Systematic Review and Meta-Analysis

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Correlation between mitochondrial DNA 4977 bp deletion and presbycusis

A system review and meta-analysis

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Abstract

Objective: Researchers have evaluated the associations between mitochondrial DNA (mtDNA) 4977 bp deletion and presbycusis. This study aimed to assess the differences of mtDNA 4977 bp deletion between presbycusis patients and controls by conducting a meta-analysis of published studies.

Methods: Databases, including PubMed, Embase, Web of Science, China National Knowledge Infrastructure (CNKI), and Wanfang Data were searched to collect case–control studies on the correlation between mitochondrial DNA 4977 bp deletion and presbycusis. The research findings of related articles were collected according to the inclusion criteria. Pooled odds ratios (ORs) and corresponding confidence intervals (CIs) were calculated. Meanwhile, subgroup analysis was performed to examine the source of heterogeneity. Revman 5.3 and Stata 12.0 software were used for data synthesis.

Results: Eight English and Chinese studies were included in the meta-analysis, the results of which showed that mitochondrial DNA 4977 bp deletion could increase the risk of presbycusis (OR = 8.16, 95% CI: 3.51–18.99), and the difference was statistically significant ($P < .01$). Analysis of the polled OR showed the incidence of mtDNA 4977 bp deletion was 8.50 times higher in Asians with presbycusis than in the control group. And the OR in the studies of occidentals was 7.24. Sample source analysis was also performed with the sample source divided by temporal bone source and other sources (hair and blood). The OR was 4.18 and 22.36 for the temporal bone and other sources, respectively.

Conclusion: Mitochondrial DNA 4977 bp deletion could increase the risk of presbycusis.

Abbreviations: CI = confidence interval, mtDNA = mitochondrial DNA, ORs = odds ratios.

Keywords: mitochondrial DNA, mtDNA 4977 bp deletion, presbycusis

1. Introduction

Aging is an unavoidable process of a society's development. Although some elderly people retain good hearing, presbycusis, also known as age-related hearing loss (AHL), accumulates with age and has become a severe health and social problem. Presbycusis sufferers develop a high-toned hearing loss first, which plays a major adverse role in communication, particularly in reverberant, and/or noisy listening situations. Epidemiologically, some health problems related to presbycusis have been reported, such as social isolation, cognitive decline, depression, and dementia. However, the etiology of the disease remains unknown.[1–8]

Several factors contribute to presbycusis. Oxidative stress caused by mitochondrial dysfunction plays a causal role in presbycusis.[8–10] Mitochondria are the most important energy-producing organelles in the eukaryotic cells. Mitochondrial DNA (MtDNA) is more sensitive to damage than nuclear DNA is, because there are not enough enzymes in mitochondria to repair DNA damage and its lack of protective histones.[11] Sometic mtDNA deletions have been reported to be associated with the process of aging in many tissues, and mtDNA is particularly susceptible to large-scale deletions in the sections characterized by the appearance of flanking repeats. The most abundant and prevalent pathogenic mtDNA rearrangements are common deletion of 4977-bp. Mitochondrial 4977 bp deletion occurs frequently in tissues in an aging-related manner.[12–14]

Therefore, it is not surprising that a significant number of clinical studies have researched the effects of 4977 bp deletion on aging. However, researchers have not always indicated a positive association between 4977 bp deletion and aging. Although some authors reported an association between 4977 bp deletion and

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aging,[12,13,15,16] several studies in humans have shown an association between presbycusis and mtDNA deletion.[17–19] It is still unknown how relevant it is and whether mtDNA 4977 can be used as a susceptibility gene for presbycusis. The primary aim of the current meta-analysis is to explore the effects of 4977 bp deletion and presbycusis by performing a quantitative analysis of available published data about this subject.

2. Materials and methods

2.1. Search strategy and selection criteria

This systematic review and meta-analysis are developed and performed per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklists.[20] Ethical approval was unnecessary in this study because it was a meta-analysis analyzing existing articles and did not need handle individual patient data.

Relevant literature search was performed in:

(1) PubMed,
(2) Embase,
(3) Web of Science,
(4) China National Knowledge Infrastructure (CNKI), and
(5) Wanfang Chinese databases.

The medical subject headings (MeSH) and free terms were all included in our search terms, which are listed as follows: "Presbycusis", "Age-Related Hearing Impairment", "age-related hearing loss", "mitochondrial DNA 4977-bp deletion", "common deletion". Our search logic in the PubMed database was listed as follows: (presbycusis[Mesh] OR presbycuses OR Age-Related Hearing Impairment OR age-related hearing loss) AND ((((common deletion) OR 4977 bp deletion) OR 4977 bp) OR mitochondrial DNA 4977-bp deletion). All research we searched was reported before June 5, 2018. We also manually checked all articles listed in the reference lists of the retrieved literature. The detailed steps of the literature search are shown in Figure 1.

