Association between Serum Lipid Levels and Sensorineural Hearing Loss in Korean Adult Population

Wonyoung Jung1, Jiyoung Kim2, In Young Cho3, Keun Hye Jeon4, Yun-Mi Song1,*

1Department of Family Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
2Department of Family Medicine, Seoul National University Hospital, Seoul, Korea
3Department of Family Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea
4Department of Family Medicine, CHA Gumi Medical Center, Gumi, Korea

Background: Hearing loss (HL) has been suggested to be associated with impaired microcirculation of the inner ear. This cross-sectional study aimed to evaluate an association between HL and serum lipid levels.

Methods: The study comprised 10,356 Korean adults who participated in the fifth Korea National Health and Nutrition Examination Survey (2010–2012). We defined HL as the average hearing thresholds exceeding 25 dB at predetermined frequency levels by pure tone audiometry. Serum lipid levels were measured using an enzymatic assay. The associations between lipid levels and HL were evaluated using a multiple logistic regression model after adjusting for covariates including age, sex, hypertension, diabetes, smoking status, alcohol, physical activity, educational level, household income, and noise exposure. Stratified analyses were performed to examine the effect of the covariates on the association between lipid levels and HL.

Results: The high-density lipoprotein cholesterol (HDL-C) level was inversely associated with high-frequency (HF)-HL, with an odds ratio (95% confidence interval) of 0.78 (0.64–0.96) for 1-mmol/L increase in the HDL-C level. Neither the triglyceride nor the low-density lipoprotein cholesterol level was associated with HF-HL. For low-frequency HL, association with any of the serum lipid components was absent. A stratified analysis showed that the inverse association between HDL-C levels and HF-HL was evident (P trend <0.05) in some subjects with specific characteristics such as older age (≥65 years), female sex, non-hypertensive state, and non-regular physical activity. However, a significant interaction between HDL-C levels and all of the stratified variables was absent (P for interaction >0.05).

Conclusion: The HDL-C level has a linear inverse association with the risk of HF-HL. Given the known protective role of HDL-C against atherosclerotic changes, this finding seems to support the concept of impaired microcirculation in the inner ear as a mechanism for HF-HL.

Keywords: Lipids; Cholesterol; HDL Cholesterol; Hearing Loss; Sensorineural Hearing Loss; High-Frequency Hearing Loss
INTRODUCTION

According to the World Health Organization estimates, 466 million people (or 6.1% of the global population) suffered from disabling hearing loss (HL) in 2018, and the number is expected to further increase with rapid growth of aging population. In Korea, the prevalence of disabling HL in speech frequencies (unilateral or bilateral) was estimated to be 10.43% among people ≥40 years. HL is a significant health problem that can deteriorate emotional, behavioral, and social function, and the quality of life of an affected person. Moreover, HL is associated with an increased risk of dementia and mortality. In spite of great advancements in medical science, a known effective treatment for restoring hearing function is lacking. Therefore, prevention of occurrence and progression of HL seems important, which requires understanding the pathogenesis of HL and identification of modifiable risk factors of HL. HL can be caused by several factors, which includes cochlear aging, environmental noise exposure and genetic predisposition. Aging and noise exposure are two well-known most common causes of HL; whereas other risk factors remain controversial.

In a cohort study comprising middle-aged population, carotid intima-media thickness, which reflects subclinical atherosclerosis was found to have a significant association with HL. Dyslipidemia is one of the most important risk factors of atherosclerosis which can be managed through lifestyle modification and lipid-lowering agents such as HMG-CoA (β-Hydroxy-β-methylglutaryl-CoA) reductase inhibitors. Over the last several decades, the prevalence of dyslipidemia among Koreans has been gradually increasing, which may be closely related to the recent increase in morbidity and mortality from atherosclerosis-related cardiovascular diseases. Therefore, it would be meaningful to clarify whether the higher serum lipid level is causally associated with HL.

Several studies have addressed this issue. However, the findings were inconsistent between the studies and the relation between the role of dyslipidemia and HL remains unclear. Therefore, we conducted this study in a large number of Korean adults. Additionally, we also evaluated the factors that may modify the relation between HL and dyslipidemia.

METHODS

1. Study Subjects

Study subjects comprised 10,356 Korean adults (4,509 males and 5,847 females) aged ≥40 years, who had undergone both audiometry and laboratory tests for the fifth Korea National Health and Nutrition Examination Survey (KNHANES, 2010–2012). The KNHANES was a nation-wide survey consisting of a health survey, nutrition survey, and medical examinations conducted in a representative sample of Korean population selected through a complex multi-stage probability sampling. Among the initial 18,185 participants of the survey, 7,829 persons were excluded from the study because of the following reasons: <40 years (6,880 persons), history of otitis media (775 persons), hearing aid use or on cochlear implant (64 persons), abnormal findings on external ear examination (five persons), external auditory meatus stenosis (45 persons), tympanic abnormality in the otoscope (25 persons), and those who had restricted daily life and social activities because of hearing problems (35 persons).

