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Original Article

Associations of Blood Lipids with the Risk and Prognosis of Sudden Sensorineural Hearing Loss: A Meta-analysis

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BACKGROUND: Patients with sudden sensorineural hearing loss (SSNHL) may lose their hearing. The relationship between SSNHL and total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) levels is still unclear. The association of TC, TG, HDL-C, and LDL-C levels with the risk and prognosis of SSNHL was explored in this study.

METHODS: After searching for literature in different databases, 13 researches were used to summarize the risk and prognosis of SSNHL associations with TC, TG, HDL-C, and LDL-C using meta-analysis.

RESULTS: Total cholesterol had a significant association with the risk of SSNHL (95% CI, 1.34-2.91). Adjustment for confounding factors and grouping criteria of TG were all significant sources of heterogeneity. One of the significant sources of heterogeneity in the LDL-C subgroup analyses was an adjustment for confounders. Sensitivity analysis revealed a robust association between TC and the risk of SSNHL. There was a significant publication bias in the association between TC and SSNHL prognosis

CONCLUSION: High TC level is a risk factor for SSNHL.

KEYWORDS: Sudden sensorineural hearing loss, meta, blood lipids

INTRODUCTION

Sudden sensorineural hearing loss (SSNHL) is a hearing loss ≥30 dB in 3 successive frequencies over a short time.[1] Patients with SSNHL may lose their hearing.[2] Sudden sensorineural hearing loss can be divided into 2 types, 1 is primary SSNHL caused by viral infections, autoimmune diseases, or vascular insufficiency and the other is secondary SSNHL associated with tumors, radiation, and stroke.[3]

As elevated cholesterol levels increase the risk of vascular insufficiency and elevated estrogen during pregnancy promotes elevated cholesterol levels, pregnancy may induce SSNHL.[4] Elevated progesterone levels in the third trimester allow venous stasis in the hyperdynamic state during pregnancy, which, in turn, increases the risk of thrombosis and disrupts cochlear circulation, ultimately leading to SSNHL.[5] Patients with blood disorders including aplastic anemia and leukemia may also develop SSNHL. Patients with anemia have reduced hemoglobin, which leads to insufficient oxygen supply to the organs. Cochlear hair cells respond to acoustic stimuli through capillaries around it and their metabolic demands are high, so the lack of oxygen supply seriously affects hearing.[6] Additionally, diabetes and hyperlipidemia are also causative factors for SSNHL of vascular origin.[7] A 1% increase in glycosylated hemoglobin A1c is associated with a 37% increase in microvascular disease.[8] Repeated antigenic challenges of immune diseases, such as rheumatoid arthritis and relapsing polychondritis, can induce cochlear vestibular dysfunction.[9] Vestibular and cochlear schwannomas affect hearing levels.[10]

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Sudden sensorineural hearing loss prevalence and prognosis are also influenced by high levels of total cholesterol (TC) and triglyceride (TG).[11] Total cholesterol level is significantly associated with SSNHL severity.[12] However, a previous meta-analysis has reported no correlation between serum lipid levels and SSNHL.[13] The reasons for this might be a small included studies number and the quantitative analysis in the association between TC and low-density lipoprotein cholesterol (LDL-C) with SSNHL.

This present meta-analysis study investigated the connection between blood lipids such as TC, TG, LDL-C, and high-density lipoprotein cholesterol (HDL-C) with SSNHL risk and prognosis.

METHODS

Ethical approval is not necessary for this study as the findings are conducted based on previously published data.

Retrieval Strategy

According to the pre-defined search strategies (Supplementary Tables 1-3), the keywords included sudden hearing loss, sudden sensorineural deafness, hearing loss, TC, TG, HDL, LDL, and lipids were systematically searched in PubMed, Web of Science, and Embase databases, in which, the same category keywords were connected via "OR," while the different categories were connected via "AND.". The retrieval through combining the subject headings and free words and adjusting the search formula according to the different databases characteristics has been completed on April 18, 2022, with no language restrictions. Besides, references cited in relevant reviews and included literature were also screened.

Literature Screening

The inclusion criteria were as follows: (1) patients with SSNHL; (2) observational studies such as case–control and cohort studies; (3) reported associations of TC, TG, HDL-C, and LDL-C with SSNHL risk and prognosis; and (4) provided or calculable odds ratios (ORs) and relative risks (RRs) (95% CI).

The exclusion criteria for our study were as follows: (1) non-authoritative sources, including reviews and conference abstracts; (2) studies that the primary outcome was the mean difference in blood lipid levels; and (3) in cases of duplicate publications or multiple articles presenting the same data, only the most comprehensive reports were considered, excluding the others.

Data Extraction and Quality Assessment

Firstly, according to the above criteria, 2 investigators separately accomplished the bibliographic retrieval. After through selecting the literature to be included in the analysis, data extraction was performed separately according to the information included the first author, the publication year, the study type, the study region, the basic study subject characteristics (sample size, age, sex, etc.), the diagnostic criteria for SSNHL, the grouping criteria for blood lipids, confounding factors, and studies ending. Then, 2 investigators exchanged and audited the extraction forms, and discussed resolving any inconsistencies between forms.