2.2. Inclusion criteria

The following inclusion criteria were applied to select studies in the meta-analysis:

(1) articles evaluating the relationship of the mtDNA 4977 bp deletion and presbycusis;
(2) the object of study was human;
(3) a case–control study;
(4) published in either English or Chinese;
(5) cases were diagnosed as presbycusis, according to clinical diagnostic criteria, and the control group had normal hearing;
(6) the frequency distribution of mtDNA 4977 bp deletions in the case and control groups could be provided directly or indirectly.

2.3. Exclusion criteria

The exclusion criteria were as follows:

(1) duplicate publications,
(2) incomplete information,
(3) insufficient data,
(4) no control group,
(5) review articles or conference literature.

2.4. Statistical methods

The odds ratio (OR) of mtDNA 4977 bp deletion in presbycusis compared with those without hearing loss was calculated with a random-effects model or a fixed-effects model, using between-study heterogeneity derived from the Mantel–Haenszel model. The effects model was applied, depending on the P value of the chi-squared statistic. When the I^2 value >50% and P was <0.05, the random-effects model was applied, and when the I^2 value <50%, the fixed-effects model was applied to combine effect size. The extent of homogeneity was assessed by I-squared statistics (I^2 <25%, no heterogeneity; I^2 = 25%–50%, moderate heterogeneity; I^2 = 50%–75%, moderate heterogeneity, I^2 >75%, high heterogeneity). To explore the origin of homogeneity, subgroup analysis was performed for ethnic groups (Asian and Occidental) and organ (auditory organ and other organs). Sensitivity analysis was used to evaluate the stability of the result of the meta-analysis. We conducted meta-regression to identify the possible sources of heterogeneity. The forest plot was computer-generated. Publication bias was statistically assessed by 2 formal methods: by Begg rank correlation and Egger regression test. We also employed the trim-and-fill method to identify and correct for funnel plot asymmetry arising from publication bias. Two-sided P value <.05 was considered statistically significant except for the test for publication bias, where P <.10 was used. Statistical calculations were performed by using Stata version 12.0 and Review Manager 5.3.

3. Results

3.1. Search results and characteristics of the eligible studies

Figure 1 shows details of the literature search. Two of our investigators (Sun HY and Han BA) independently abstracted the initial data. Discrepancies were resolved by consensus, and 341 articles were preliminarily selected. Screening by title and abstract was conducted according to information given in the title and abstract. After a thorough discussion, 45 articles were found to be related to this study. These articles then were subjected to second-stage review. Finally, 8 studies were included for the meta-analysis, covering data from a total of 458 samples. The information of authors, publication year, national sources, materials, ages, and sample size of each study are listed in Table 1 and Table 2.

3.2. Pooled analysis

The meta-analysis exhibited that the overall pooled OR of mtDNA 4977 bp deletion in presbycusis compared with the control group was 8.16 (95% confidence interval [CI]: 3.51 to 18.99, P <.01). The value of I^2 was 51%, indicating that the studies were moderately heterogeneous. Therefore, the random-effects model was used to combine effect size (Fig. 2).

3.3. Subgroup analysis: Ethnic group

Asian: Analysis of the polled OR showed the incidence of mtDNA 4977 bp deletion was 8.50 times higher in Asians with presbycusis than in the control group [OR = 8.50 (95% CI: 2.71 to 26.68, P <.01, Fig. 3A)]. Occidental: the OR in the studies of occidentals was 7.24 (95% CI: 1.90–27.55, P <.05, Fig. 3B).