2. Audiometric Measurement and Frequency-Specific Hearing Loss

Pure tone audiometry test at six frequency levels (500, 1,000, 2,000, 3,000, 4,000, and 6,000 Hz) was performed by trained medical doctors, using an automated diagnostic audiometer (SA 203; Entomed, Malmo, Sweden) in a double-walled audiovisual booth. We defined HL on the basis of average hearing thresholds at predetermined frequency levels. Low-frequency hearing loss (LF-HL) was defined as the average hearing thresholds exceeding 25 dB at three lower test frequencies (500, 1,000, and 2,000 Hz). High-frequency hearing loss (HF-HL) was defined as the average hearing thresholds exceeding 25 dB at three higher test frequencies (3,000, 4,000, and 6,000 Hz).

3. Lipid Measurement

Lipid levels including total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDLC) were measured by enzymatic method using an automated analyzer (Hitachi Automatic Analyzer 7600; Hitachi, Tokyo, Japan) after at least 12 hours of overnight fasting.

For assessing the level of serum low-density lipoprotein cholesterol (LDL-C), both direct measurement by an enzymatic homogenous assay using an automated analyzer (Hitachi Automatic Analyzer 7600; Hitachi) and estimation with Friedewald’s formula were used. For the study subjects who participated in the survey between 2010 and 2011, direct measurements of LDL-C levels were performed. In the 2012 survey, LDL-C was directly measured in some subjects whose serum TG level exceeded 200 mg/dL, while in other subjects who had lower TG, LDL-C level was calculated using Friedewald’s formula.

The study subjects were categorized into two groups according to the cut-off level of dyslipidemia for each lipid component recommended by the Korean society of lipid and atherosclerosis: TC ≥200 mg/dL, TG ≥150 mg/dL, HDLC for male ≥40 mg/dL and for female ≤50 mg/dL, and LDL-C ≥130 mg/dL. To investigate the association of serum lipid levels and HL, study subjects were classified into four groups according to the quartile distribution of each lipid profile. In addition, different cut-off levels in quartiles only for HDLC were used for males and females.

4. Other Variables

Trained research nurses measured blood pressure (BP) three times while study subjects were sitting, and the averaged value of second and third measurement was used for analysis. Hypertension was defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or currently taking blood pressure lowering medication. Diabetes was defined by high fasting glucose levels (≥126 mg/dL), or
Table 1. Characteristics of study subjects and the presence of frequency-specific hearing loss

