Original Article

Association of sensorineural hearing loss and pseudoexfoliation syndrome: a meta-analysis

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Background: Previous studies that assessed the association of sensorineural hearing loss (SNHL) and pseudoexfoliation syndrome (PEX) produced contradictory results. We conducted a meta-analysis to further evaluate this relationship.

Methods: Eligible studies that evaluated the association between SNHL and PEX were identified. Summary odds ratios (ORs) and 95% confidence intervals (CIs) were calculated employing random-effects models. Subgroup analysis and meta-regression were performed to assess heterogeneity by several covariates. Publication bias was tested by Begg's funnel plot and Egger's regression test.

Results: A total of 14 eligible studies, involving 1,142 PEX patients and 9,914 controls, were included in this meta-analysis. Overall analysis showed that patients with PEX, when compared with the control group, experienced a significantly increased risk for hearing loss [OR: 3.74 (95% CI: 2.56 to 5.47); P<0.001]. Substantial heterogeneity was observed. Subgroup analysis revealed a decrease in this heterogeneity in age- and sex-matched studies and in studies that used the same definition of hearing loss. Meta-regression analysis showed that definition of hearing loss contributed to substantial heterogeneity (P=0.044). No evidence of publication bias was observed.

Discussion: We found that PEX is associated with an increased risk of SNHL. The effect of PEX on the prevalence of hearing loss indicates that PEX is clearly a systemic disease with potential otological complications.

Keywords: Sensorineural hearing loss (SNHL); pseudoexfoliation syndrome (PEX); meta-analysis

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Introduction

Pseudoexfoliation syndrome (PEX), also known as exfoliation syndrome, is an age-related disease characterized by the abnormal production and deposition of pseudo-exfoliation fibrous material, which mainly occurs in the front of the eye (1). Diffuse pseudo-exfoliation deposits are believed to be the cause of many ocular and extraocular complications, such as glaucoma, lens opacity, cataract surgery complications, retinal vascular occlusion, and age-related macular degeneration (2-5). PEX is now considered a systemic disease because these substances are also present in other parts of the body, including the skin, vascular structures and internal organs (such as the heart, kidneys, gallbladder, and lungs) and inner ears (6).

The inner ear is a complex organ. Like the structure of the anterior segment of the eye, the tectorial membrane and basement membrane of the inner ear come from the neuroectoderm. According to previous studies, these membranes in the inner ear may also be where the pseudoexfoliation material deposits (7). The accumulation of this substance on these structures will affect the function of the inner ear and cause hearing loss.

Many epidemiological and experimental studies have evaluated the relationship between sensorineural hearing loss (SNHL) and PEX, but the results are inconsistent. Some studies (8-19) have shown an association between PEX and increased risk of SNHL, while other studies (20,21) have shown no association. In view of the possibility of diagnosing PEX through slit lamp examination to identify individuals at increased risk of SNHL, research on this issue may have important clinical significance. In addition, it is of special importance for the early diagnosis and treatment of patients with hearing and vision loss (double sensory loss). In view of the evidence from recent studies, the goal of this study is to assess the correlation between PEX and SNHL risk through a systematic review and meta-analysis of all available epidemiological studies. This meta-analysis adopts a standardized program and is conducted in accordance with the PRISMA reporting checklist (available at https://aes.amegroups.com/article/view/10.21037/aes-21-68/rc) (22).

Methods

Literature search

We searched PubMed, Embase, and ISI Web of Science through computers and identified relevant publications. The retrieval time was from 1966 to November 2020. Both the title and open text fields are used to identify the article, with no application date or language restrictions. Search for the following medical terms and their combinations: (I) PEX, exfoliative syndrome; (II) hearing impairment, hearing dysfunction, hearing disorder, hearing loss, ear symptoms. The related article function is also used, and the reference list of all retrieved studies and related reviews is supplemented by manual search to expand the search scope. If multiple articles are published using the same case series, only the most complete series of studies will be included.