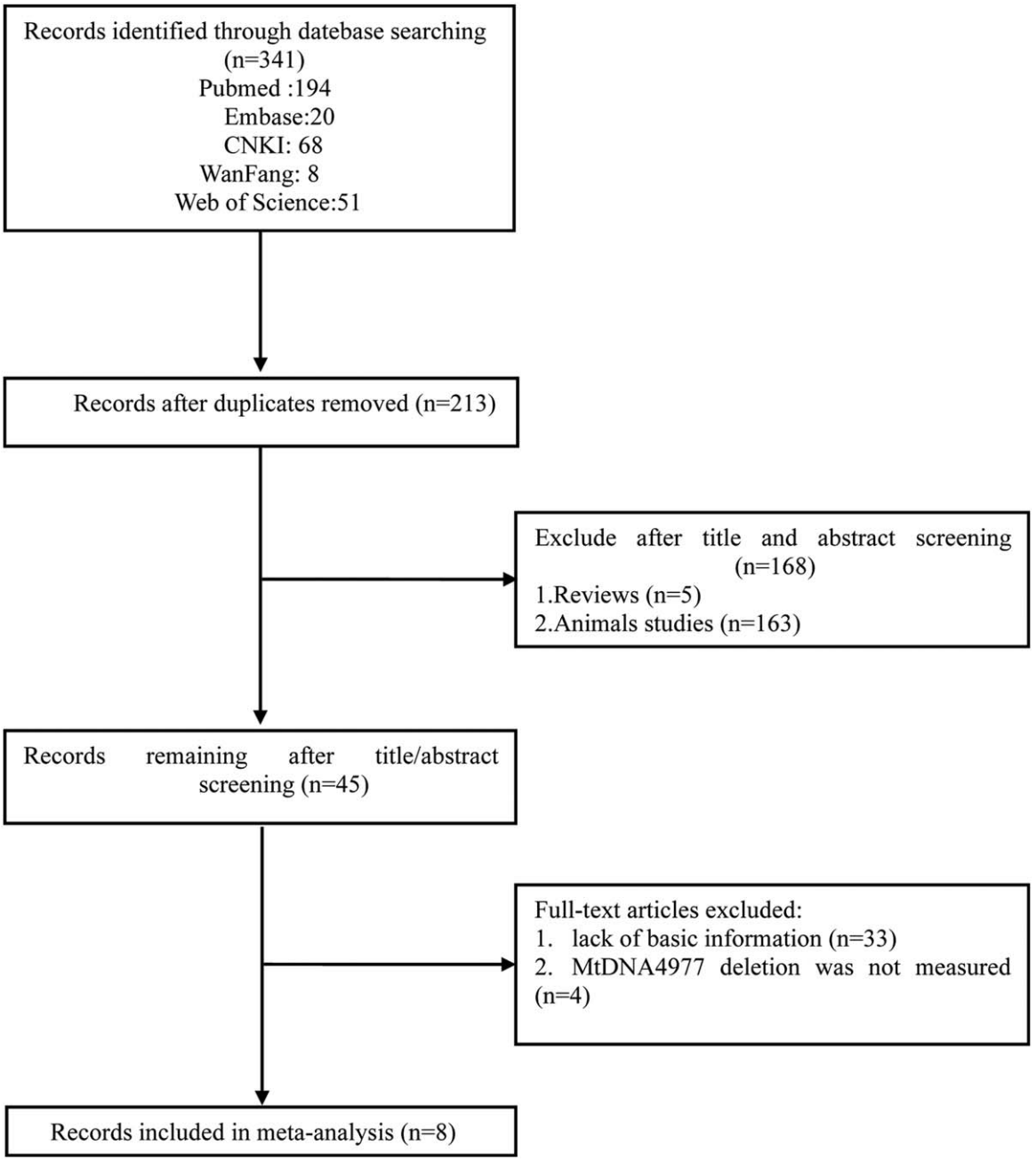

Figure 1. Flow chart of the study selection process. After careful discussion among the 3 reviewers, 8 studies were included to perform the meta-analysis.

Table 1

Characteristics of the trials included in the meta-analysis.

					Age			Presbycusis			Control	
Study	Year	Country	Materials	Methods	Presbycusis	Control	Event	No event	Total	Event	No event	Total
Liu H	2015	China	Hair	PCR	60-83	63-81	59	28	87	8	87	95
Markaryan	2008	United Stat	Temporal	PCR	9,39	73,78,86	3	0	3	0	2	2
Fu S	2007	China	Blood	PCR	68.7	NA	6	14	20	0	20	20
Dai P	2004	China	Temporal	PCR	67.9	63.8	17	17	34	4	15	19
Han W	2000	China	Temporal	PCR	67.9	63.8	47	32	79	16	36	52
Dai P	1998	China	Temporal	PCR	NA	NA	2	0	2	0	5	5
Bai U	1997	United Stat	Temporal	PCR	50-89	36-76	14	3	17	8	9	17
Seidman	1996	United Stat	Temporal	PCR	56	3	2	1	3	0	3	3

Table 2

Characteristics of included studies.

Study	Year	Symmetry of hearing loss	Frequency range (kHz)	Hearing threshold (dB)	Matched for age	Matched for sex	Excluded for noisy environment	Excluded for ototoxic drugs	Accompany with vertigo and tinnitus
Liu H	2015	Yes	2.5–8	≥30, average	Yes	NA	Yes	Yes	No
Markaryan A	2008	NA	NA	NA	No	NA	NA	Yes	No
Fu S	2007	Yes	NA	NA	Yes	NA	No	Yes	No
Dai P	2004	NA	0.125–8	≥30, average	Yes	NA	Yes	Yes	No
Han W	2000	Yes	High frequency	NA	Yes	NA	No	Yes	NA
Dai P	1998	NA	NA	NA	No	NA	NA	NA	NA
Bai U	1997	NA	NA	NA	No	NA	NA	NA	NA
Seidman MD	1996	NA	NA	NA	No	Yes	NA	NA	NA

NA = not avaliable.