| Characteristic                                      | Low-frequency hearing loss | Hearing loss | High-frequency hearing loss | P-value |
|-----------------------------------------------------|-----------------------------|--------------|----------------------------|---------|
|                                                     | No (n=7,326)                | Yes (n=3,030) | P-value*                   |         |
| Age (y)                                             |                             |              |                            |         |
| 40–49                                               | 2,581 (92.2)                | 220 (7.9)    | <0.001†                    |         |
| 50–54                                               | 1,345 (85.5)                | 228 (14.5)   | 780 (49.6)                 | 793 (50.4) |
| 55–59                                               | 1,112 (79.2)                | 292 (20.8)   | 534 (38.3)                 | 870 (62.0) |
| 60–64                                               | 921 (67.5)                  | 443 (32.5)   | 301 (22.1)                 | 1,063 (77.9) |
| ≥65                                                 | 1,367 (42.5)                | 1,847 (57.5) | 221 (6.9)                  | 2,993 (93.1) |
| Sex                                                 |                             |              |                            |         |
| Male                                                | 3,188 (70.7)                | 1,321 (29.3) | 0.940                      |         |
| Female                                              | 4,138 (70.8)                | 1,709 (29.2) | 2,628 (45.0)               | 3,219 (55.1) |
| High total cholesterol (≥200 mg/dL)                 |                             |              |                            |         |
| No                                                  | 4,219 (70.0)                | 1,810 (30.0) | 2,139 (35.5)               | 3,890 (64.5) |
| Yes                                                 | 3,107 (71.8)                | 1,220 (28.2) | 1,601 (37.0)               | 2,726 (63.0) |
| High triglyceride (≥150 mg/dL)                      |                             |              |                            |         |
| No                                                  | 4,916 (70.8)                | 2,026 (29.2) | 2,678 (38.6)               | 4,264 (61.4) |
| Yes                                                 | 2,410 (70.6)                | 1,004 (29.4) | 1,062 (31.1)               | 2,352 (68.9) |
| Low HDL-C (<40 mg/dL for male, <50 mg/dL for female)|                             |              |                            |         |
| No                                                  | 4,243 (72.6)                | 1,599 (27.4) | <0.001                     |         |
| Yes                                                 | 3,083 (68.3)                | 1,431 (31.7) | 1,553 (34.4)               | 2,961 (65.6) |
| High LDL-C (≥130 mg/dL)                             |                             |              |                            |         |
| No                                                  | 4,808 (70.4)                | 2,018 (29.6) | 2,410 (35.3)               | 4,416 (64.7) |
| Yes                                                 | 2,518 (71.3)                | 1,012 (28.7) | 1,330 (37.7)               | 2,200 (62.3) |
| Taking medication for dyslipidemia                  |                             |              |                            |         |
| No                                                  | 6,632 (71.6)                | 2,625 (28.4) | <0.001*                    |         |
| Yes                                                 | 592 (65.3)                  | 314 (44.7)   | 262 (26.9)                 | 644 (71.1) |
| Hypertension‡                                        |                             |              |                            |         |
| No                                                  | 4,640 (71.1)                | 1,375 (29.9) | <0.001                     |         |
| Yes                                                 | 2,668 (61.9)                | 1,655 (38.1) | 1,076 (24.8)               | 3,265 (75.2) |
| Diabetes§                                            |                             |              |                            |         |
| No                                                  | 6,261 (72.7)                | 2,250 (27.3) | <0.001*                    |         |
| Yes                                                 | 850 (61.5)                  | 532 (38.5)   | 291 (21.1)                 | 1,091 (78.9) |
| Household income, quartile‡                          |                             |              |                            |         |
| Lowest                                              | 1,365 (51.4)                | 1,289 (48.6) | <0.001†                    |         |
| Low-middle                                          | 1,370 (71.5)                | 546 (28.5)   | 657 (34.3)                 | 1,259 (65.7) |
| Middle                                              | 1,432 (76.2)                | 447 (23.8)   | 764 (40.7)                 | 1,115 (59.3) |
| High-middle                                         | 1,344 (80.1)                | 335 (20.0)   | 787 (46.9)                 | 892 (53.2) |
| Highest                                             | 1,721 (82.4)                | 368 (17.6)   | 1,044 (50.0)               | 1,045 (50.0) |
| Education level achieved                             |                             |              |                            |         |
| Elementary school                                   | 1,777 (52.0)                | 1,643 (48.0) | <0.001†                    |         |
| Middle school                                       | 1,093 (70.9)                | 449 (29.1)   | 472 (30.6)                 | 1,070 (69.4) |
| High school                                         | 2,499 (81.0)                | 586 (19.0)   | 1,457 (47.2)               | 1,628 (52.8) |
| University                                          | 1,869 (87.7)                | 262 (12.3)   | 1,196 (56.2)               | 933 (43.8) |
| Smoking¶                                            |                             |              |                            |         |
| Never                                               | 4,440 (71.9)                | 1,736 (28.1) | <0.001                     |         |
| Ever                                                | 2,802 (70.0)                | 1,203 (30.0) | 998 (24.9)                 | 3,007 (75.1) |
| Alcohol consumption¶                                |                             |              |                            |         |
| None                                                | 3,486 (66.9)                | 1,726 (33.1) | 0.170†                     |         |
| ≤1/wk                                               | 2,102 (73.3)                | 616 (26.7)   | 1,165 (42.9)               | 1,553 (57.1) |
| 2–3/wk                                              | 1,038 (77.6)                | 299 (22.4)   | 454 (34.0)                 | 883 (66.0) |
| ≥4/wk                                               | 588 (67.4)                  | 284 (32.6)   | 197 (22.6)                 | 675 (77.4) |
| Regular physical activity**                         |                             |              |                            |         |
| No                                                  | 3,897 (70.8)                | 1,608 (29.2) | <0.001                     |         |
| Yes                                                 | 3,344 (71.6)                | 1,329 (28.4) | 1,644 (35.2)               | 3,029 (64.8) |

