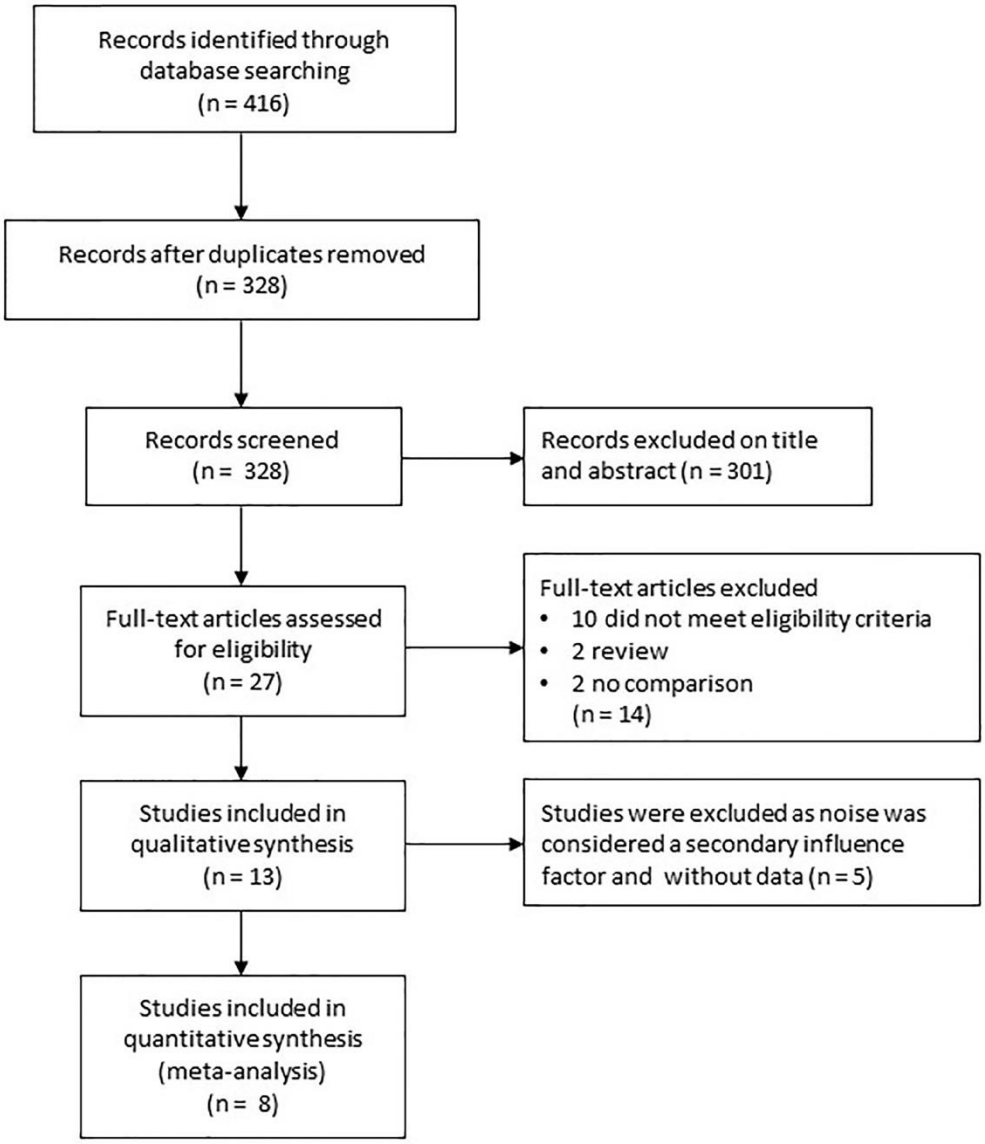

Figure 1. Flow diagram of the study selection process

The eight case-control studies were conducted in USA, Sweden, Germany, France and Brazil and involved 1,846 cases and 75,571 controls. Table 1 summarizes the studies, including sample size for each, methods and main results. The majority of studies investigated associations with occupational noise (Preston-Martin et al., 1989; Edwards et al., 2007; Corona et al., 2012; Han et al., 2012), while some included leisure noise (Edwards et al., 2005; Schlehofer et al., 2007; Hours et al., 2009; Fisher et al., 2014). Of the eight studies, two