Inclusion and exclusion criteria

Related research needs to meet the following criteria: (I) a case-control study to assess the correlation between SNHL and PEX; (II) an unrelated case-control design; (III) an odds ratio (OR) with a 95% confidence interval (CI) or other data that can be used to estimate OR (95% CI). SNHL is defined as any low, medium, and high frequency hearing impairment. Exclusion criteria include: unpublished papers, non-human studies, letters/case reports, editorials, comments, studies lacking searchable raw data, studies lacking a suitable control group, and studies using insufficient case definitions.

Data extraction

Research data was extracted by two independent researchers using a standardized data collection form, and if there are differences, they will be discussed. The information collected from each study includes: first author and year of publication, country of origin, subject ethnicity, study design, exposure and evaluation results, number of cases and control groups, correlation, point estimate and 95% CI, and any adjustment/stratification/matching variables.

Quality assessment

The quality of the included studies was independently assessed by the same two investigators using the Newcastle-Ottawa Scale (NOS) (23). NOS uses a "star" rating system to judge the quality of research based on three aspects: selection, comparability and exposure (case-control study) or results (cohort study). The score ranges from 0 (worst) to 9 (best). The higher the score, the better the methodological quality. A score of ≥7 is considered high quality.

Statistical analysis

In this meta-analysis, the correlation between SNHL and PEX was estimated by calculating combined ORs and 95% CI. A random effects model was used to conservatively estimate the effects of potential population differences in the study using the methods of Der Simonian and Laird. The significance of the combined OR was determined by the Z test ($P<0.05$ is considered statistically significant).

The heterogeneity is determined by Q test and I^2 statistics. I^2 values of more than 50% are defined as having obvious heterogeneity. For the Q statistic, a P value <0.1 is considered statistically heterogeneity. Through subgroup analysis based on race, case composition, sample method, sample size, age and gender matching, and hearing loss

