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REVIEW ARTICLE

The relationship between serum homocysteine levels and sudden sensorineural hearing loss: a meta-analysis

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Abstract

Objective There was disagreement over the association between serum/plasma homocysteine (HCY) levels and sudden sensorineural hearing loss (SSNHL). Through the use of a meta-analysis, this study aims to determine whether there is a significant difference in serum homocysteine levels between the SSNHL group and the control group.

Design The Cochrane Library, EMBASE, and PubMed databases were all thoroughly searched. The two independent reviewers thoroughly examined the initially searched articles. The data results were calculated by standard mean difference (SMD) or odds ratios (OR). Review Manager (version 5.3) was applied to statistical data.

Study sample There were 766 participants in the 6 trials with continuous outcomes that were part of the meta-analysis A. In addition, meta-analysis B, which included 961 people, contained a total of 3 studies with dichotomous results.

Results Both meta-analyses revealed the same conclusion that serum/plasma HCY levels in the SSNHL patients are higher than those in the controls (SMD 0.41, 95 % confidence interval (CI) 0.11 to 0.72, $P < 0.01$; OR 3.27, 95 % CI 2.16 to 4.94, $P < 0.01$).

Conclusion This study demonstrated that the SSNHL patients' serum/plasma HCY levels were greater than those of the control group.

Keywords Homocysteine · HCY · Sudden sensorineural hearing loss · SSNHL · Meta-analysis

Abbreviations

HCY	Homocysteine
SSNHL	Sudden sensorineural hearing loss
CI	Confidence interval

Introduction

Sudden sensorineural hearing loss (SSNHL) is defined as hearing loss that occurs within 72 h with at least 30 decibels (dB) in 3 adjacent frequencies [1]. Aside from hearing loss, it may be accompanied by other symptoms such as ear fullness, tinnitus, vertigo, and so on [2, 3]. Every year, approximately 15,000 new cases of SSNHL are diagnosed worldwide, and one in every 100 patients with sensorineural hearing loss is SSNHL [4]. Individual psychology and life quality can be affected to varying degrees [5]. Numerous theories on the origin of this condition have been advanced, including vascular injury, viral infections, and autoimmunity [6–9]. The cochlea is an organ without collateral circulation and is supplied by the vagus artery, making the vascular hypothesis the most logical explanation for the etiology of SSNHL when compared to alternative hypotheses [10]. In some aspects, the clinical manifestations of unilateral SSNHL resemble ischemic vascular disease, such as transient ischemic attack (TIA), acute myocardial infarction (AMI), or amaurosis fugax, which all occur suddenly [11]. Therefore, we speculate whether the sudden onset of

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SSNHL, in terms of pathogenesis, as seen in these acute ischemic diseases, is caused by an increase in the concentration of certain substances in the blood that cause vascular damage, or a decrease in substances that protect blood vessel endothelial cells.

Elevated serum/plasma homocysteine (HCY) is a developing risk factor that is independently linked to vascular damage disorders, such as peripheral vascular disease, cerebral vascular disease, and coronary artery disease [12–14]. Increased HCY levels are advantageous to the dysfunction of the vascular endothelial cells, smooth muscle cells, and extracellular matrix [15]. It is well known that the production of atheromatous cholesterol plaques and thrombosis, both of which can result in occlusive vascular disease, may be facilitated by associated vascular endothelial injury [16]. It has been hypothesized that elevated HCY levels may contribute to small vascular—the auditory artery and its branches, for instance—endothelial dysfunction [17].

As the relationship between HCY and SSNHL is still debatable, we conducted a meta-analysis of research on the link between serum/plasma HCY levels and SSNHL. We anticipate this analysis may help to support the vascular theory of SSNHL.