(Continued on next page)
Table 1. Continued

| Characteristic                        | Levels          | Low-frequency hearing loss | Hearing loss | High-frequency hearing loss | P-value |
|---------------------------------------|-----------------|-----------------------------|-------------|----------------------------|---------|
|                                       |                 | No (n=3,726)                | Yes (n=3,030) | P-value*                   | No (n=3,740) | Yes (n=6,616) | P-value |
| Workplace noise exposure              | No              | 6,412 (70.7)                | 2,656 (29.3) | 0.915                      | 3,367 (37.1) | 5,701 (62.9) | <0.001* |
|                                       | Yes             | 914 (71.0)                  | 374 (29.0)   |                            | 373 (29.0)   | 915 (71.0)   |         |
| Other place noise exposure            | No              | 7,194 (70.8)                | 2,973 (29.2) | 0.513                      | 3,676 (36.2) | 6,491 (63.8) | 0.518*  |
|                                       | Yes             | 132 (69.8)                  | 57 (30.2)    |                            | 64 (33.9)    | 125 (66.1)   |         |
| Sudden loud noise exposure            | No              | 5,864 (71.1)                | 2,387 (28.9) | 0.482                      | 3,213 (38.9) | 5,093 (61.1) | <0.001* |
|                                       | Yes             | 1,462 (69.5)                | 643 (30.0)   |                            | 527 (25.0)   | 1,578 (75.0) |         |
| Protection for workplace noise††     | No              | 7,148 (70.7)                | 2,970 (29.4) | 0.518                      | 3,667 (36.2) | 6,451 (63.8) | 0.030*  |
|                                       | Yes             | 178 (74.8)                  | 60 (25.2)    |                            | 73 (30.7)    | 165 (69.3)   |         |
| Protection for sudden loud noise††    | No              | 7,156 (70.7)                | 2,972 (29.3) | 0.204                      | 3,681 (36.3) | 6,447 (63.7) | 0.002*  |
|                                       | Yes             | 170 (74.6)                  | 58 (25.4)    |                            | 59 (25.9)    | 169 (74.1)   |         |
| Earphone use in a loud environment    | No              | 7,008 (70.5)                | 2,972 (29.5) | 0.004                      | 3,582 (35.6) | 6,478 (64.4) | <0.001* |
|                                       | Yes             | 238 (80.4)                  | 56 (19.6)    |                            | 158 (53.4)   | 138 (46.6)   |         |

Values are presented as number (%) for categorical variables or mean±standard deviation for continuous variables.

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

*P-value was obtained by (1) chi-square tests for categorical variables and (2) t-test for continuous variables. †P trend was obtained by Cochran-Mantel-Haenszel test. ‡Hypertension was defined by (1) systolic blood pressure of more than or equal to 140 mm Hg or (2) diastolic blood pressure of more than or equal to 90 mm Hg or currently taking blood pressure lowering medication. §Diabetes was defined by high fasting glucose (≥126), hemoglobin A1c (≥6.5), or currently taking glucose lowering treatment. §Diabetes was defined by high fasting glucose (≥126), hemoglobin A1c (≥6.5), or currently taking glucose lowering treatment. ‡‡Household income level was categorized by quintile distribution of monthly household income. ¶For smoking, never-smoker was defined by one who has never smoked, or who has smoked less than 100 cigarettes in his or her lifetime. Ever-smoker was defined by one who has smoked at least 100 cigarettes in his or her lifetime. ∥Alcohol consumption was categorized by the question, “How often do you drink alcohol?” **Regular physical activity was defined by satisfying at least one of the following: (1) vigorous-intensity activity in a bout of at least 20 minutes duration for 3 or more days a week; (2) moderate-intensity activity in a bout of at least 30 minutes duration for 5 or more days a week; and (3) walking in a bout of at least 30 minutes per 5 or more days a week. ††Protection for workplace noise and protection for sudden loud noise was defined by one who answered “yes” to the following question “Did you use an earplug or an earmuff for protecting hearing?”
hemoglobin A1c levels ≥6.5, or currently taking glucose-lowering treatment.

Information on demographic and socioeconomic characteristics (household income, education level), lifestyle factors (smoking status, alcohol consumption, and regular physical activity), past medical histories, noise exposure history, and protection for noise exposure were collected using a self-administered standardized questionnaire of KNHANES. We defined “noise exposure” as satisfying at least one of the following: workplace noise exposure, noise exposure other than workplace, sudden noise exposure, or the use of earphone in a loud environment. To check workplace noise exposure, we used a question asking whether the subjects had ever worked for more than 3 months in an environment with loud noise such as mechanical sound or generator-making sound. Other place noise exposure was checked by a question asking whether the subject had ever been exposed to loud noise at least 5 hours a week in a place other than the workplace. We checked sudden noise exposure by the following question: “Have you experienced a sudden loud noise such as gunshot or blowing sound?” We checked the use of earphone in a loud environment by the answer “yes” to the following question: “Have you used earphone to listen to loud music in a loud environment such as bus or subway?” We also checked protection from workplace noise and sudden loud noise, which was defined by the answer “yes” to the following question: “Did you use an earplug or earmuff to protect hearing?”

For smoking status, study subjects were classified into two groups: “never-smoker” for persons who had never smoked or had smoked <100 cigarettes in his or her lifetime; “ever-smoker” for persons who had smoked at least 100 cigarettes in his or her lifetime.17)

Regular physical activity was defined by satisfying at least one of the following: vigorous-intensity activity in a bout of at least 20 minutes duration for ≥3 days a week; moderate-intensity activity in a bout of at least 30 minutes duration for ≥5 days a week; walking in a bout of at least 30 minutes for ≥5 days a week.