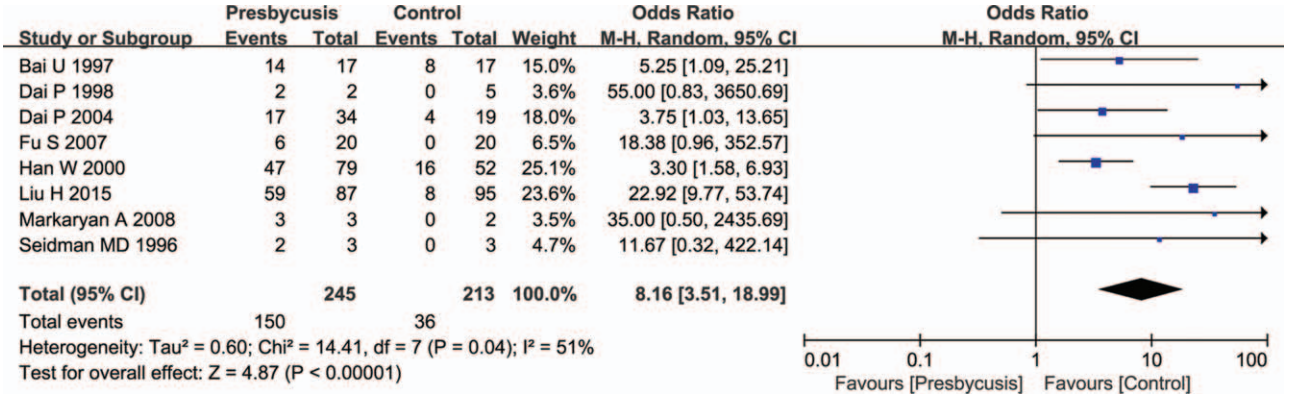

Figure 2. Comparison of mtDNA 4977 bp deletion between presbycusis group and control group in the 8 included studies. Calculation based on random-effects model. Results are expressed as OR and 95% CI. Meta-analysis showed that the overall pooled OR of mtDNA 4977 bp deletion in presbycusis compared with control group was 8.16. CI = confidence intervals, OR = odds ratio.