Methods

Literature search

We searched for English studies included in PubMed, EMBASE, and the Cochrane Library comprehensively, by employing combinations of the keywords listed below: homocysteine, HCY, 2-amino-4-mercaptobutyric acid, sudden sensorineural hearing loss, SSHL, SSNHL, SHL, sudden hearing loss, sudden deafness, hearing loss, deafness. The reference lists of related literature were also manually searched to prevent the omission of other potentially qualified studies.

Selection criteria

1. The studies were included, if they involved the serum/plasma homocysteine (HCY) concentration of SSNHL patients and healthy controls.
2. The related data provided in the studies can be applied to a meta-analysis. A study was excluded when the data for HCY levels are not expressed in the form of mean ± standard deviation (continuous outcomes) or dichotomous outcomes.
3. None of the participants took the drugs (folate, multivitamin, methotrexate, and so on.) that could have influenced the result of the experiment.
4. Participants did not have cardiovascular disease

Study selection and data extraction

Two reviewers independently evaluated each study according to the predetermined inclusion and exclusion criteria. A third reviewer would offer proof to resolve issues when the other two reviewers' opinions differed. The first author's name, publication year, national sources, study design, level of evidence, the number of participants in case group and control group, participants' ages and genders, data type, and serum/plasma HCY concentrations were all taken from the literature that met the inclusion criteria.

Quality assessment

Two reviewers used the Newcastle–Ottawa Quality Assessment Scale to rate the studies included in the meta-analysis, and a third reviewer offered suggestions to settle any potential discrepancies. A score of seven or higher was given to each of the reviewed studies, reflecting their quality.

Statistical analysis

Statistical results for continuous outcomes were represented by SMD and a 95 % CI, and statistical results for dichotomous outcomes were represented by Risk ratio (RR) and a 95 % CI. The inverse variance method was applied to continuous variables, and Mantel–Haenszel analysis was adopted for dichotomous variables [18]. The difference was statistically significant when $P < 0.05$.

We assessed statistical heterogeneity based on the I-square (I^2) value. It was considered statistically significant when $P < 0.01$. The statistical heterogeneity was classified into four categories based on the I^2 value: homogeneous($I^2 < 25$ %), low heterogeneity($25\ \% \le I^2 < 50$ %), moderate heterogeneity($50\ \% \le I^2 < 75$ %), and highly heterogeneity($I^2 \le 75$ %) [19]. The fixed-effects model is used to pool the data from a study where there is homogeneity or low heterogeneity. The random-effects model [20, 21] is used to pool data from studies with moderate to high levels of heterogeneity [20, 21]. It was decided to use Review Manager 5.3 for data synthesis.

Results

Literature search

42 studies in all were discovered during the initial literature search (Fig. 1). By reading the titles and abstracts of all papers, 27 articles that did not meet the inclusion criteria were eliminated. Full-text reviews were conducted on