5. Statistical Analysis
All analyses were conducted considering the complex design and sampling weight used for the fifth KNHANES. Descriptive data were presented as number (%) for categorical variables and mean±standard deviation for continuous variables. The chi-square test, Cochrane-mantel-Haenzel test, and t-test were performed to evaluate univariate associations between baseline characteristics and HL. Odds ratios and 95% confidence intervals were estimated using the multiple logistic regression analysis to examine the independent associations between baseline characteristics and HL. Error terms were estimated using the multiple logistic regression model, given their relations with age-related HL in previous studies.5,13,14)

Additionally, we evaluated whether age, sex, noise exposure, hypertension, diabetes, smoking, alcohol consumption, or regular physical exercise modified the associations between serum lipid profiles and frequency-specific HL by using stratified analyses considering two different levels by each variable. Finally, sensitivity analyses were performed after excluding study subjects who reported taking dyslipidemia medication.

We used the SAS ver. 9.4 (SAS Institute Inc., Cary, NC, USA) for the statistical analyses. P-value <0.05 was considered statistically significant for all the analyses.

6. Ethics Statement
The Institutional Review Board of Samsung Medical Center approved the present study (SMC-2019-09-105). The institutional review board waived informed consent because the data used for this study do not include any identifiable personal information and was opened to public for health research.

RESULTS
Table 1 shows the distribution of general characteristics of study subjects. Among the 10,356 study subjects aged ≥40 years, 29.3% had a LF-HL and 63.9% had a HF-HL. LF-HL was more prevalent with increase in age (P trend <0.001). Gender had no effect on the LF-HL prevalence. Subjects who had reported taking medications for dyslipidemia, hypertension, and diabetes, and who had low HDL-C, lower income level, and lower education level, were more likely to have LF-HL. Ever-smokers and subjects who did not perform regular physical activity were more likely to have LF-HL. Compared to non-drinker, drinkers showed lower prevalence of LF-HL. Previous noise exposure was unrelated to LF-HL. The prevalence of LF-HL was lower among the subjects who reported earphone use in a loud environment.
Prevalence of HF-HL increased gradually with increase in age (P trend <0.001). HF-HL was more prevalent among men compared to women. Subjects who had reported taking medications for dyslipidemia, hypertension, diabetes, higher TG, lower HDL-C, and with lower income, or lower education level were more likely to have HF-HL. Ever-smokers and subjects who were involved in regular physical activity were more likely to have HF-HL. A J-shaped relation was observed between alcohol consumption and HF-HL. Subjects with previous exposures to workplace noise and sudden loud noise were more likely to have HF-HL, while subjects who used earphone in a loud environment were less likely to have HF-HL. Subjects with a previous history of using protection for workplace noise and sudden loud noise had a higher prevalence of HF-HL than those who did not use protection.

Table 2 shows the relation of lipid profile with LF-HL and HF-HL evaluated by multiple logistic regression analysis after adjusting for covariates shown in Table 1. Any of the lipid profiles was not associated with LF-HL. TC, TG, and LDL-C were also not associated with HF-HL. However, as compared with the lowest HDL-C group, higher HDL-C group had a significantly lower risk of HF-HL (P trend <0.05); the highest quartile HDL-C group was 22% less likely to have a HF-HL.

Table 3 shows the findings from stratified analysis. The multiple logistic regression analysis after adjusting for covariates was repeatedly
Table 2. Multivariable adjusted association between serum lipid levels and frequency-specific hearing loss