According to the Newcastle–Ottawa Scale (NOS),[14] the methodological qualities of the included studies were evaluated such as subject selection, comparability, and exposure. Studies earning a score of 7-9 were designated as high-quality, those with scores ranging from 4 to 6 were classified as moderate-quality, and those scoring below 4 were considered low-quality.

Statistical Analysis

Odds ratios and 95% CIs were used to assess the relationships of TC, TG, HDL-C, and LDL-C with the risk of SSNHL and clinical recovery (CR). Heterogeneity was decided by cochran's Q and I^2 tests.[15] A random-effects model was used to be analyzed significant consistency in studies ($P < .05$, and/or $I^2 > 50\%$); otherwise, a fixed-effects model was used ($P < .05$, and/or $I^2 \leq 50\%$).

Subgroup analyses were performed by region, diagnostic criteria for SSNHL, grouping criteria for blood lipids, and adjustment for confounding factors to explore the effect of grouping factors on statistical heterogeneity and pooled results. The one-by-one elimination test was employed to ascertain the impact of a single included study on the results of the meta-analysis.[16] Significant publication bias could be assessed by egger tests in these studies.[17] Under significant publication bias, the trim-and-fill method was used to assess the stability of the combined results.[18] Stata 12.0 was used to statistical analyses.

RESULTS

Literature Retrieval

In this study, 182, 275, and 139 articles were retrieved from PubMed, Embase, and Web of Science databases, respectively. After removing duplicate literatures, a total 400 studies remained. Subsequently, 379 articles, non-conformance the inclusion criteria, were removed. After reading the full texts of the 21 remaining studies, 8 were removed, leaving 13 studies for inclusion in the final study[11,19-30] (Figure 1).

Features of the Included Literature

Among the 13 included studies, 9[19,21-27,29] reported the relationship between blood lipids and the risk of SSNHL, 2[28,30] reported the relationship between blood lipids and the prognosis of SSNHL, and 2 reported both associations.[11,20] In total, 11 case–control studies centered on the risk of developing SSNHL; however, the SSNHL standards were not completely consistent (Table 1). The other 4 studies explored prognostic factors in SSNHL (Table 2). Among these 4 studies, 2 each were case–control and cohort studies, respectively; however, the criteria for CR were not completely consistent. All the studies were conducted in China, Korea, Germany, Italy, Russia, and Iran and were published from 2005 to 2021.

Quality Assessment

The included studies showed moderate quality, with scores of 5-9 in methodological quality assessment (Supplementary Table 4). The recall and confounding were major types biases in these studies (Supplementary Table 5).

Meta-analysis

Nine studies were used to assess the differences in SSNHL risk between high and low TC groups (Figure 2A). The heterogeneity test results revealed significant statistical heterogeneity between the high and low TC groups ($I^2 = 89.9\%$, $P < .001$). The combined random-effects model results displayed that TC was connected with the risk of developing SSNHL (OR [95%CI] = 1.98 (1.34, 2.91), $P < .001$). Seven