(Corona et al., 2012; Han et al., 2012) also evaluated other environmental risk factors including exposure to radiation. Six studies (Preston-Martin et al., 1989; Edwards et al., 2005; Schlehofer et al., 2007; Hours et al., 2009; Corona et al., 2012; Han et al., 2012) used similar procedures to collect data, using either an interview or questionnaire. Two other studies (Edwards et al., 2007; Fisher et al., 2014) chose the Job Exposure Matrix, which was a cross-classification between numerous occupations and actual noise measurements taken during different time periods.

As shown in Table 1, because different noise features were observed in these studies, the OR results varied, and the conclusions obtained from the individual studies were inconsistent. Three studies (Preston-Martin et al., 1989; Edwards et al., 2005; Hours et al., 2009) indicated an association between noise exposure and AN, whereas the other studies (Schlehofer et al., 2007; Edwards et al., 2007; Corona et al., 2012; Han et al., 2012; Fisher et al., 2014) did not.

Furthermore, four studies assessed the risk of leisure noise exposure and occupational noise exposure. Of these, three (Edwards et al., 2005; Hours et al., 2009; Fisher et al., 2014) showed an association between leisure noise exposure and increased risk of AN. However, it is noteworthy that the study (Schlehofer et al., 2007) with a negative conclusion had a limited sample size.

Table 1. The descriptions and the quality assessment results of the studies

Study	Cases/controls	Noise Exposure Source	Assessment	Results: OR (95% CI)	Conclusion	Study Quality
Preston-Martin et al. (1989) USA	86/86	Occupational noise exposure	Interview and questionnaire	• <5 years=2.9(1.00-8.60) • 5-15 year=1.7(0.60-4.67) • ≥15 years=3.5(1.12-11.17)	Increased risk of acoustic neuroma was associated with increased duration of noise exposure.	Moderate (7 points)
Edwards et al. (2005) Sweden	146/564	Occupational and leisure noise exposure	Interview and questionnaire	Duration-occupational and leisure noise: • <5 years=1.51(0.77-2.95) • 5-15years=1.64(0.91-2.91) • ≥15 years=1.56(0.91-2.66) Noise sources- • Occupational=1.79(1.11-2.89) • Leisure=2.2 (1.20-4.23)	Exposures to occupational and regular nonoccupational loud noise were all associated with an increased risk of acoustic neuroma	High (8 points)
Schlehofer et al. (2007) Germany	94/190	Occupational and leisure noise exposure	Interview and questionnaire	Noise character-occupational noise: • Intermittent=1.01(0.42-2.43) • Persistent=2.31(1.15-4.66) • Explosive=2.49(0.32-19.32) Noise sources– • Occupational=2.02(1.20-3.39) • Leisure=0.96(0.35-2.63)	Exposure to persistent noise in occupational activities increased the risk for acoustic neuroma. However, recreational exposure to noise was not associated with an increased risk.	Moderate (7 points)
Hours et al. (2009) France	108/212	Occupational and leisure noise exposure	Interview and questionnaire	Duration-occupational noise: • <2 years=1.10(0.37-3.34) • 2-5 years=2.16(0.77-6.05) • ≥ 5 years=3.72(1.45-9.59) Noise character-occupational noise: • Intermittent=1.86(0.90-3.88) • Continuous=3.27(2.24-8.61) • Explosive=2.39(1.17-4.92) Noise sources– • Occupational=2.26(1.08-4.72) • Leisure=4.94(1.32-18.48)	The risk for acoustic neuroma was associated with loud noise exposure either in a leisure or in a work setting. The association was particularly strong in subjects with noise exposure over a long period.	Moderate (7 points)