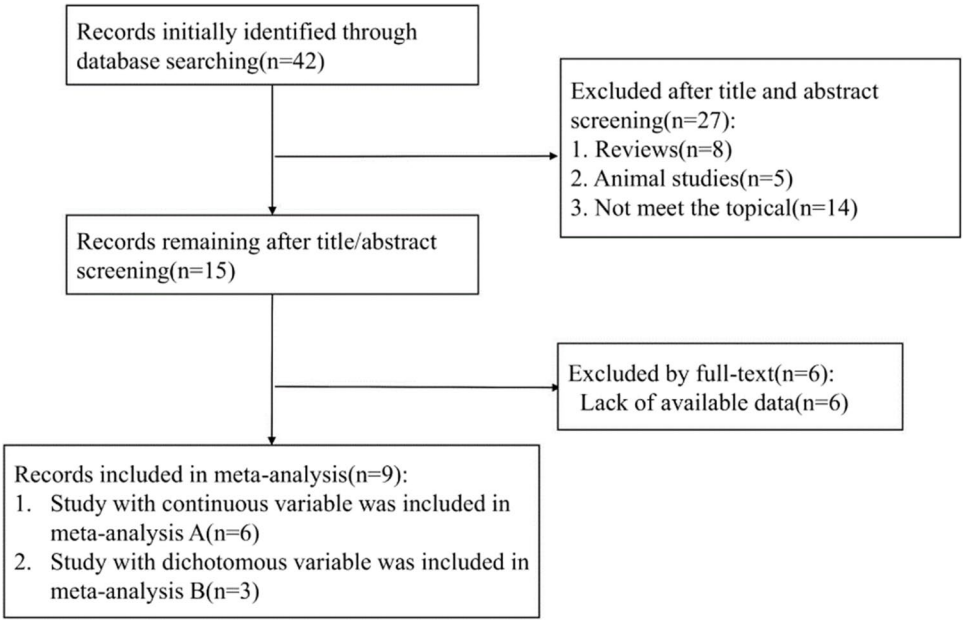

Fig. 1 Flow chart of the study selection process

the final 15 studies. Only nine studies were left that could be included after six studies [22–27] were eliminated for not providing pertinent information that could be used in a meta-analysis.

Study characteristics

The meta-analysis A pooled six [28–33] of the nine studies that provided statistical results for continuous outcomes. In meta-analysis B, additional three studies [34–36] that provided statistical findings for dichotomous outcomes were gathered. Table 1 displays the major traits of the nine pieces of literature that were included. The meta-analysis A consisted of 766 subjects (358 participants in the SSNHL group vs 408 participants in the control group), demographic data (such as gender and age), and laboratory data results are listed in Table 2. The meta-analysis B consisted of 961 subjects (207 participants in the SSNHL group vs 754 participants in the control group), and demographic data (such as gender and age) and laboratory data results are listed in Table 3. The included cross-sectional trial's level of evidence was rated as level 1, and the included case–control trial's level 2.

Meta-analysis A

After combining the data from the six trials, there was moderate heterogeneity ($I^2 = 74\ \%$), hence a random-effects model should be used to analyze the data (Fig. 2). The serum/plasma HCY levels in the SSNHL group were higher than those in the control group, according to the meta-analysis A (SMD 0.41, 95 % CI 0.11 to 0.72, $P = 0.008$).

Table 1 Characteristics of included studies

Author	Year	Country	Study design	LOE	Sample size (SSNHL/control)	Data type
Cadoni, G [28]	2004	Italy	CCT	2b	43/24	CO
Cadoni, G [29]	2007	Italy	CCT	2b	30/60	CO
Capaccio, P [30]	2005	Italy	CCT	2b	67/134	CO
Fasano, T [31]	2017	Italy	CCT	2b	131/77	CO
Huang, Y [32]	2019	China	CCT	2b	54/45	CO
Lee, E. J [33]	2010	South Korea	CCT	2b	33/68	CO
Fusconi, M [34]	2011	Italy	CCT	2b	40/120	DO
Fusconi, M [35]	2012	Italy	CCT	2b	49/210	DO
Passamonti, S. M [36]	2015	Italy	CCT	2b	118/415	DO

CCT case–control trial, *LOE* level of evidence, *2b* level 2, *CO* continuous outcomes, *DO* dichotomous outcomes

Table 2 Characteristics of included studies

Author	Mean (SD) HCY		Sex (M/F)		Age, year*	
	SSNHL	Control	SSNHL	Control	SSNHL	Control
Cadoni, G [28]	11.39 (8.3)	7.19 (2.2)	20/23	14/10	F: 47 (23–70)	F: 45 (31–62)
					M: 47 (17–70)	M: 34 (16–42)
Cadoni, G [29]	8.57 (2.50	9.22 (2.37)	13/17	26/34	F: 46 (25–72)	F: 49 (24–77)
					M: 45 (23–69)	M: 50 (23–74)
Capaccio, P [30]	14 (2.9)	11.3 (3.1)	40/27	80/54	53.6 (11.3)#	53.6 (11.3)#
Fasano, T [31]	13.5 (0.62)	13.0 (2.4)	71/60	42/35	54 (15–88)	52.5 (15–88)
Huang, Y [32]	14.77 (6.45)	12.59 (2.77)	NA		36.5 (18–69)	34.7 (20–65)
Lee, E. J [33]	9.43 (6.1)	7.21 (4.2)	17/16	26/42	48.24 (14.50) #	43.91 (16.96)#