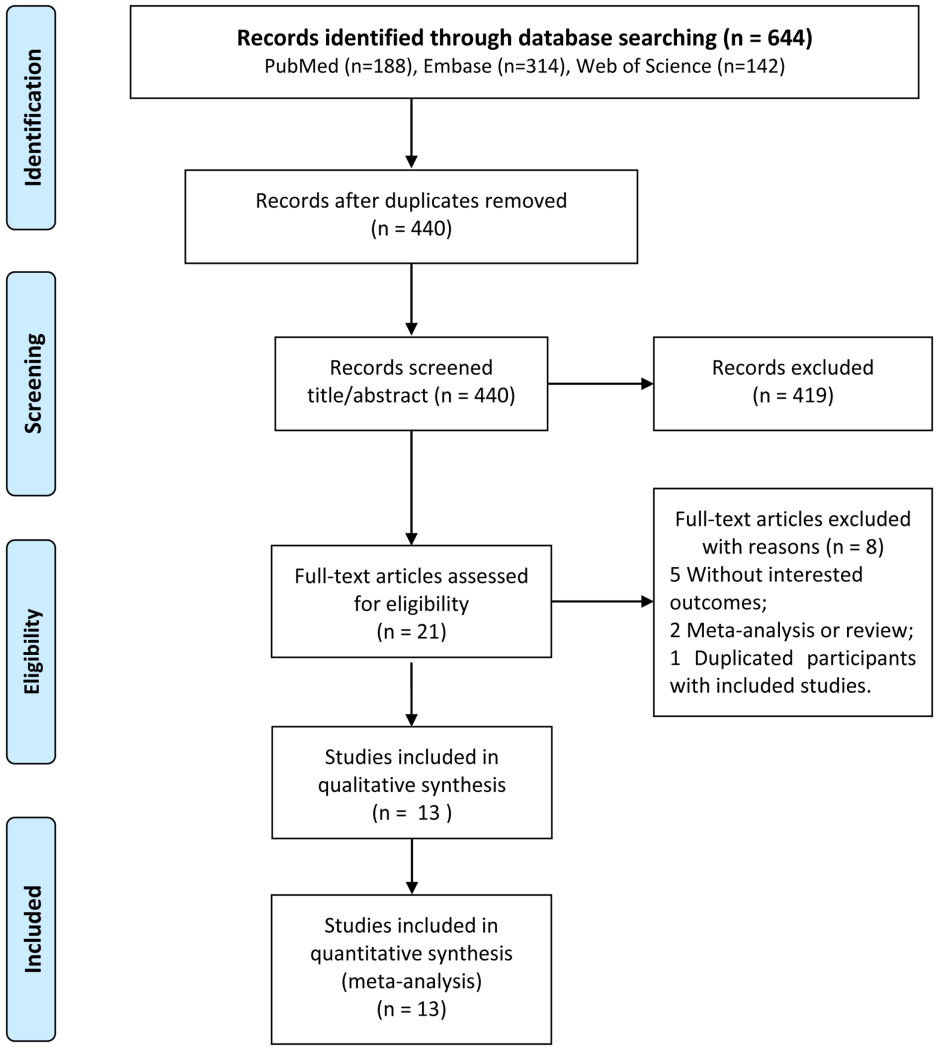

Figure 1. Flow chart.

studies were included to analyze the heterogeneity test in the high TG vs. low TG groups (Figure 2B), and the results showed significant heterogeneity (I^2 = 83%, P < .001). whereas, there was no significant association between TG level and SSNHL (OR (95%CI) = 1.17 (0.97, 1.42), P = .109). As shown in Figure 2C, there was significant heterogeneity between the low and high HDL-C groups (I^2 = 87.3%, P < .001). High-density lipoprotein cholesterol levels and the risk of developing SSNHL showed no significant difference (OR (95%CI) = 1.52 (0.89, 2.61), P = .128). High and low LDL-C levels showed significant heterogeneity (I^2 = 71.9%, P = .002), while LDL levels revealed no significant difference with the risk of SSNHL (OR (95%CI) = 1.30 (0.97, 1.75), P = .077) (Figure 2D).

The meta-analysis results showed that the association of TC, TG, HDL-C, LDL-C, and non-CR in patients with SSNHL before treatment showed no significant heterogeneity in the included studies on TC (I^2 = 21.1%, P = .282) and TG (I^2 = 0.0%, P = .735) (Figure 3). High-density lipoprotein cholesterol (I^2 = 66.6%, P = .050) and LDL-C (I^2 = 70.7%, P = .033) showed significant heterogeneity in the included studies. The pooled results of the random-effects model for TC, TG, HDL-C, and LDL-C were OR (95% CI) = 1.60 (0.81, 3.17); OR (95% CI) = 1.00 (0.72, 1.37); and OR (95% CI) = 1.97 (0.79, 4.87); OR (95% CI) = 0.84 (0.31, 2.26), respectively. These results revealed no significant correlation between LDL-C, HDL-C, TG, TC, and non-CR.

Subgroup Analysis

The source of heterogeneity was investigated by subgroup analysis (Table 3). For TC, subgroup analysis did not reveal a significant source of heterogeneity. The combined results of the 3 Asian subgroups (Area), hearing loss ≥ 60 dB HL (defined as SSNHL), and an increase of 1 mg/dL (cutoff) were not statistically significant (P > .05). For TG, the results showed that except for the combined results of the 2 subgroups, multivariate-adjusted and ≥ 150 vs. < 150 mg/dL (cutoff), which were statistically significant (P < .05). Adjustment for confounding factors and grouping criteria of TG were all significant sources of heterogeneity. The subgroup analysis results of the HDL-C revealed that the combined results of hearing loss ≥60 dB HL (SSNHL) and <40/50 mg/dL vs. ≥40/50 mg/dL (cutoff) were statistically significant (P < .05). No significant sources of heterogeneity were identified. For LDL-C, hearing loss ≥20 dB HL (defined as SSNHL) and no multifactor adjustment were 2 subgroups that were statistically different from the combined results (P < .05). One of the sources of significant heterogeneity was adjustment to the confounding factors.

Table 1. Characteristics of the Included Studies of the Relationship Between Lipids and Sudden Sensorineural Hearing Loss Risk