| Variable                          | Low-frequency hearing loss |                       | High-frequency hearing loss |                       |
|----------------------------------|----------------------------|------------------------|----------------------------|------------------------|
|                                  | No | Yes | OR (95% CI)* | P-value | No | Yes | OR (95% CI)* | P-value |
| Total cholesterol (mg/dL)        |    |     |             |         |    |     |             |         |
| Q1 (<169)                        | 1,735 | 822 | 1          | 885 | 1,672 | 1 |
| Q2 (169–191)                     | 1,865 | 736 | 0.93 (0.76–1.12) | 0.423 | 934 | 1,867 | 1.11 (0.93–1.32) | 0.236 |
| Q3 (192–215)                     | 1,822 | 711 | 0.93 (0.79–1.11) | 0.423 | 942 | 1,591 | 1.05 (0.87–1.27) | 0.615 |
| Q4 (≥216)                        | 1,904 | 761 | 0.96 (0.80–1.15) | 0.650 | 979 | 1,886 | 1.05 (0.88–1.25) | 0.599 |
| Per 1 mmol/L increase            | 7,326 | 3,030 | 1.13 (0.92–1.39) | 0.243 | 3,740 | 6,616 | 1.17 (0.98–1.41) | 0.088 |
| Triglyceride (mg/dL)             |    |     |             |         |    |     |             |         |
| Q1 (<79)                         | 1,886 | 669 | 1          | 1,098 | 1,487 | 1 |
| Q2 (79–114)                      | 1,781 | 771 | 0.97 (0.81–1.18) | 0.787 | 960 | 1,592 | 0.90 (0.74–1.10) | 0.313 |
| Q3 (115–170)                     | 1,819 | 791 | 0.88 (0.73–1.07) | 0.202 | 876 | 1,734 | 0.85 (0.70–1.03) | 0.096 |
| Q4 (≥171)                        | 1,840 | 769 | 0.96 (0.79–1.17) | 0.689 | 806 | 1,803 | 1.03 (0.85–1.24) | 0.790 |
| Per 1 mmol/L increase            | 7,326 | 3,030 | 0.98 (0.95–1.02) | 0.366 | 3,740 | 6,616 | 0.98 (0.95–1.01) | 0.223 |
| High-density lipoprotein cholesterol (mg/dL) |    |     |             |         |    |     |             |         |
| Q1 (M: <38.21, F: <42.28)        | 1,673 | 856 | 1          | 746 | 1,783 | 1 |
| Q2 (M: 38.21–44.31, F: 42.28–49.34) | 1,806 | 751 | 0.91 (0.76–1.09) | 0.310 | 914 | 1,643 | 0.77 (0.63–0.94) | 0.010 |
| Q3 (M: 44.32–52.37, F: 49.35–57.42) | 1,903 | 721 | 0.97 (0.81–1.15) | 0.695 | 1,015 | 1,609 | 0.79 (0.65–0.95) | 0.011 |
| Q4 (M: ≥52.38, F: ≥57.43)        | 1,944 | 702 | 0.93 (0.77–1.11) | 0.413 | 1,065 | 1,581 | 0.78 (0.64–0.94) | 0.010 |
| Per 1 mmol/L increase            | 7,326 | 3,030 | 0.87 (0.69–1.01) | 0.247 | 3,740 | 6,616 | 0.78 (0.64–0.96) | 0.017 |
| Low-density lipoprotein cholesterol (mg/dL) |    |     |             |         |    |     |             |         |
| Q1 (<95.94)                      | 1,775 | 814 | 1          | 866 | 1,723 | 1 |
| Q2 (95.94–116.75)                | 1,840 | 749 | 1.03 (0.85–1.24) | 0.759 | 952 | 1,637 | 1.04 (0.85–1.27) | 0.708 |
| Q3 (116.76–139.05)               | 1,875 | 714 | 0.94 (0.80–1.11) | 0.477 | 958 | 1,631 | 0.99 (0.82–1.20) | 0.911 |
| Q4 (≥139.06)                     | 1,836 | 753 | 0.92 (0.76–1.11) | 0.384 | 964 | 1,625 | 0.94 (0.78–1.13) | 0.482 |
| Per 1 mmol/L increase            | 7,326 | 3,030 | 0.86 (0.70–1.09) | 0.165 | 3,740 | 6,616 | 0.84 (0.70–1.01) | 0.060 |

Values are presented as number or OR (95% CI), unless otherwise stated.

OR, odds ratio; CI, confidence interval; M, male; F, female.

*OR and 95% CI was estimated by multiple logistic regression analysis after adjusting for age, sex, hypertension, diabetes, smoking, alcohol consumption, education level, physical activity, household income, and noise exposure.
Table 3. Stratified analysis for the association between serum HDL-C levels and high-frequency hearing loss