continued

Table 1 continued

Fisher et al. (2014) Sweden	451/710	Occupational and leisure noise exposure	Questionnaire and job exposure matrix	• Occupational (with protection) =1.44(0.84-2.46) • Occupational (without protection) =1.27(0.85-1.87) • Leisure =1.55(1.11-2.16)	No association between occupational exposure to loud noise and acoustic neuroma. However, the results provide some evidence for associations between leisure-time exposures to loud noise and acoustic neuroma	Moderate (7 points)
Edwards et al. (2007) Sweden	599/73432	Occupational noise exposure	Job exposure matrix	≥ 5 years • 75-84dB = 0.99(0.80-1.23) • ≥85dB = 0.93(0.67-1.28) ≥ 10 years • 75-84dB = 1.09(0.89-1.32) • ≥85dB = 0.99(0.72-1.36) ≥ 15 years • 75-84dB = 1.00(0.83-1.22) • ≥85dB = 1.04(0.76-1.42)	No increased risk of acoustic neuroma associated to occupational noise exposure, even after a long period of observation time.	High (8 points)
Corona et al. (2012) Brazil	44/104	Occupational noise exposure	Interview	0.62(0.29-1.32)	Did not reveal occupational noise as a risk factor for vestibular nerve Schwannoma.	Moderate (6 points)
Han et al. (2012) USA	343/343	Occupational noise exposure	Interview and questionnaire	0.45(0.33-0.61)	No association was found.	Moderate (6 points)

Note: The order for included studies follows two criteria, i.e., Criteria 1: the studies showed the OR>1, followed by the studies with OR<1; Criteria 2: studies within the same category were arranged in chronological order.

3.2 Quality assessment of retrieved studies

As shown in Table 1, utilizing NOS, gave the retrieved studies scores of six or above indicating moderate or high quality. Table 2 shows detailed quality assessment outcomes of the included studies using the NOS. All of these studies had well defined cases and controls, together with ascertainment of noise exposure and measurement methods. However, not all had good comparability between cases and controls as a result of study design, except that of Hours et al. (2009) and Edward et al. (2007). Moreover, bias in selection of controls was found in two studies (Corona et al., 2012; Han et al., 2012), and non-response rate was inconsistent between the case and control groups in 3 studies (Hours et al., 2009; Fisher et al., 2014; Edwards et al., 2007) also leading to decline in study quality. Inappropriate representativeness of cases was found in the study by Hours et al. (2009) because some patients managed by simple surveillance may have failed to take part in the study.

Table 2. Assessment results of the included studies

	Definition of Cases	Representativeness of Cases	Selection of Controls	Definition of Controls	Comparability of Cases and Controls*	Ascertainment of Exposure	Method of ascertainment of Exposure	Non-response rate
Preston-Martin et al. (1989)	+	+	+	+	-/-	+	+	+
Edwards et al. (2005)	+	+	+	+	+/-	+	+	+
Schlehofer et al. (2007)	+	+	+	+	-/-	+	+	+

Hours et al. (2009)	+	-	+	+	+/+	+	+	-
Fisher et al. (2014)	+	+	+	+	+/-	+	+	-
Edwards et al. (2007)	+	+	+	+	+/+	+	+	-
Corona et al. (2012)	+	+	-	+	-/-	+	+	+
Han et al. (2012)	+	+	-	+	-/-	+	+	+

*: The study can be awarded a maximum of two marks for this item, with only one mark for the other items.

3.3 Meta-analysis results

As mentioned in the Methodology section, a quality-effects model was constructed to calculate OR and 95% CI for the exposure-response analysis. In the present study, the weight was measured by combining impact of the quality of the literature and number of participants in each included study, rather than considering the sample size only. As shown in Figure 2, the OR was 1.02 (95% CI: 0.64 - 1.63). There was no significant relationship between overall noise exposure and AN. The meta-analysis showed a high heterogeneity among eight included studies ($p < 0.01$, I^2=85%). This may be due to having different exposure categories for the risk factors and using different clinical assessment methods. For example, four studies investigated the association between AN and occupational noise exposure only, whereas the others demonstrated both occupational and leisure noise exposure. Moreover, the assessments varied from interview, questionnaire and the job exposure matrix. As a result, sensitivity analysis and subgroup analysis were performed to overcome these heterogeneities.