Study	Area	Design	Patients	Defined of SSNHL	Groups	n, male/female	Age, years
Aimoni, C 2010	Italy	CCS	ISSNHL	A sudden hearing loss (≥30 dB HL), within 3 frequencies, developing over 72 hours	Case	141, 75/66	54.6 ± 15.8
					Control	271, 142/129	55.0 ± 15.8
Cadoni, G 2007	Italy	CCS	ISSNHL	A sudden hearing loss (≥20 dB HL)	Case	30, 13/17	46 (23-72)
					Control	60, 26/34	49 (23-77)
Cadoni, G 2010	Italy	CCS	ISSNHL	A sudden hearing loss (≥20 dB HL)	Case	43, 19/24	50 ± 14
					Control	43, 26/17	43 ± 11
Chien, CY 2015	Taiwan	CCS	SSNHL	30 dB in 3 contiguous frequencies using a pure-tone audiogram with an onset within 3 days	Case	181, 91/90	48.7 ± 14.1
					Control	181, 99/82	46.4 ± 11.0
Jalali, MM 2020	Iran	CCS	SSNHL	A hearing loss of at least 30 dB in 3 consecutive frequencies occurring within a 72-hour period	Case	81, 44/37	45.2 ± 14.6
					Control	243, 132/111	44.9 ± 14.3
Kaneva, AM 2019	Russia	CCS	ISSNHL	A sudden hearing loss (≥20 dB HL)	Case	27, 27/0	39.7 (27-51)
					Control	27, 24/0	32.3 (25-47)
Lee, JS 2015	Korea	CCS	SSNHL	A hearing loss of at least 30 dB in 3 consecutive frequencies occurring within a 72-hour period	Case	324, 162/162	49.64 ± 16.52
					Control	972, 452/520	48.78 ± 14.70
Li, X 2021	China	CCS	SSNHL	A hearing loss of 30 dB for at least 3 consecutive frequencies	Case	2288, 1197/1091	49.7 ± 15.3
					Control	2288, 1200/1088	51.0 ± 13.4
Marcucci, R 2005	Italy	CCS	SSNHL	A hearing loss of 30 dB for at least 3 consecutive frequencies	Case	155, 67/88	54 (19-79)
					Control	155, 67/88	54 (19-78)
Rudack, C 2006	Germany	CCS	SSNHL	A hearing loss of 60 dB in at least 3 frequencies	Case	142, 77/65	51.2 ± 17.2
					Control	88, 48/40	49.8 ± 13.6
Weng, T 2013	China	CCS	SSNHL	A hearing loss of 30 dB for at least 3 consecutive frequencies	Case	250, 113/137	56.41 (15-84)
					Control	250, 113/137	56.41 (15-84)

CCS, case–control study; (I) SSNHL, (Idiopathic) sudden sensorineural hearing loss; NR, not reported.

Sensitivity Analysis and Publication Bias Test

The sensitivity analysis of the risk of SSNHL results displayed that the combined results of indicators other than TC were not robust (Table 4). For the prognostic association of SSNHL, the combined results of TC and TG levels were robust, whereas HDL-C and LDL-C levels were not robust.

Using Egger tests evaluated significant publication bias between the studies (Table 4). Total cholesterol showed a significant publication bias ($P = .005$) about the risk of SSNHL. Three virtual studies were conducted by the trim-and-fill method (Supplementary Figure 1). The combined results, OR (95% CI) = 1.56 (1.08, 2.25), and $P = .018$, indicated the meta-analysis results had a high stability. A significant publication bias was observed for LDL-C levels ($P = .006$) in the prognostic association of SSNHL. The trim-and-fill method results showed that the program did not fill in the fictitious negative results to enhance the symmetry of the funnel plot; moreover, the meta-analysis results did not vary, suggesting that the LDL-C bias may have been caused by bias due to small sample size.

DISCUSSION

This study analyzed 13 studies to explore the association between TG, TC, LDL-C, and HDL-C levels and SSNHL risk and prognosis. Generally, the main types of included studies showed recall and confounding biases. The meta-analysis results suggested that TC obviously associated with the risk of SSNHL, while the TG, HDL-C, LDL-C, and TC levels were not markedly correlated with the prognosis of patients with SSNHL. Subgroup analyses of TG levels showed that adjustments for confounding factors and grouping criteria for TG were significant sources of heterogeneity. Whether confounders were adjusted was also a source of significant heterogeneity in the LDL-C subgroup analyses. Sensitivity analysis confirmed the robustness of the correlation between TC level and the risk and prognosis of SSNHL. The findings from the meta-analysis were consistent with these results.

Table 2. Characteristics of the Included Studies of the Relationship between Lipids and Sudden Sensorineural Hearing Loss Prognosis

Study	Area	Design	Patients	n, Male/Female	Age, years	Defined of CR	Adjusted Factors
Lee, JS 2015	Korea	CCS	SSNHL	324, 162/162	49.64 ± 16.52	Final hearing level ≤25 dB	Age, BMI, lipid profiles
Li, X 2021	China	CCS	SSNHL	2288, 1197/1091	49.7 ± 15.3	Hearing gain >30 dB	lipoprotein a, ApoAI, ApoB, lipid profiles
Shao, MM 2021	China	PCS	ISSNHL	232, 105/127	NR	Hearing gain>10 dB	TC, TG, LDL-C, LDL-C/HDL-C ratio
Zhou Y 2019	China	RCS	ISSNHL	228, 120/108	43.9 ± 13.3	Final hearing level ≤25 dB	NR

ApoAI, apolipoprotein AI; ApoB, apolipoprotein B; CCS, case–control sStudy; CR, clinical recovery; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NR, not reported; PCS, prospective cohort study; RCS, retrospective cohort study; TC, total cholesterol; TG, triglycerides.