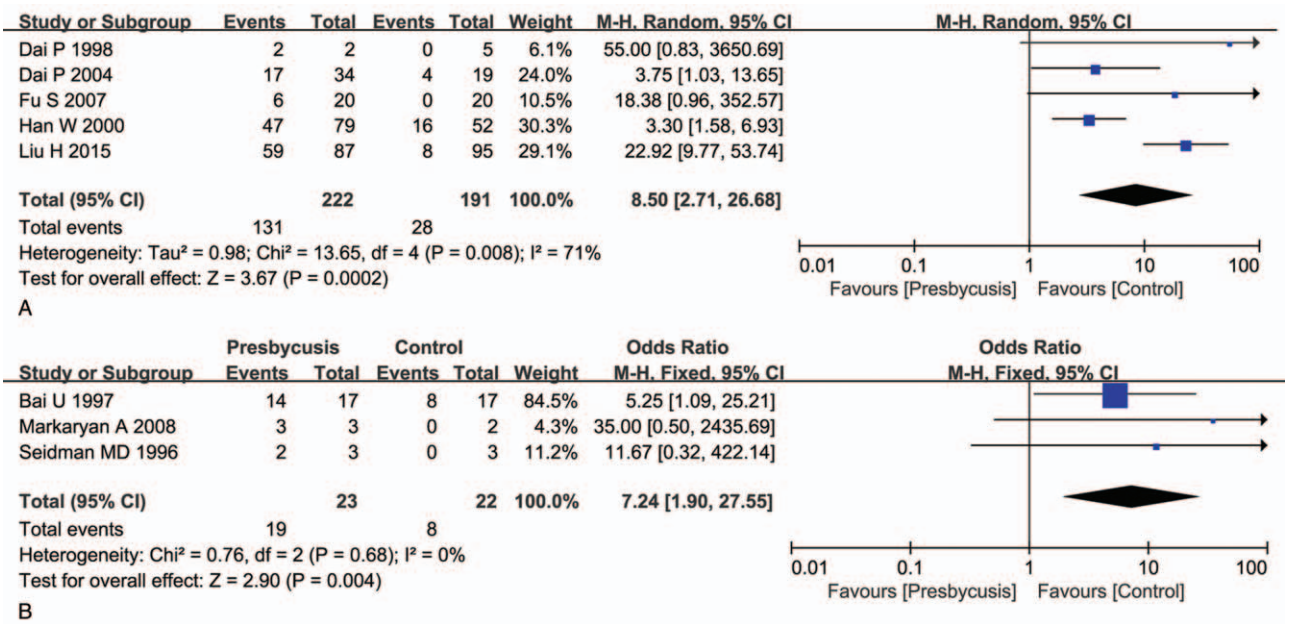

Figure 3. Subgroup analysis in Asian group and Occidental group. A shows the results on Asian group, and B shows the Occidental group results. A: Calculation based on random-effects model. Results are expressed as OR and 95% CI. The OR value in the studies was 8.50 (95% CI: 2.71–26.68, $P < .01$). B: Calculation based on fixed-effects model. Results are expressed as OR and 95% CI. The OR value in the studies was 7.24 (95% CI: 1.90–27.55, $P < .05$). CI = confidence intervals, OR = odds ratio.

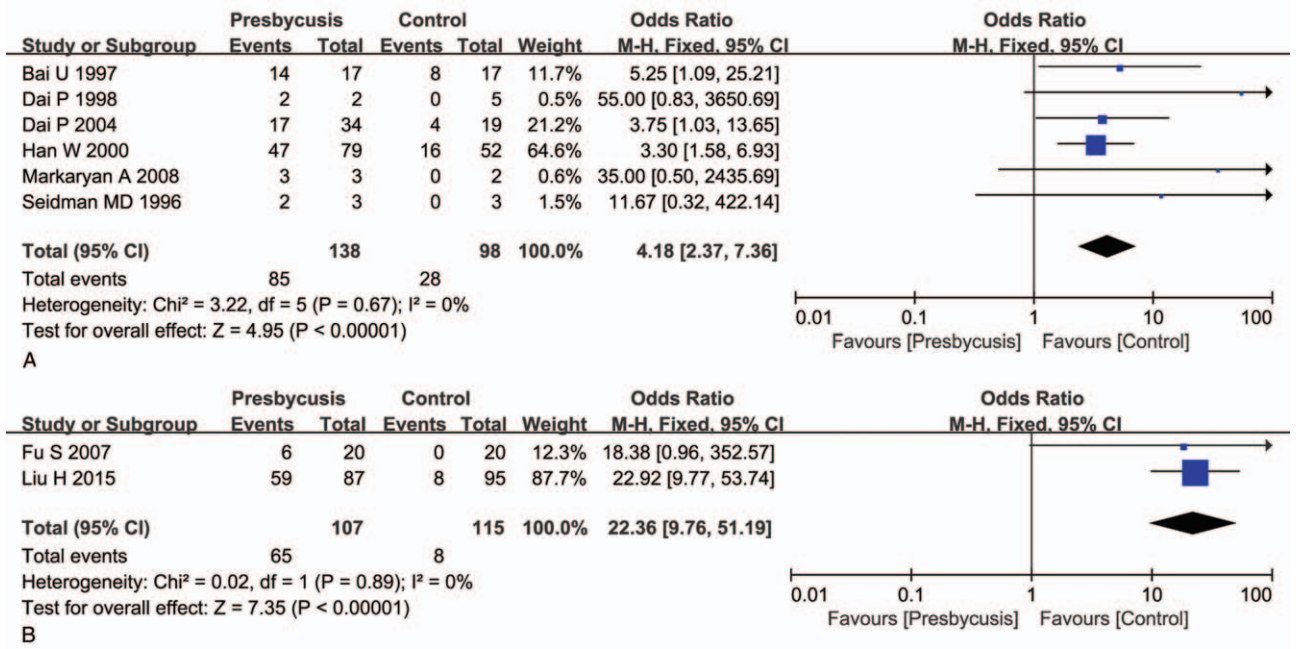

Figure 4. Subgroup analysis in temporal bone source and other sources. Analysis was also according to sample source. A shows the results on the temporal bone source group, and B shows the other sources group. A: Calculation based on fixed-effects model. Results are expressed as OR and 95% CI. The OR value in the studies was 4.10 (95% CI: 2.37–7.36, $P < .01$). B: Calculation based on fixed-effects model. Results are expressed as odds ratio (OR) and 95% CI. The OR value in the studies was 22.36 (95% CI: 9.76–51.19, $P < .01$). CI = confidence intervals, OR = odds ratio.

3.4. Subgroup analysis: Sample source

Analysis was also performed with the sample source divided by temporal bone source and other sources (hair and blood). The OR was 4.18 (Fig. 4A) and 22.36 (Fig. 4B) for the groups, temporal bone, and other sources, respectively.