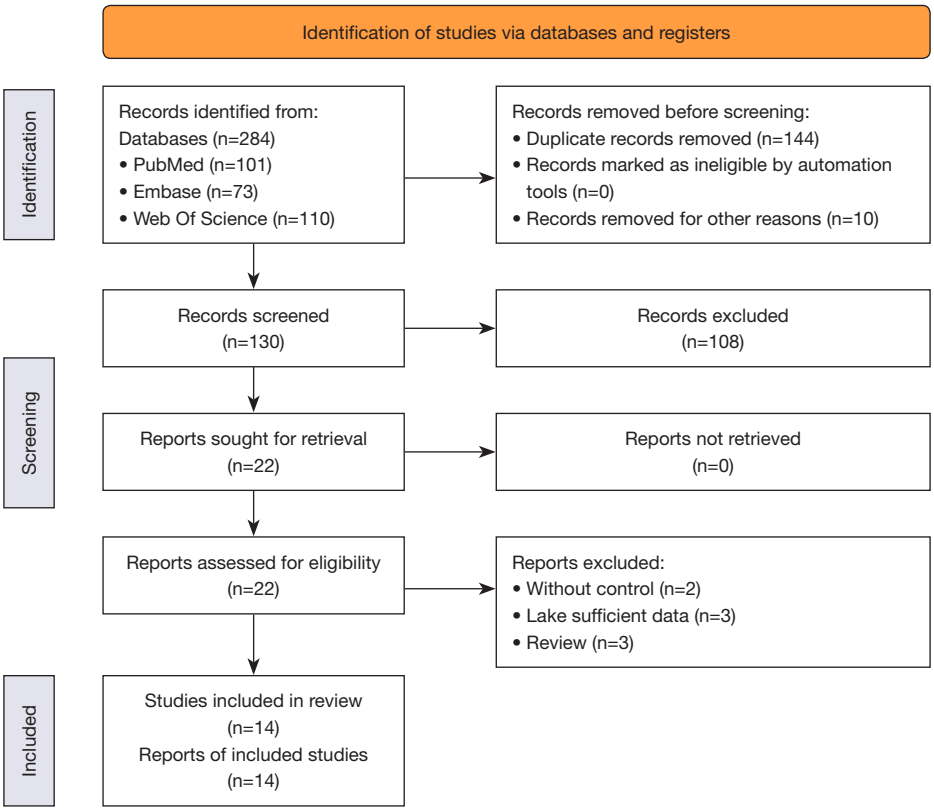

Figure 1 Flow diagram of the studies included in this meta-analysis.

definitions, the size of combined OR in each class and their respective heterogeneity tests were examined. Through meta-regression analysis, the influence of these variables on the heterogeneity of cross-stratigraphic research is studied. The reliability of the results of the meta-analysis was determined by omitting one study for each round of sensitivity analysis. The Begg funnel chart and Egger test were used to statistically evaluate publication bias. The possible publication bias is represented by an asymmetric graph. A P value of less than 0.05 in the Egger test is considered to represent a statistically significant publication bias (24). All analyses were performed using STATA software version 11.2 (Stata, Texas College Station).

Results

Literature search and characteristics

The detailed process steps of selecting included documents are shown in *Figure 1*. The initial search found 284 potentially relevant studies. Through the electronic database to delete duplicate content and delete irrelevant topics, leaving 22 full-text articles for further qualification evaluation. Eight articles were excluded for the following reasons: review articles (n=3) (25-27); insufficient article data (n=3) (28-30); lack of control group (n=2) (31,32). In the end, 14 articles met the inclusion criteria and were included in this meta-analysis (8-21).

Table 1 lists the design characteristics and participant characteristics of the included studies. All studies are case-control designs. Of the 14 articles identified, 2 were population-based and 12 were based on hospital research. The research areas are: six studies were conducted in Turkey, three studies were conducted in Iran, and one each was conducted in Poland, Iceland, Malaysia, Greece and Egypt. These studies involved 1,142 PEX patients and 9,914 control patients. The average score of the NOS results was 7.57 (range, 7 to 9), indicating that the quality of each research methodology is good.

Association between SNHL and PEX

The forest diagram (*Figure 2*) shows the correlation

Table 1 Overview of literatures included in the meta-analysis

Study (first author)	Year of publication	Country	Study design	No. of case	No. of control	Definition of sensorineural hearing loss	Covariates adjusted	NOS score
Yildirim	2017	Turkey	PB	100	1,909	NA	Sex	7
Temporale	2016	Poland	HB	28	23	With hearing thresholds >25 dB hearing level	Age, sex	8
Tryggvason	2016	Iceland	PB	158	123	defined by the Liden-Jerger procedure	Age, education, lifestyle, chronic diseases	8
Singham	2014	Malaysia	HB	68	55	With hearing thresholds >20 dB hearing level	Age, sex	8
Papadopoulos	2012	Greece	HB	47	22	Defined by the American National Standards Institute (ANSI) 1969	Age, sex	8
Samarai	2012	Iran	HB	50	50	Defined by the ISO7029 standard	Age, sex	8
Zojaji	2011	Iran	HB	33	33	With hearing thresholds >20 dB hearing level	Age, sex	8
Shazly	2011	Egypt	HB	320	7,418	NA	Age, sex	7
Turgut	2010	Turkey	HB	34	40	With hearing thresholds >20 dB hearing level	Age	7
Erbek	2009	Turkey	HB	32	23	NA	Age, sex	7
Yazdani	2008	Iran	HB	83	83	defined by the ISO7029 standard	Age, sex	8
Ozturk	2008	Turkey	HB	63	38	With hearing thresholds >25 dB hearing level	Age	7
Turacli	2007	Turkey	HB	51	22	With hearing thresholds >20 dB hearing level	Age	7
Aydoğan Ozkan	2006	Turkey	HB	75	75	With hearing thresholds >25 dB hearing level	Age, sex, systemic diseases	9

PB, population based; HB, hospital based; NOS, Newcastle-Ottawa Scale; NA, data not available.

between SNHL and PEX. Overall, compared with the control group, the risk of hearing loss in PEX patients was significantly increased [OR: 3.74 (95% CI: 2.56 to 5.47); P<0.001]. However, the included studies have obvious heterogeneity (P<0.001, I^2=75.2%).