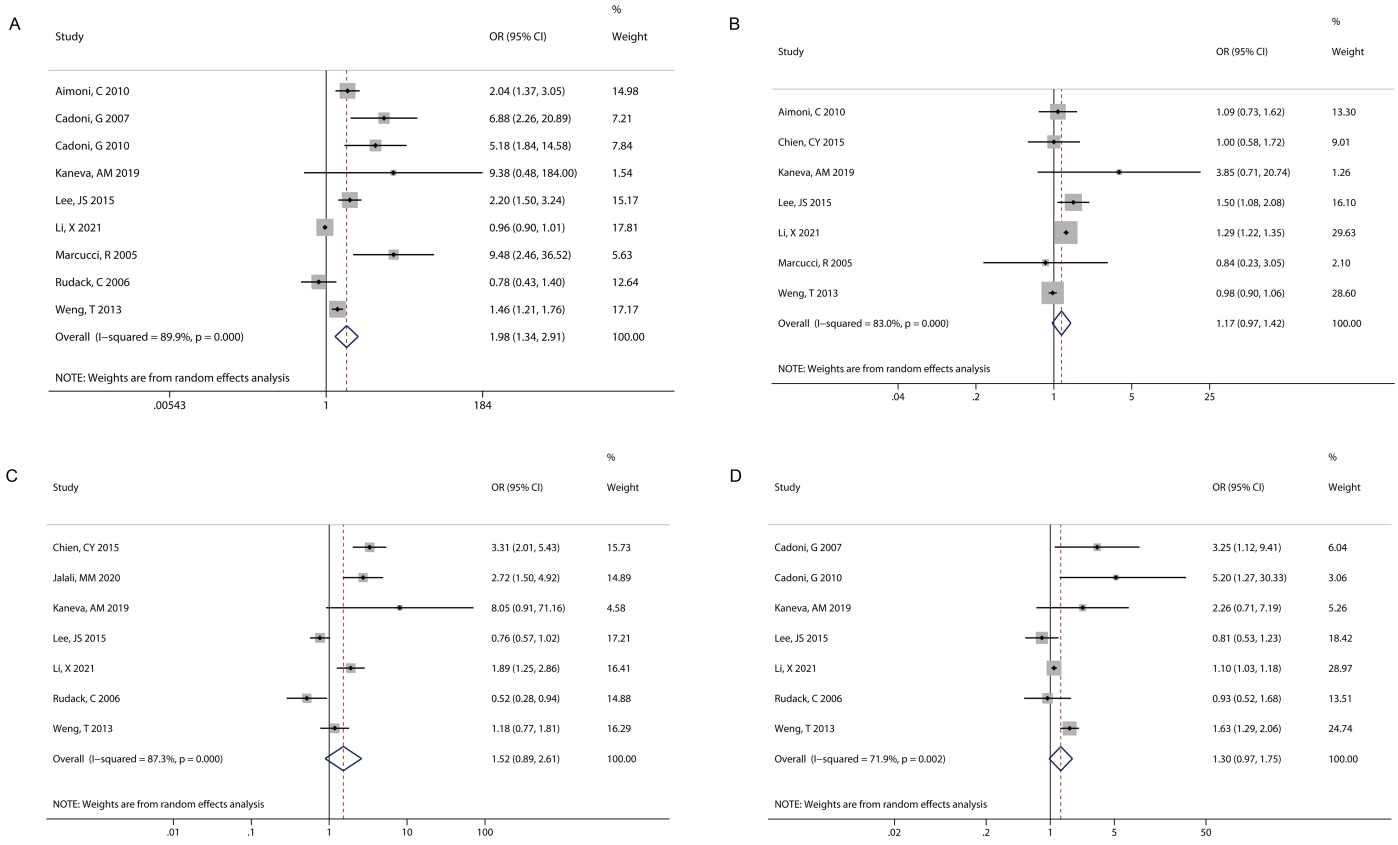

Figure 2. Forest plot of studies included in the meta-analysis of TC (A), TG (B), HDL-C (C), and LDL-C (D) and the risk of SSNHL. TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; SSNHL, sudden sensorineural hearing loss.

The higher the TC level, the higher the risk of SSNHL. A study including 250 SSNHL patients and 250 participants reported that the patients had significantly higher TC levels compared to those in the participants in the normal group.[29] Serum TC level is associated with thrombotic diseases, which are risk factors for SSNHL.[31] One risk factor for SSNHL is dyslipidemia, which is characterized by hypercholesterolemia. Dyslipidemia disrupts blood flow and induces vascular inflammation through plaque formation, vascular occlusion, and vascular remodeling, ultimately leading to damage to target organs (e.g., the cochlea).[32] The study discovered that high TC level, as a risk factor for recovery from idiopathic SSNHL, could impair cochlear function through influencing the formation of blood clots caused by endothelial dysfunction in the inner ear.[33] The inner ear, being highly metabolic, is sensitive to transient ischemia, and high TC level resulting from this sensitivity can lead to abnormal oxygen supply in target organs.[34]

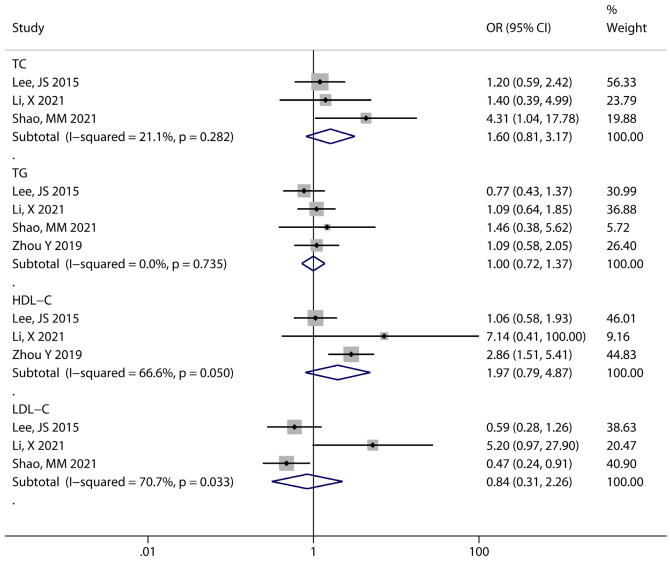

Figure 3. Forest plot of the studies included in the meta-analysis of TC, TG, HDL-C, and LDL-C and the prognosis of SSNHL. TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; SSNHL, sudden sensorineural hearing loss.