| Variable                  | No. of subjects | Quartile distribution of HDL-C | P trend* | P interaction† |
|---------------------------|-----------------|-------------------------------|---------|----------------|
|                           |                 | Q1 | Q2 | Q3 | Q4 |               |         |
| Age (y)                   |                 |    |    |    |    |               | 0.555   |
| 40–64                     | 7,555           | 1  | 0.79 (0.57–1.09) | 0.86 (0.64–1.16) | 0.83 (0.60–1.16) | 0.527   |
| ≥65                       | 2,801           | 1  | 0.77 (0.62–0.96) | 0.68 (0.60–0.84) | 0.74 (0.59–0.92) | 0.002   |
| Sex                       |                 |    |    |    |    |               | 0.226   |
| Men                       | 4,509           | 1  | 0.79 (0.59–1.05) | 0.89 (0.67–1.17) | 0.74 (0.54–1.00) | 0.173   |
| Women                     | 5,847           | 1  | 0.76 (0.59–0.97) | 0.70 (0.55–0.88) | 0.81 (0.64–1.02) | 0.024   |
| Hypertension              |                 |    |    |    |    |               | 0.528   |
| No                        | 6,015           | 1  | 0.76 (0.60–0.96) | 0.72 (0.56–0.91) | 0.75 (0.59–0.94) | 0.030   |
| Yes                       | 4,341           | 1  | 0.79 (0.58–1.07) | 0.92 (0.69–1.24) | 0.82 (0.60–1.12) | 0.380   |
| Diabetes                  |                 |    |    |    |    |               | 0.698   |
| No                        | 8,611           | 1  | 0.78 (0.63–0.96) | 0.78 (0.64–0.96) | 0.79 (0.65–0.97) | 0.056   |
| Yes                       | 1,382           | 1  | 0.71 (0.42–1.18) | 0.85 (0.52–1.40) | 0.71 (0.41–1.24) | 0.360   |
| Smoking                   |                 |    |    |    |    |               | 0.281   |
| Never                     | 6,176           | 1  | 0.79 (0.61–1.02) | 0.73 (0.58–0.93) | 0.83 (0.66–1.06) | 0.078   |
| Ever                      | 4,005           | 1  | 0.74 (0.54–1.01) | 0.85 (0.63–1.13) | 0.69 (0.52–0.94) | 0.081   |
| Alcohol                   |                 |    |    |    |    |               | 0.889   |
| No                        | 5,212           | 1  | 0.79 (0.61–1.03) | 0.75 (0.59–0.95) | 0.77 (0.60–1.00) | 0.081   |
| Yes                       | 4,927           | 1  | 0.75 (0.57–0.99) | 0.82 (0.63–1.07) | 0.79 (0.61–1.02) | 0.210   |
| Regular physical activity |                 |    |    |    |    |               | 0.368   |
| No                        | 5,505           | 1  | 0.68 (0.53–0.87) | 0.70 (0.55–0.91) | 0.68 (0.53–0.88) | 0.007   |
| Yes                       | 4,673           | 1  | 0.90 (0.68–1.21) | 0.90 (0.68–1.19) | 0.91 (0.69–1.19) | 0.870   |
| Noise exposure            |                 |    |    |    |    |               | 0.277   |
| No                        | 7,139           | 1  | 0.76 (0.60–0.96) | 0.82 (0.66–1.03) | 0.85 (0.69–1.06) | 0.139   |
| Yes                       | 3,217           | 1  | 0.79 (0.57–1.09) | 0.71 (0.52–0.98) | 0.64 (0.46–0.89) | 0.056   |

Values are presented as OR (95% CI), unless otherwise stated. Statistically significant results are marked in bold. OR and 95% CI was estimated by multiple logistic regression analysis after adjusting for age, sex, hypertension, diabetes, smoking, alcohol consumption, education level, physical activity, household income, and noise exposure if applicable.

HDL-C, high-density lipoprotein cholesterol; OR, odds ratio; CI, confidence interval.

*P trend was obtained by linear regression model in which quartile levels of HDL-C were included as an ordinal variable. †P for interaction was obtained by putting an interaction term (quartile level of HDL-C×each stratifying variable) in the by multiple logistic regression model.
done in each two different strata for age, sex, hypertension, diabetes, smoking, alcohol consumption, physical exercise, and noise exposure. The inverse association between HDL-C and HF-HL was evident (P trend <0.05) in the limited subjects who were older (≥65 years), female, non-hypertensive and non-regular physical exerciser. However, significant interactions between HDL-C and age, hypertension, diabetes, alcohol drinking, regular physical activity, and noise exposure were absent (P for interaction >0.05).

Supplements 1 and 2 shows the findings from analyses after excluding the 906 subjects (8.5%) who had reported taking lipid-lowering medications. For HDL-C, the findings from the new analyses did not differ from the findings before excluding the 906 subjects. In contrast, both TC (per 1 mmol/L) and LDL-C (per 1 mmol/L) were associated with HF-HL (P trend <0.05) after excluding the 906 subjects, whereas significant association between TC and HF-HL, and between LDL-C and HF-HL in main analysis was absent.

DISCUSSION

In this large-sized cross-sectional study in Korean adults aged over 40 years, we found that higher HDL-C level was associated with lower risk of HF-HL. The highest quartile HDL-C group was 27% less likely to be affected by HF-HL, compared with the lowest quartile HDL-C group. However, we could not identify a significant association between HL and TG or LDL-C.