Subgroup, sensitivity analyses, and meta-regression

We further explored the heterogeneity between SNHL and PEX studies through subgroup analysis and sensitivity analysis. A hierarchical analysis of subgroups based on race, case composition, sample method, sample size, age and gender matching, and hearing loss definitions revealed that there is a significant relationship between SNHL and PEX in all subgroups. Subgroup analysis also showed that heterogeneity was reduced in studies that matched age and gender and used the same definition of hearing loss. In addition, in the sensitivity analysis, one study was omitted at a time, and the combined OR of the remaining studies was calculated, and consistent results were obtained. The combined ORs were statistically significant and the results were similar. The OR ranged from 3.45 (95% CI: 2.38 to 5.01) to 4.16 (95% CI: 3.01 to 5.76). Meta-regression analysis explored the impact of key characteristics of the study (i.e., subgroup factors) on heterogeneity, and the results showed that the definition of hearing loss was the key to the heterogeneity (P=0.044) (*Table 2*).

Publication bias

This meta-analysis uses the Begg funnel chart and the Egger test to assess publication bias. Begg's funnel chart did not show any obvious evidence of asymmetry, and Egger's test did not detect publication bias (P=0.663). These results

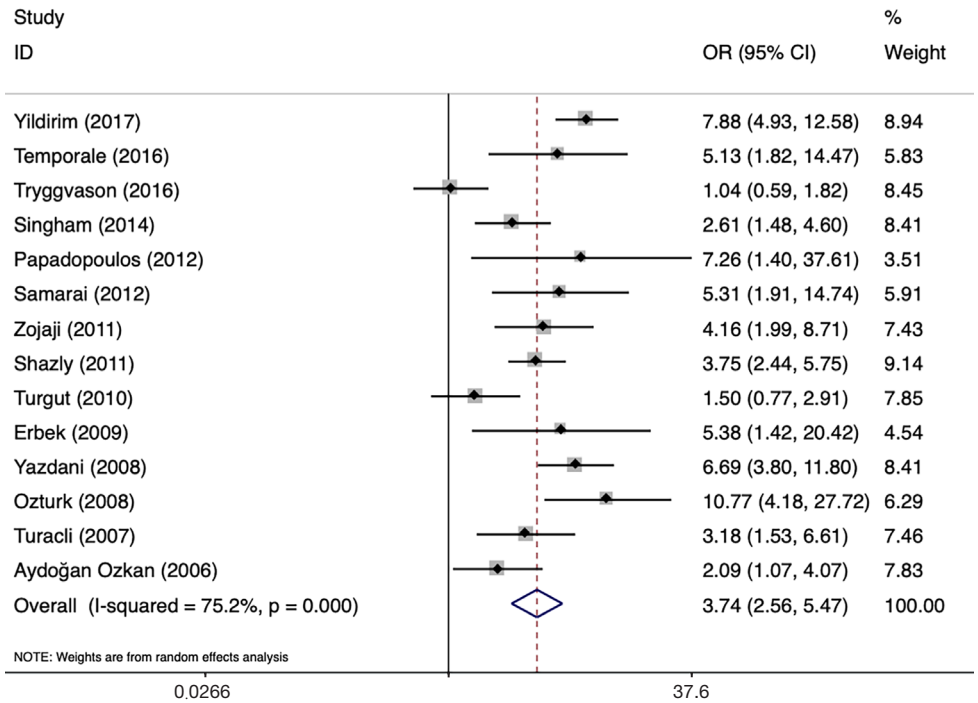

Figure 2 Forest plot of the association between sensorineural hearing loss and pseudoexfoliation syndrome in the present study. CI, confidence interval; OR, odds ratio.

indicate that the publication bias in the SNHL and PEX studies is not statistically significant in this meta-analysis (*Figure 3*).