In this study, TG, HDL-C, and LDL-C levels and the risk of SSNHL were not significantly correlated. Triglyceride level and the prognosis of idiopathic SSNHL were not significantly associated.[28] However, the data suggest a better prognosis of idiopathic SSNHL when for TG levels of 1.7-2.3 mmol/L. It is likely because irreversible cochlear ischemia develops when TG levels are too high.[28] However, these results remain controversial. The increase of TC level could increase the risk of SSNHL patients with abnormal TG levels were 29% more likely to develop SSNHL than normal participants.[35] High-density lipoprotein cholesterol, as an inverse predictor of cardiovascular disease, and the higher level, the more cholesterol is excreted from the body.[36] High-density lipoprotein cholesterol levels were reportedly lower in patients with SSNHL.[24] Another study found slightly increased HDL-C concentrations in patients with SSNHL.[27] In short, the role of HDL-C in SSNHL is unclear. Low-density lipoprotein cholesterol is now part of the primary lipid measurement for assessing atherogenic lipoprotein

Table 3. Results of Subgroup Analyses

Outcomes	Number of Study	OR (95% CI)	*P*	Heterogeneity Test	
				I^2 (%)	P_H
Risk of SSNHL					
TC					
Overall (high vs. low)	9	1.98 (1.34, 2.91)	<.001	89.9	<0.001
Area					
European	6	3.26 (1.46, 7.30)	.004	79.1	<0.001
Asian	3	1.41 (0.92, 2.15)	.117	94.0	<0.001
Defined of SSNHL					
Hearing loss ≥20 dB HL	3	6.08 (2.92, 12.67)	<.001	0.0	0.895
Hearing loss ≥30 dB HL	5	1.75 (1.15, 2.66)	.009	92.8	<0.001
Hearing loss ≥60 dB HL	1	0.78 (0.43, 1.41)	.408	NA	NA
Adjusted					
Yes	4	2.04 (1.05, 3.98)	.037	92.6	<0.001
No	5	2.32 (1.11, 4.88)	.026	78.9	0.001
Cutoff					
Increased 1 mg/dL	2	1.14 (0.62, 2.08)	.673	74.7	0.047
≥200 vs. <200 mg/dL	6	2.49 (1.32, 4.72)	.005	90.7	<0.001
>147 vs. ≤147 mg/dL	1	9.48 (2.46, 36.52)	.001	NA	NA
TG					
Overall (high vs. low)	7	1.17 (0.97, 1.42)	.109	83.0	<0.001
Area					
European	3	1.17 (0.71, 1.92)	.546	12.0	0.321
Asian	4	1.17 (0.94, 1.46)	.149	90.9	<0.001
Defined of SSNHL					
Hearing loss ≥20 dB HL	1	3.85 (0.72, 20.74)	.117	NA	NA
Hearing loss ≥30 dB HL	6	1.15 (0.95, 1.40)	.147	83.0	<0.001
Adjusted[#]					
Yes	3	1.29 (1.23, 1.36)	<.001	0.0	0.590
No	3	1.01 (0.78, 1.31)	.934	21.6	0.279
Cutoff[#]					
Increased 1 mg/dL	1	0.98 (0.90, 1.06)	.573	NA	NA
≥150 vs. <150 mg/dL	4	1.30 (1.17, 1.44)	<.001	7.5	0.356
>85 vs. ≤85 mg/dL	2	1.06 (0.73, 1.55)	.752	0.0	0.710
HDL-C (low vs. high)					
Overall	7	1.52 (0.89, 2.61)	.128	87.3	<0.001
Area					
European	2	1.66 (0.12, 23.69)	.711	82.4	0.017
Asian	5	1.68 (0.96, 2.96)	.071	88.6	<0.001
Defined of SSNHL					
Hearing loss ≥20 dB HL	1	8.05 (0.91, 71.15)	.061	NA	NA
Hearing loss ≥30 dB HL	5	1.68 (0.96, 2.96)	.071	88.6	<0.001
Hearing loss ≥60 dB HL	1	0.52 (0.29, 0.94)	.029	NA	NA
Adjusted					
Yes	2	1.19 (0.49, 2.89)	.707	86.3	<0.001
No	5	1.76 (0.83, 3.76)	.144	91.8	<0.001
Cutoff					
Decreased 1 mg/dL	2	0.80 (0.36, 1.80)	.593	79.6	0.027
<40/50 vs. ≥40/50 mg/dL[&]	4	2.57 (1.81, 3.66)	<.001	27.8	0.245
<60 vs. ≥60 mg/dL	1	0.76 (0.57, 1.03)	.073	NA	NA
LDL-C (high vs. low)					
Overall	7	1.30 (0.97, 1.75)	.077	71.9	0.002
Area					
European	4	2.07 (0.92, 4.65)	.078	59.2	0.061
Asian	3	1.17 (0.85, 1.60)	.333	83.7	0.002
Defined of SSNHL					
Hearing loss ≥20 dB HL	3	3.12 (1.54, 6.29)	.002	0	0.703
Hearing loss ≥30 dB HL	3	1.17 (0.85, 1.60)	.333	83.7	0.002
Hearing loss ≥60 dB HL	1	0.93 (0.52, 1.68)	.820	NA	NA
Adjusted[#]					
Yes	2	1.02 (0.78, 1.32)	.908	49.7	0.158
No	5	1.73 (1.11, 2.69)	.016	46.0	0.116
Cutoff					
Increased 1 mg/dL	2	1.32 (0.78, 2.24)	.303	71.9	0.002
≥130 vs. <130 mg/dL	4	1.29 (0.81, 2.08)	.283	69.1	0.021
≥100 vs. <100 mg/dL	1	2.26 (0.71, 7.19)	.169	NA	NA