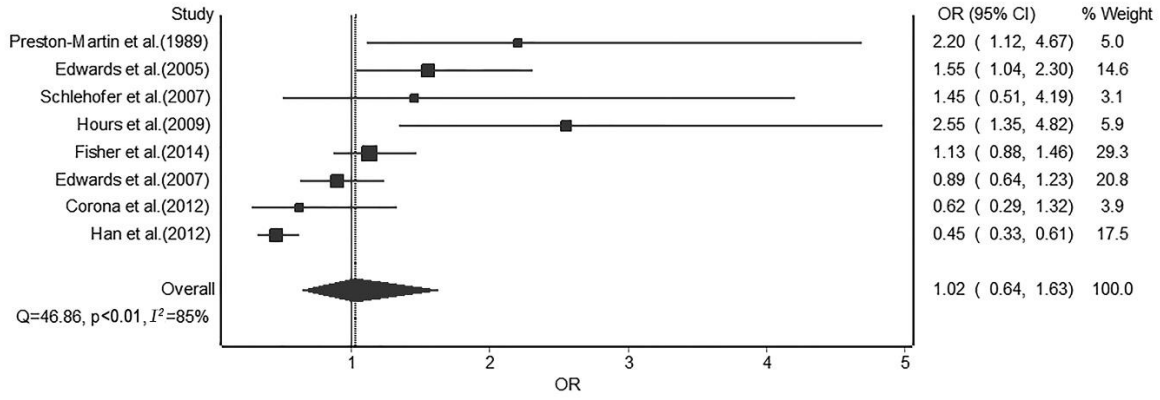

Figure 2. Forest plot of studies on the association between the acoustic neuroma and overall noise exposure.

The robustness of the meta-analysis was further explored by conducting sensitivity analysis. As shown in Table 3, substantial heterogeneity was still found (i.e., I^2 ranged from 63% to 87%) when each study was excluded individually (Higgins et al., 2003).

Table 3. Summary of sensitivity analyses when each study was excluded individually

Excluded study	OR	95% CI	I^2
Preston-Martin et al. (1989)	0.98	0.61,1.58	85%
Edwards et al. (2005)	0.96	0.57,1.61	85%
Schlehofer et al. (2007)	1.01	0.63,1.64	87%
Hours et al. (2009)	0.97	0.62,1.52	84%
Fisher et al. (2014)	0.97	0.54,1.76	87%
Edwards et al. (2007)	1.07	0.59,1.91	87%
Corona et al. (2012)	1.05	0.64,1.70	87%
Han et al. (2012)	1.21	0.86,1.70	63%

Further analysis was conducted by examining noise source, exposure time and intensity in different subgroups (Figure 3). Four studies intended to explore the relationship between leisure noise and AN. Within these studies, there were 656 cases and 1,413 controls from

France and Sweden with similar age and sex. Using similar assessment methods (i.e., interview or questionnaire), a significant association between leisure noise exposure and high incidence of AN was found in three studies. Using a quality-effects model, the OR was 1.73 (95% CI: 1.10 - 2.73). This suggested that leisure noise exposure was significantly associated with an increased risk of AN. Furthermore, the OR of AN with occupational noise exposure more than five years (OR=1.81, 95% CI: 1.14 - 2.85) was higher than that in occupational noise exposure below five years (OR=1.42, 95%CI: 0.84 - 2.39). This means that occupational noise exposure of more than five years was associated with an increased risk of AN. Similarly, there was a relationship between AN and the continuous occupational noise exposure (OR=2.77, 95% CI: 1.70 - 4.49) rather than the intermittent occupational noise exposure (OR=1.45, 95% CI: 0.86 - 2.61).