Discussion

Sensory disturbances are common in the elderly. Hearing and vision loss usually increase with age. More and more scientific evidence shows that the frequency of simultaneous loss of hearing and vision is more frequently than would be expected (33). Therefore, further research on the relationship between hearing and vision loss is very important, which may have important public health and clinical significance. To the best of our knowledge, this study is the first meta-analysis to investigate the relationship between PEX and hearing loss. Our results show that PEX increases the incidence of SNHL by 2.74 times.

SHNL is caused by damage to cochlear cells and/or surrounding structures, as well as disturbances in the quality of auditory nerve stimulation and/or the central nervous system's understanding of the quality of stimulation. The underlying mechanism between PEX and SNHL is not fully understood, but several possible theories and hypotheses have been proposed. First, both the inner ear basement membrane and the anterior eye membrane are formed by the ectoderm. Some studies have found that both the inner ear cover membrane and the basement membrane have pseudo-exfoliation substances (7). Pseudo-exfoliated substances deposited on the cochlear basement membrane and/or covering membrane may cause changes in the chemical composition of the surrounding environment, resulting in uneven energy transmission to the nerve sensory hair cells (31). Secondly, the deposition of pseudo-exfoliation material on the blood vessel wall may damage the blood supply of the inner ear and temporal lobe, leading to dysfunction of the auditory receptors and auditory cortex (18). Third, the pathology and biochemistry of these diseases may be similar, or they may have common susceptibility factors, such as age, cellular oxidative stress, and insufficient cytoprotective mechanisms (11,19,34). Fourth, previous studies demonstrated that PEX patients have an increased risk for abdominal and aortic aneurisms as well as pelvic organ prolapse (35,36). PEX syndrome is very much a disease of the extracellular matrix leading to tissue laxity, which contributes to those 3 disorders. This tissue laxity almost certainly arises from the altered expression

Table 2 Combined odds ratio of sensorineural hearing loss related to pseudoexfoliation syndrome by study design and population characteristics

Groups	Studies (n)	OR	95% CI		P (overall effect)	Heterogeneity		P for meta-regression
			Lower bound	Upper bound		I^2 (%)	P	
Overall	14	3.74	2.56	5.47	<0.001	75.2	<0.001	–
Ethnicity								0.570
Caucasian	13	3.88	2.57	5.86	<0.001	76.4	<0.001	
Asian	1	2.61	1.48	4.60	0.001	–	–	
Case component								0.189
PEX	6	5.22	2.57	10.58	<0.001	73.6	0.002	
PEX/PEXG	8	3.09	2.02	4.73	<0.001	73.0	0.001	
Sample method								0.474
PB	2	2.88	0.39	20.97	0.297	96.6	<0.001	
HB	12	3.82	2.79	5.23	<0.001	51.2	0.020	
Sample size								0.840
<100	6	3.35	2.10	5.36	<0.001	35.9	0.168	
≥100	8	3.87	2.28	6.59	<0.001	84.0	<0.001	
Age and sex matching								0.544
Yes	9	3.92	2.97	5.18	<0.001	21.9	0.249	
No	5	3.28	1.31	8.23	0.011	90.3	<0.001	
Definition of hearing loss								0.044
>20	4	2.62	1.74	3.95	<0.001	33.1	0.214	
>25	3	4.65	1.69	12.84	0.003	6.8	0.300	
IOS7029	2	6.34	3.86	10.41	<0.001	0	0.698	
Others	5	3.83	1.65	8.88	0.002	87.0	<0.001	

PEX, pseudoexfoliation syndrome; PEXG, pseudoexfoliation glaucoma; PB, population based; HB, hospital based; OR, odds ratio; CI, confidence interval.

and/or activity of LOXL1, an enzyme that is strongly associated with PEX and that cross-links elastic fibers. Altered LOXL1 activity could bring about dysfunction of spiral ligament fibrocytes or structural changes to the extracellular matrix that could significantly impact hearing function (37).