NA, not available; OR, odd ratio.
[#]Significant source of heterogeneity.
[&]Male <40 mg/dL or female <50 mg/dL.

risk.[37] Another study showed that elevated LDL-C levels are not an absolute maker in atherosclerosis, because, small and dense LDL-C is more likely to cause atherosclerosis than other low-density lipoprotein cholesterol subtypes.[38] These findings may assist in elucidating

Table 4. Outcomes of the Sensitivity Analysis and Test of Publication Bias

Outcomes	No. of Studies	Sensitivity Analysis		Egger's Test
		SMDs (95% CI)	Robust	*P*
Risk of SSNHL				
TC	9	1.77 (1.21, 2.58) to 2.34 (1.35, 4.06)	Yes	.005
TG	7	1.12 (0.90, 1.38) to 1.29 (1.23, 1.35)	No	.852
HDL-C	7	1.29 (0.76, 2.19) to 1.82 (1.04, 3.19)	No	.305
LDL-C	7	1.22 (0.86, 1.72) to 1.46 (1.04, 2.05)	No	.233
Non-CR of SSNHL				
TC	3	1.24 (0.67, 2.30) to 2.35 (0.78, 7.05)	Yes	.430
TG	4	0.94 (0.63, 1.42) to 1.12 (0.76, 1.65)	Yes	.517
HDL-C	3	1.69 (0.34, 8.42) to 2.99 (1.61, 5.58)	No	.691
LDL-C	3	0.52 (0.31, 0.85) to 1.53 (0.18, 12.73)	No	.006

Non-CR, non-clinical recovery.

the conflicting results of LDL-C and SSNHL in different studies. Some researchers have proposed the TC/HDL-L ratio as an indicator of insulin resistance-related atherogenic dyslipidemia.[39] Jalali et al[19] reported a higher proportion of patients with SSNHL with TC/HDL-C ≥5 compared to that in healthy participants.

This study has some limitations, mainly due to the small number of studies contributed to the lack of significant in the analysis of multiple indicators. The sensitivity analysis also suggested unstable results. In addition, most of the outcomes were heterogeneous. Significant sources of heterogeneity could not be identified through the association analysis of TC and HDL-C levels and the risk of SSNHL. Despite these limitations, this study had several strengths. Based on previous studies, this study incorporated the relevant recent literature and further clarified the correlation between the risk and prognosis of SSNHL and TC. In addition, the methodological quality of the literature was high, and the control of the selection and attrition biases was reasonable in this study. The subgroup analysis found inconsistent diagnostic criteria and lipid grouping criteria for SSNHL in the current study, which affected the extrapolation of the results. Follow-up studies should use internationally recommended criteria for diagnosis and grouping. In conclusion, the results demonstrated that a high TC level is a risk factor for SSNHL.

Ethics Committee Approval: N/A.

Informed Consent: N/A.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – X.-C.G., J.L.; Design – Y.-M.Z.; Supervision – X.-C.G., Y.-M.Z.; Resources – J.L., Y.-Q.W.; Materials – Y.-Q.W.; Data Collection and/or Processing – J.L., Y.-Q.W.; Analysis and/or Interpretation – Y.-M.Z.; Literature Search – Y.-M.Z., Y.-Q.W.; Writing – J.L.; Critical Review – X.-C.G.

Declaration of Interests: The authors have no conflicts of interest to declare.