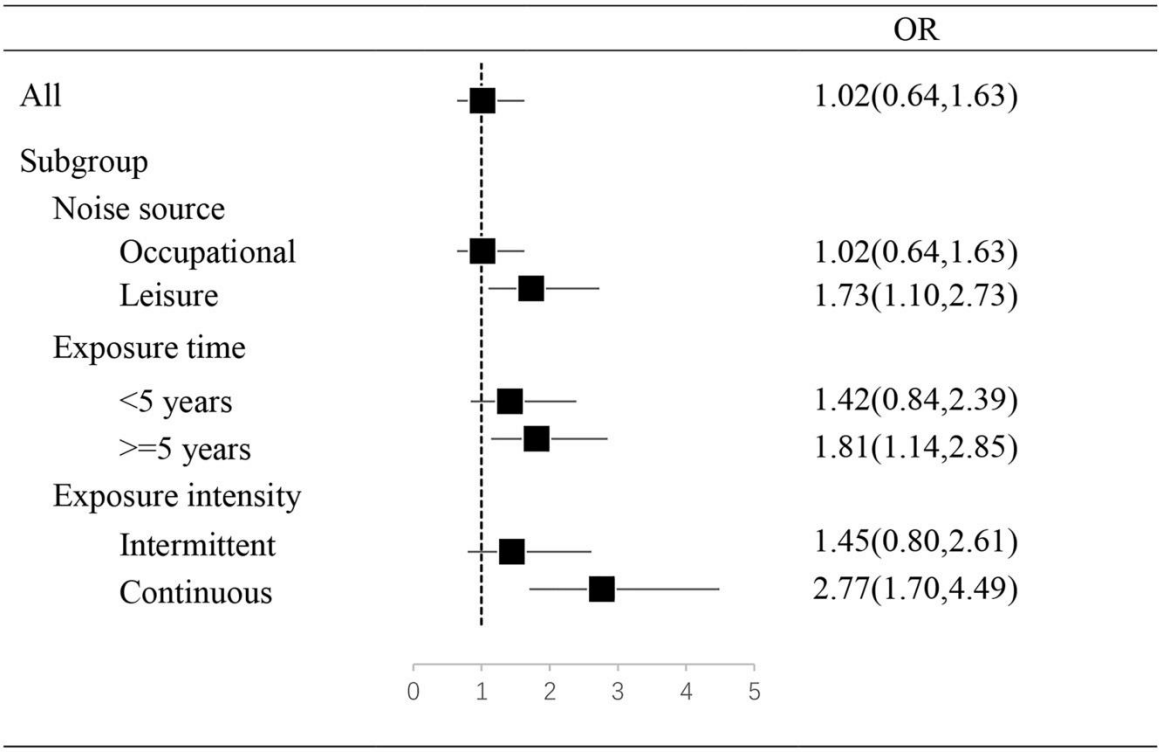

Figure 3. Risk of subgroup studies on the association between acoustic neuroma and noise exposure.

4. Discussion

Noise can be described as “an unwanted sound” (Seidman & Standring, 2010) that has many negative impacts on people’s daily life. For example, noise in the speech setting may interfere or disrupt verbal communication. In addition, any noise exposure of significant intensity and duration increases the risk of permanent hearing damage, known as noise induced hearing loss (NIHL) (Zhao et al., 2010; Kurabi et al., 2017).

Early studies have suggested possible biological mechanisms for the association between AN and noise exposure. Mechanical damage induced by noise exposure may destroy the hair cells in the Organ of Corti and the eighth Cranial Nerve (Hamernik et al., 1984; Bohne et al., 2007). During repair, DNA errors may occur during cell division, leading to disordered proliferation of cells (Fisher et al., 2014). An alternative possible mechanism is that loud noise exposure can damage the Styria Vascularize and lead to a mixing of cochlear fluids by changing the tight cell junction of the Reticular Lamina (Henderson & Hamernik, 1995), and consequently causing the hair cells to be immersed in fluid with a non-physiological complement of electrolytes. Because electrolyte balance is very important for maintaining normal function of the nerve cells, the damage induced by this electrolyte disequilibrium could lead to degeneration of the eighth Cranial Nerve, and consequently the Schwann cells as the supporting cells of the nerve system may lose the ability to protect the auditory nerve fibers (Hours et al., 2009). Indeed some animal studies have shown that free radicals that can cause DNA damage were found in vestibular ganglion cells after exposure to loud acoustic stimulation (Van Campen et al., 2002; Watanabe et al., 2004). This suggests that noise could be responsible for the development of AN (Hours et al., 2009). Lastly, nerve growth factors may be induced by loud noise and subsequently contribute to tumorigenesis (Hamernik et al., 1984; Lesser & Pollak, 1990).