In this study, the results of subgroup analysis and sensitivity analysis were similar and robust, and neither subgroup analysis nor single study significantly changed the correlation. A significant positive correlation was observed in all subgroups except for the subgroup study designed by population base. There is obvious heterogeneity in PEX and SNHL risk studies. Considering the differences in population characteristics, the determination of SNHL, and the adjustment of confounding factors, this is not surprising. Fortunately, in the subgroup analysis, heterogeneity was reduced in studies that matched age and gender and used the same definition of hearing loss. Both PEX and SNHL are age-related diseases. SNHL is very common and is closely related to male gender and age (20). In some analytical studies, due to the lack of adjustment for age and gender, their results may be biased. In addition, our meta-regression analysis shows that the definition of hearing loss also leads to heterogeneity to a large extent, which indicates that different definitions of hearing loss and the determination of hearing loss may have an important impact on the results of these studies.

Meta-analysis has advantages over individual research,

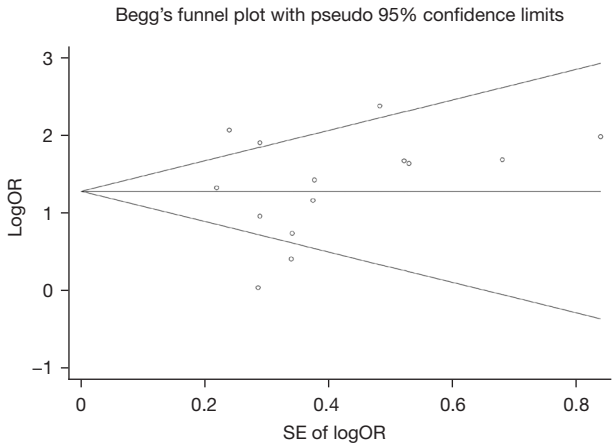

Figure 3 Begg's funnel plot with pseudo 95% confidence limits of the association between sensorineural hearing loss and pseudoexfoliation syndrome. OR, odds ratio; SE, standard error.

but our research has some potential limitations. First, since only a few studies meet our eligibility criteria, we have assembled the results of studies using different designs and different definitions of hearing loss. Second, most studies are conducted in the Middle East, so these results may not be generalized to other regions. Third, the included study is a case-control design, so the causal relationship between PEX and SNHL cannot be determined.

Despite the limitations of this study, this meta-analysis presents some valuable findings. It provides aggregated data on a large number of cases and controls in order to better understand the association between PEX and SNHL risks. In addition, this research extends several questions. The first question is whether PEX has a causal effect on SNHL, or whether it is just a surrogate marker for other biological risk factors. This problem should be solved by considering several issues, including the interval between the onset of the two diseases, the use of standardized hearing loss definitions, and control measures for confounding factors, etc. Second, what is the exact mechanism by which PEX increases the risk of hearing loss? Further research, including well-designed longitudinal clinical trials and basic scientific research, is necessary to address these issues in order to better understand this connection and provide convincing evidence for clinical practice to prevent hearing disorders.

Conclusions

This meta-analysis shows an association between PEX and increased risk of SNHL. The effect of PEX on the prevalence and severity of hearing loss indicates that PEX is clearly a systemic disease that includes otological complications, in addition to the multiple other disorders that have been demonstrated to occur at higher frequency in individuals with PEX syndrome.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://aes.amegroups.com/article/view/10.21037/aes-21-68/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://aes.amegroups.com/article/view/10.21037/aes-21-68/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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