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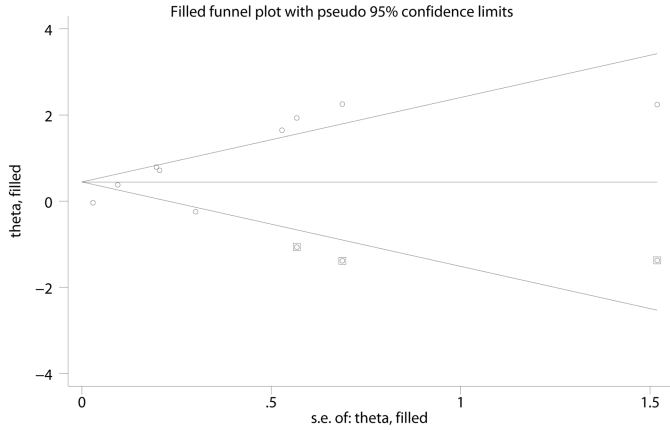

Supplementary Figure 1. Trim-and-fill analysis to estimate the number of possible missing studies for the association between TC and the risk of SSNHL. The squares represent the possible missing studies. TC: total cholesterol. SSNHL: sudden sensorineural hearing loss.

Supplementary Table 1. PubMed Retrieval Steps and Results

Search	Query	Items found
#1	("hearing loss, sudden"[MeSH Terms] OR "sudden hearing loss"[All Fields] OR "sudden deafness"[All Fields])	3951
#2	(("sudden"[All Fields] OR "suddenness"[All Fields]) AND ("hearing loss, sensorineural"[MeSH Terms] OR "sensorineural hearing loss"[All Fields] OR "sensorineural deafness"[All Fields]))	3239
#3	#1 OR #2	5016
#4	(("total"[All Fields] AND "cholesterol"[MeSH Terms]) OR "total cholesterol"[All Fields] OR "tc"[All Fields]) OR ("lipoproteins, hdl"[MeSH Terms] OR ("lipoproteins"[All Fields] AND "HDL"[All Fields]) OR "hdl lipoproteins"[All Fields] OR "high density lipoprotein"[All Fields]) OR ("lipoproteins, ldl"[MeSH Terms] OR ("lipoproteins"[All Fields] AND "ldl"[All Fields]) OR "ldl lipoproteins"[All Fields] OR "low density lipoprotein"[All Fields]) OR ("triglycerid"[All Fields] OR "triglycerides"[MeSH Terms] OR "triglycerides"[All Fields] OR "triglyceride"[All Fields] OR "triglycerids"[All Fields] OR "tg"[All Fields])	436419
#5	"lipids"[MeSH Terms] OR "lipids"[All Fields] OR "lipid"[All Fields]	1596554
#6	#4 OR #5	1797549
#7	#3 AND #6	188

Supplementary Table 2. Embaser Retrieval Steps and Results

Search	Query	Items found
#1	(sudden AND ('hearing loss'/exp OR 'hearing loss' OR 'deafness'/exp OR deafness)) OR ('sudden sensorineural deafness')	7004
#2	('lipids'/exp OR lipids OR 'total cholesterol'/exp OR 'total cholesterol' OR tc OR 'high-density lipoprotein'/exp OR 'high-density lipoprotein' OR 'hdl'/exp OR hdl OR 'low-density lipoprotein'/exp OR 'low-density lipoprotein' OR 'ldl'/exp OR ldl OR 'triglycerides'/exp OR triglycerides OR tg)	1900471
#3	#1 AND #2	314

Supplementary Table 3. Web of Science Retrieval Steps and Results

Search	Query	Items found
#1	((sudden hearing loss) OR (sudden deafness) OR (sudden sensorineural deafness)) (All Fields)	3372
#2	(lipids OR ((total cholesterol) OR TC) OR ((high-density lipoprotein) OR HDL) OR ((low-density lipoprotein) OR LDL) OR (triglycerides OR TG)) (All Fields)	1236842
#3	#1 AND #2	142

Supplementary Table 4. Quality Assessment (the Newcastle–Ottawa Scale) of the Case–Control Studies

Study	Representativeness of the cases	Case definition adequate	Ascertainment of exposure	Same method of ascertainment for cases and controls	Control for important factor or additional factor	Selection of Controls	Definition of Controls	Non- Response rate	Total quality scores
Aimoni, C 2010	☆	☆	☆	☆	☆	☆	☆	☆	8
Cadoni, G 2007	☆	☆	☆	☆	--	--	☆	☆	6
Cadoni, G 2010	☆	☆	☆	☆	--	--	☆	☆	6
Chien, CY 2015	--	☆	☆	☆	--	--	☆	☆	5
Jalali, MM 2020	--	☆	☆	☆	☆	--	☆	☆	6
Kaneva, AM 2019	--	☆	☆	☆	--	--	☆	☆	5
Lee, JS 2015	☆	☆	☆	☆	☆	☆	☆	☆	8
Li, X 2021	--	☆	☆	☆	☆	--	☆	☆	6
Marcucci, R 2005	--	☆	☆	☆	☆	--	☆	☆	6
Rudack, C 2006	☆	☆	☆	☆	--	☆	☆	☆	7
Weng, T 2013	--	☆	☆	☆	--	--	☆	☆	5

Supplementary Table 5. Quality Assessment (the Newcastle–Ottawa Scale) of the Cohort Studies

Study	Representativeness of the exposed cohort	Selection of the unexposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Control for important factor or additional factor	Outcome assessment	Follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Total quality scores
Shao, MM 2021	☆	☆	☆	☆	☆	☆	☆	☆	8
Zhou Y 2019	☆	☆	☆	--	--	☆	☆	☆	6