SD standard deviation, *NA* no data available, *M* male, *F* female

#Mean (SD). *Mean (range)

Table 3 Characteristics of included studies

Author	HCY < 15 µmol/l		HCY ≥ 15 µmol/l		Sex (M/F)		Age, year	
	SSNHL	Control	SSNHL	Control	SSNHL	Control	SSNHL	Control
Fusconi, M [34]	24	107	16	13	17/23	NA	52.25 (15)#	NA
Fusconi, M [35]	31	184	18	26	22/27	NA	52.28 (18–80)	NA
Passamonti, S. M [36]	99	390	19	25	58/61	120/295	48 (34–57)*	41 (32–52)*

OR odds ratio, *NA* no data available, *CI* confidence interval, *M* male, *F* female

*Median (interquartile range). #Mean (standard deviation)

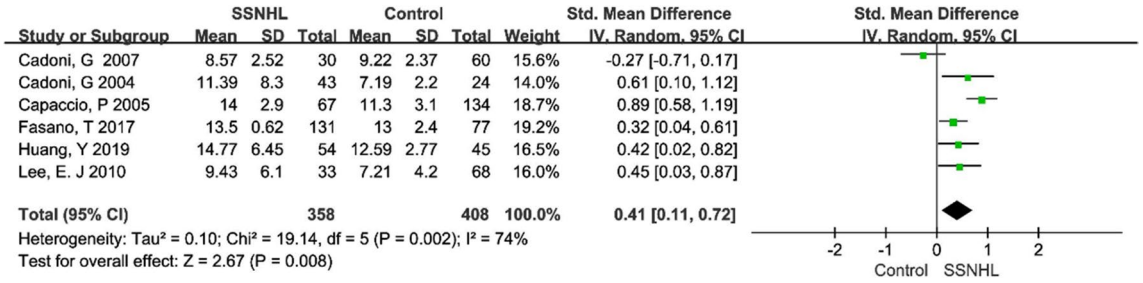

Fig. 2 Meta-analysis A, the comparison of HCY in the SSNHL group and control group with continuous outcomes

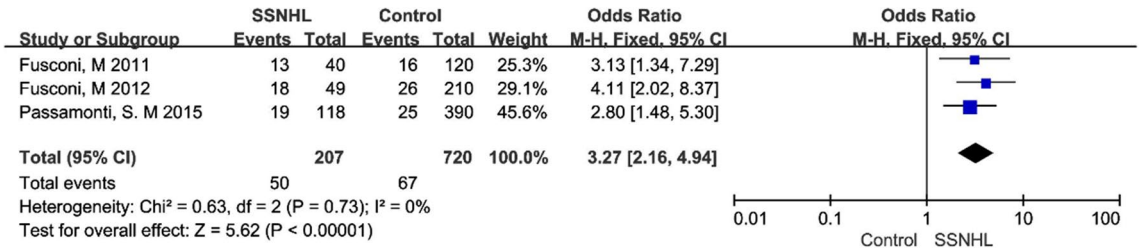

Fig. 3 Meta-analysis B, the comparison of HCY in the SSNHL group and control group with dichotomous outcomes

Meta-analysis B

No heterogeneity was found after pooling data from the 3 studies ($I^2 = 0$ %), which indicates a fixed-effects model should be applied for data analysis (Fig. 3). The serum/plasma HCY levels in the SSNHL group were 3.27 times higher than those in the control group, according to the meta-analysis B (OR 3.27, 95 % CI 2.16 to 4.94, $P < 0.01$).