Several important components of noise should be considered when exploring the relationship between noise exposure and occurrence of AN. Noise can be characterized by its source, nature, and duration (McJury & Frank, 2000). For example, noise can be occupational in nature (originating from workplace), or can originate from all other settings, such as environmental noise (e.g., traffic noise), or be related to leisure activities (e.g., hoovers, lawn mowers, or loud music).

Different noise sources may have different underlying mechanisms behind their damage effects. According to the previous studies, loud impulse noise can destroy up to 60% of the Outer Hair Cells in the Cochlea instantly, whereas continuous noise (such as occupational noise) wears the Cochlea down gradually, and would cause 60% destruction only after exposure for several years (Hamernik et al., 1984; Hamernik et al., 1984). It is noteworthy that leisure noise characterized by very high-levels and a greater proportion of low-frequency components may be more destructive to the auditory nerve and surrounding tissue, and hence be more likely to increase the risk of development of AN (Fukushima et al., 1990; Berglund et al., 1996; Sadhra et al., 2002; Noreña & Eggermont, 2005).

Several recent studies have explored the influence of the different sources of noise, occupational noise or leisure music on the occurrence of AN separately (Edwards et al., 2005; Schlehofer et al., 2007; Hours et al., 2009; Fisher et al., 2014). Three of these studies (Edwards et al., 2005; Hours et al., 2009; Fisher et al., 2014) found loud noise from leisure activity, such as music, to present a higher risk in the development of AN. In these articles, after adjusting for race, education, cigarette smoking, alcohol consumption, use of cell phones, and family history of cancer, the authors identified the highest OR of occupational noise to be 2.26 (1.08 - 4.72), whereas the highest OR of leisure noise is 4.94 (1.32 - 18.49). This suggests an increased risk of AN from leisure noise in particular.

This meta-analysis indicates that the type of noise exposure could potentially influence the risk of AN development, particularly relating to leisure noise exposure. Because it is different from noise exposure at work, people may not take precautions to protect their hearing when they are exposed to noise during entertainment or undertaking domestic tasks. Therefore, more detailed risk factors should be further explored.

In this analysis we searched multiple databases and reference lists, with study selection, data extraction and quality assessment being undertaken by two independent researchers. We also addressed the importance by running subgroup analysis for each exposure setting–outcome scenario or different sources of bias. We used advanced statistical techniques as well, such as the quality-effects model which gives more credible and conservative results than the random-effects model (Doi et al., 2015) and performs reasonably well in the presence of statistical heterogeneity (Doi et al., 2011).

However, our review needs to be considered in light of several limitations. Firstly, although the present meta-analysis review has been conducted systematically and comprehensively using various approaches for quality analysis, the outcomes derived from this review are certainly affected by the inherent shortcomings of the included observational studies. There are several possible limitations in the included studies, such as bias in recalling noise exposure history, inappropriate study design in terms of blinding and the other factors that may affect noise exposure (e.g. the use of hearing protection devices in the workplace). Moreover, the poor comparability between cases and controls, and inconsistent non-response rate between the case and control groups also lead to a decline in study quality.

Secondly, due to some heterogeneity for exposure and assessment methods, there is a possibility that the conclusions may not exclude the influence of other confounding factors, such as x-ray exposure (Han et al., 2012), chemicals exposure (Prochazka et al., 2010) and smoking (Palmisano et al., 2012). Furthermore, more epidemiological data should be

collected in developing countries, because most of the current studies were conducted in western populations, which might limit the generalization of the findings. In addition, the publication bias was not assessed due to the limited studies we included for this systematic review.

5. Conclusion

The results of this systematic review suggest an elevated risk of AN among individuals who have been exposed to occupational noise when some subgroup analysis are conducted. Long duration and high intensity of occupational noise exposure an individual receives would appear to make the development of AN more likely. Moreover, leisure noise exposure seems to play a significant role in the development of AN. However, due to the heterogeneity among the included studies, the association between noise and AN is weak. The continuous long-term consequences should not however be ignored.

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