3.5. Sensitivity analysis

The stability of the pooled ORs of the mtDNA 4977 bp deletion was estimated by eliminating each of the included studies in turn. Sensitivity analysis showed that no significant alteration of the pooled ORs was found as any of the included studies was omitted (Fig. 5).

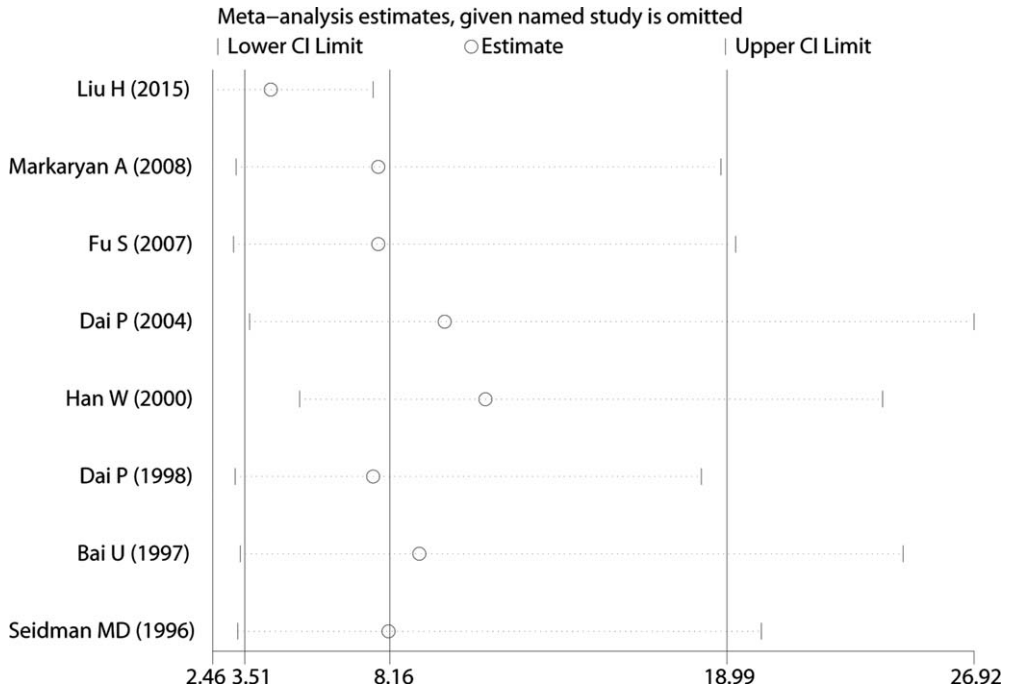

Figure 5. Sensitivity analysis of the pooled effective size on mtDNA 4977 bp deletion between presbycusis and control groups.

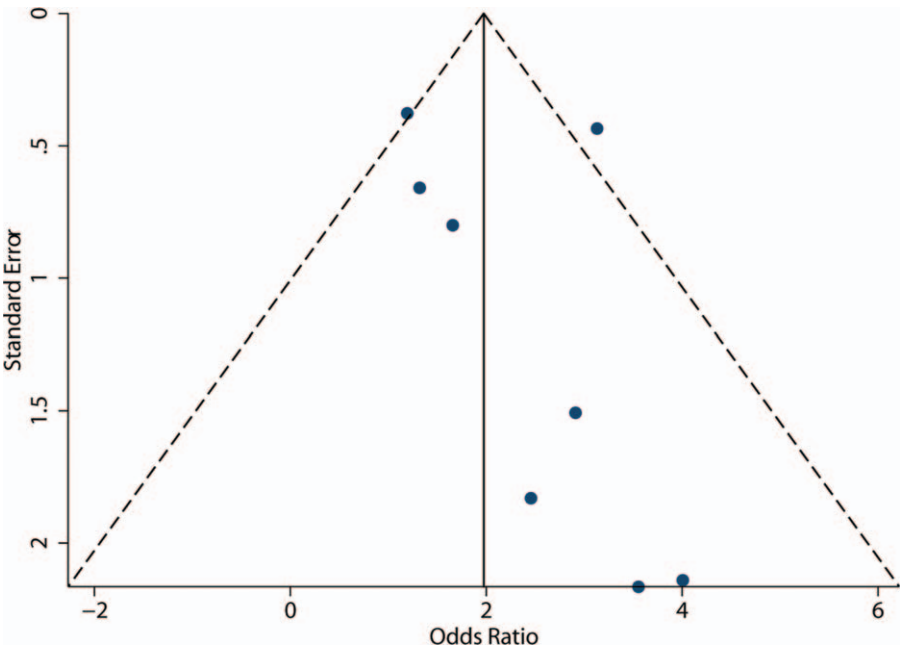

Figure 6. Funnel plot shows the possibility of a small publication bias.