Sensitivity analysis

The sensitivity analysis of meta-analysis A demonstrated that the outcome of the pooled analysis would not change if any of the studies were excluded. The pooled analysis employing a random-effects model revealed that SSNHL had significantly higher serum/plasma HCY levels than the control group (SMD 0.41, 95 % CI 0.11 to 0.72, $P=0.008$). Similar results were obtained using the fixed-effects model (SMD 0.45, 95 % CI 0.30 to 0.60, $P<0.01$).

The sensitivity analysis of meta-analysis B showed that removing any of the studies would not reverse the result of the pooled analysis. The pooled analysis using the fixed-effects model revealed that the group's serum/plasma HCY levels were 3.27 times higher than those in the control group (OR 3.27, 95 % CI 2.16 to 4.94, $P<0.01$). Similar results were obtained using the random-effects model (OR 3.27, 95 % CI 2.17 to 4.95, $P<0.01$).

Publication bias

Because the studies we included were typically insufficient to analyze a dissymmetric funnel [37], publication bias should not be utilized to judge the conclusions of the two meta-analyses.

Discussion

To our knowledge, hyperhomocysteinemia is an independent risk factor for vascular damage [12–14]. It causes abnormal coagulation and endothelial dysfunction in pathophysiology, both of which promote cardiovascular events [38]. The role of elevated HCY concentrations in causing cochlear vascular damage and thus becoming a risk factor for SSNHL is still debated, though most studies support a link between HCY concentrations and SSNHL [30, 32, 33]. Cadoni et al. [29], however, claimed that this relationship did not exist in their study. Here, we included nine research in two different meta-analyses based on the various types of data that were supplied. Six studies representing data results with continuous outcomes were combined in meta-analysis A, where the serum/plasma HCY levels of SSNHL patients were statistically different from controls (SMD 0.41, 95 % CI 0.11 to 0.72, $P=0.008$). The data from the remaining three investigations, which represented data findings using dichotomous variables, were combined in meta-analysis B, with comparable results (OR 3.27, 95 % CI 2.16 to 4.94, $P<0.01$).

In addition, with the exception of Huang et al. study's [32], which only looked at one subtype of SSNHL—total frequency deafness—all types of SSNHL patients were included in other research, which could account for the discrepancies in results.

Previous research has demonstrated a connection between the polymorphism of the methylenetetrahydrofolate reductase gene and the rise in plasma/serum HCY concentration [39]. Methylenetetrahydrofolate reductase breaks down 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, which is used as a catalyst to methylate homocysteine and turns it into methionine [40, 41]. Any irregularity in this procedure could result in homocysteine building up in cells and being exported to the plasma. Methylenetetrahydrofolate reductase gene mutations and SSNHL were shown to have a statistically significant correlation by Capaccio et al. [30]. They also discovered a significant correlation between SSNHL and serum/plasma HCY levels, suggesting that HCY may have a genetic role in the pathogenesis of SSNHL.

As far as we know, this is the first meta-analysis of the correlation between SSNHL and HCY. This study still has several shortcomings. First, there is a dearth of evidence due to the small number of papers that qualified for inclusion in this meta-analysis. Second, meta-analysis A discovered moderate heterogeneity. However, given the included research, we were unable to pinpoint the precise cause of heterogeneity. Third, subgroup analysis could not be done because of the inconsistent data expression of demographic characteristics provided by the included study. Finally, we did not assess publication bias because only a small number of articles were suitable for inclusion in these two meta-analyses.

Conclusions

In conclusion, our study showed that serum/plasma HCY levels in the SSNHL patients were higher than those in the control group. According to the results, increased serum or plasma HCY levels may be a risk factor for SSNHL. Additionally, it shows that vascular factors could be one of the causes of SSNHL. To confirm the theory that hyperhomocysteinemia is a risk factor for SSNHL through cochlear vascular injury, further pathophysiology research is necessary.

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Availability of data and material All data generated or analyzed in this study are included in this published article.

Declarations

Conflict of interest The authors declare that they have no competing interests.

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

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