These results indicate that the corresponding ORs were relatively robust.

3.6. Publication bias

The studies seem to have slight publication bias because the funnel plot was not perfectly symmetrical (Fig. 6), but Begg tests ($P = .466$) and Egger tests ($P = 1.48$) did not provide any evidence of publication bias in our study. Furthermore, the trim-and-fill method demonstrated that no research needed to be statistically corrected for funnel plot asymmetry. The methodological quality of each included study is shown in Figure 7.

4. Discussion

The present research used meta-analytic methods to evaluate the difference in mitochondrial 4977 bp deletion between presbycusis and the control group. Our research demonstrated that individuals with mitochondrial 4977 bp deletion have a closer association with presbycusis than control subjects do. Begg tests ($P = .466$) and Egger tests ($P = 1.48$) did not provide evidence of publication bias in our study. Furthermore, although the value of $I^2 = 51\%$ ($I^2 > 50$, $P < .05$), it indicated that this research contained moderate heterogeneity. Subgroup analysis was performed to evaluate the sources of heterogeneity, so the results of this research could represent the true relationship between 4977 bp deletion and presbycusis. Meanwhile, sensitivity analysis demonstrated that after any individual research was omitted, the overall conclusions and results still existed. Therefore, we are confident that the results of this meta-analysis show strong association between 4977 bp deletion and presbycusis.

Numerous studies have reported that deletions of mtDNA play a pivotal role in aging and impairment of various human organs, such as the heart,[21] brain,[15,22] skin,[5,23] cornea,[24] and skeletal muscle.[25] MtDNA deletions are abundant in cochlear tissue, which have been shown, including mtDNA 10422, 13162, 7663, 4989, 7436, 4989, and 4977 bp deletion. The most common deletion is mtDNA 4977 bp deletion, and its absence will hinder mitochondrial oxidative phosphorylation.[26] Dai et al determined mtDNA 4977 bp deletion by using nested polymerase chain reaction (PCR) in temporal bone specimens. The results demonstrated that in the presbycusis group, the percentage of mtDNA 4977 bp deletion was as high as 50%, 0.0% in the young and middle-aged group, and 21% in the age-related control group.[27] Markaryan et al studied mtDNA 4977 bp deletion in the cochlea of senior individuals. They reported that the incidence of mtDNA 4977 bp deletion was $12 \pm 2\%$ in the normal hearing control group and $32 \pm 14\%$ in the presbycusis group.[28] A study by Hong Liu et al suggested a relationship between mtDNA 4977 bp deletion in the hair shaft and the severity of hearing loss in presbycusis.[17] These studies have therefore shown that mtDNA 4977 bp deletion is universally observed in patients with presbycusis.

Although many studies and this meta-analysis have shown a certain correlation between mtDNA 4977 deletion and presbycusis, its relevance and whether mtDNA 4977 can be used as a susceptibility gene for presbycusis is still unknown. Through extensive review of related data, this study eventually included 8 Chinese and foreign literature for meta-analysis.[17,27–32] The meta-analysis showed that the risk of mtDNA 4977 deletion in presbycusis increased (OR = 7.84, 95% CI: 3.63~16.93). The OR values obtained after sensitivity analysis fluctuated between 4.57 and 10.63. The subgroup analysis results showed that mtDNA 4977 deletion had a strong association with presbycusis. From the results of this meta-analysis, we could conclude mtDNA 4977 participation in presbycusis pathogenesis.

However, the limitations of this meta-analysis should be considered. First, due to the rare related study materials included in the research, the sample size is not large enough, especially in the case of subgroup analysis of ethnic groups; the study is merely

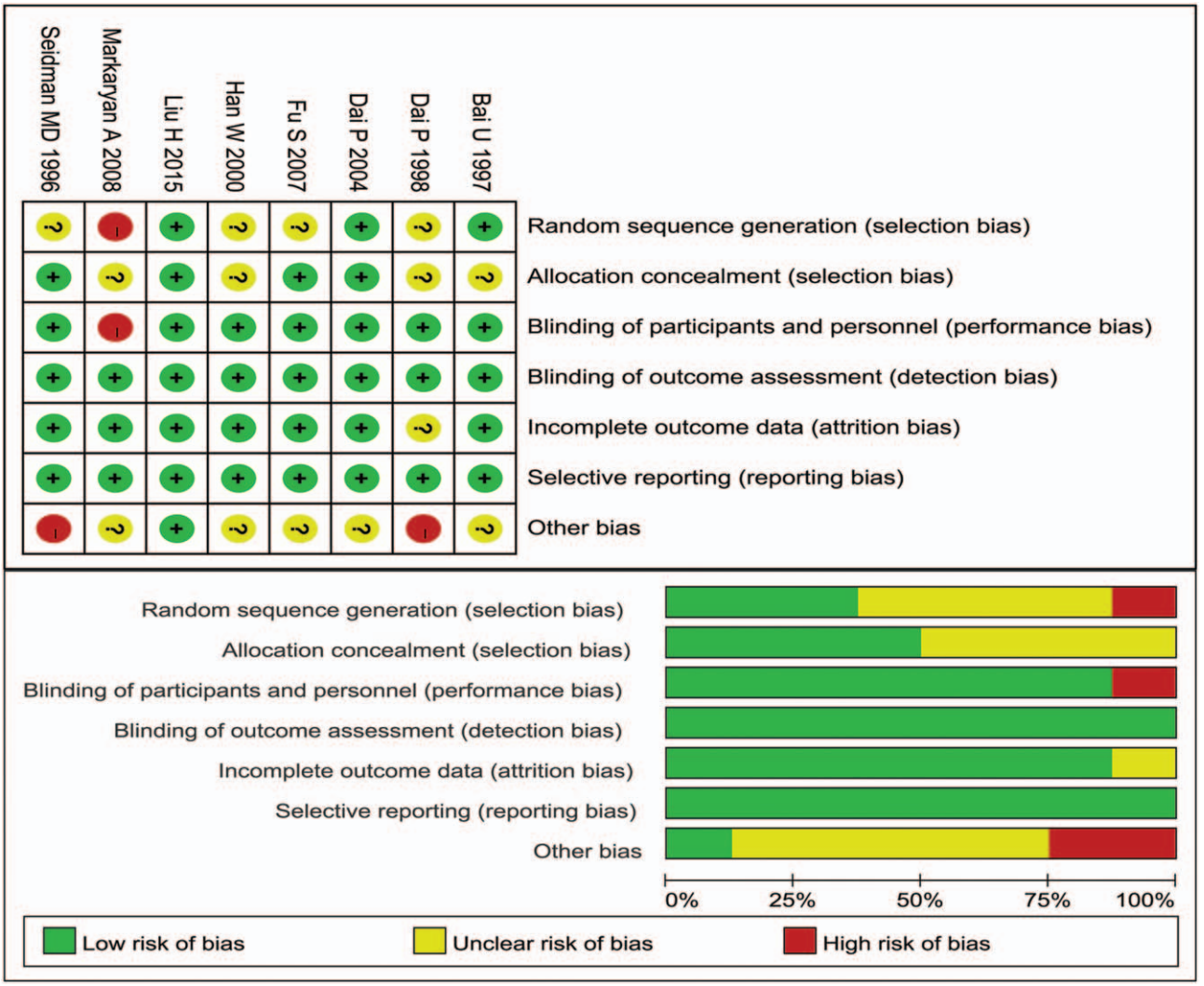

Figure 7. Risk of bias summary and graph: review authors' judgements about each domain for each included study.

comparing a limited number of reports from China and the 2 reports from the United States. Thus, it seems inappropriate to draw a conclusion and group the ethnicity based on such little information.

Second, there is no stratified analysis of factors such as age, gender, and disease severity. The matching conditions of the control group are not completely consistent; there are objectively confounding factors that prevent accurate reflection of the true situation of both groups. In addition, presbycusis is caused by multiple factors such as the external environment and individual susceptibility. Some researches demonstrated that a functional deficit will not occur until the level of deletion in tissues accumulates a significant level.[33,34] Furthermore, publication bias is inevitable because studies are not likely to report negative findings. Even if publication bias was not statistically derived, its possibility could not be excluded. At present, the mechanism of mtDNA4977 deletion in presbycusis remains unclear. Large case–control studies to provide more evidence-based assessment of mtDNA 4977 bp deletion as a cause of genetic susceptibility to presbycusis is needed.

Although this study objectively has certain limitations, sensitivity analysis, and research bias analysis results may indicate that the combined effect value is reliable and stable; the combined meta-analytic results of this study can still provide certain strong evidence for the prevention and treatment of senile spasticity. The exact mechanism of mtDNA4977 leading to presbycusis remains to be further explored. Specific gerontological biological markers and effective prevention and treatment drugs need further study. The deep exploration of the correlation between presbycusis and mtDNA CD4977 not only helps elucidate the part of the mechanism of presbycusis at the molecular level but also provides new ideas for the prevention and treatment of presbycusis.

Author contributions

Data curation: Baoai Han, Yaqin Tu, Jie Yuan.
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