Studies on the relation between dyslipidemia and HL have shown inconsistent findings. A study using KNHANES data reported that dyslipidemia was not associated with HL in young adult population aged 30–49 years.10 We think this null association was probably because degenerative changes involved in the development of HL were less likely to be evident in this young adult group included in the Korean study. In addition, over-adjustment might have resulted in such a null association, provided that the levels of each lipid component were included in multivariable-adjusted analytic model. A retrospective case-control study including 1,490 patients in a neuro-otology clinic, found that hearing thresholds were significantly better in those with increased TC levels after considering age and sex,11a negating the hazardous effect of dyslipidemia on HL. However, this study did not consider the confounding effects of covariates like noise exposure. In a study of 837 elderly (mean age, 67.5 years), HL had no association with TC, HDL-C, and LDL-C after controlling age, sex, and use of lipid-lowering medications or anti-inflammatory medications. Although a positive association between 1) TG and HL, and 2) the ratio of TC to HDL and HL was found in a cross-sectional analysis, the association was no longer observed in a longitudinal analysis.12 A systematic review including six case-control studies found no significant difference in TC and LDL-C concentrations between the sudden sensory neural hearing loss (SSNHL) case and control groups.13 On the other hand, as found in our study, several studies have suggested that worse lipid profile may have a significant relation with HL; although, most of the studies focused on SSNHL. A case-control study on 324 patients (mean age, 49.64 years) with SSNHL and 972 control subjects with normal hearing selected from the KNHANES data found that elevated TC and TG levels were associated with a higher risk of SSNHL after controlling for age, sex, height, and underlying diseases.14 The findings indicate that vascular compromise may play an important role in the pathogenesis of SSNHL. Several studies have also focused on age-related HL. In a study on 180 elderly (≥65 years) patients with bilateral HL, patients with hypercholesterolemia had worse HL than patients with normal lipid serum levels, suggesting that hypercholesterolemia is associated with age-related HL, possibly by an atherosclerotic mechanism.15 However, this study did not investigate the relation of HL with individual lipid components. Therefore, further studies are required to provide sufficient level of evidence to clarify the relation between lipid components and HL.

Aging and noise are the most common etiological factors involved in the development of HL in the adult population. Age-related hearing loss (ARHL) is a gradual and irreversible age-dependent decline of the auditory function, being reflected as a progressive increase in auditory thresholds, mainly in the high-frequency range. Noise-induced hearing loss (NIHL) is the consequence of overexposure to loud noise, characterized by a permanent increase in auditory thresholds (permanent threshold shift).

Hair cell damage has been known as a key contributor to the HL in both NIHL and ARHL.16 Hair cell damage and death are observed in minutes to hours after acoustic overexposure, while death of spiral ganglion cells is delayed by months to years.17 Dyslipidemia can contribute to HL as a main risk factor of atherosclerosis.18 Since the cochlear artery supplied by the labyrinthine artery is the only circulation for the cochlea without collaterals, blood viscosity elevation by dyslipidemia may exert significant impact on cochlear microcirculation. Moreover, atherosclerosis may cause excess generation and accumulation of free radicals, which may further contribute to ischemia-induced cochlear injury.19 In addition to hair cell damage, a recent study has suggested the role of synaptic connections between hair cells and cochlear neurons in both NIHL and ARHL, by reporting that synaptic connections between hair cells and cochlear neurons could be destroyed easily before the hair cells are damaged, which is called cochlear synaptopathy.20 Up to 50% of inner hair cell synapses can be destroyed across large cochlear regions by exposures to lower level of noise that produces only a temporary threshold shift and may leave all hair cells intact.21 Under normal aging process, a person without explicit otologic disease can also show dramatic cochlear neuropathy in regions of minimal hair cell loss.22

Although interaction was not significant, we found that the association between HDL-C and HF-HL was evident in old age group (≥65 years); however, not in younger age group. Provided that HF-HL in the elderly mainly consists of ARHL, HF-HL in old age group is more likely to be causally related to the reduction and disturbance of cochlear blood flow in advance followed by substantial hair cell damage. Hence, protective effect of high HDL-C against dysregulation of blood flow in cochlea might be more distinct in old age group. Meanwhile, cochlear
synaptopathy is a more plausible mechanism underlying HF-HL in young age group, because younger adults might have insufficient time for cochlear blood flow to progress to the advanced dysfunction. In consistent with our findings, no association between HDL-C and HF-HL in young age group was found.

Interestingly, we found that the association between HDL-C level and HF-HL was evident in the noise-exposed subjects (P trend=0.056), but not in the noise un-exposure group. Similarly, Axelson and Lindgren reported that the risk of acquiring HF-HL in males aged over 50 years was evident in people who had worked in noisy environments and had a high serum cholesterol level. As aforementioned, noise can synergistically interact with atherosclerosis by leading to the overproduction and accumulation of free radicals that lead to ischemic-cochlear injury. Although, the effect of noise on auditory aging is still a matter of debate, noise may modify the onset and progression of ARHL.

Several population studies reported that severe profound HL is more prevalent in males than in females. ARHL in men occurred earlier and more intensely; and NIHL from occupational noise exposure was more prevalent in men. In our study, HF-HL was also more prevalent in men, which is compatible with the findings of the previous studies. A study in postmenopausal women reported that the women using estrogen-only therapy experienced protective effects against HL in males aged over 50 years was evident in people who had worked in noisy environments and had a high serum cholesterol level. As aforementioned, noise can synergistically interact with atherosclerosis by leading to the overproduction and accumulation of free radicals that lead to ischemic-cochlear injury. Although, the effect of noise on auditory aging is still a matter of debate, noise may modify the onset and progression of ARHL.

In conclusion, for clinical practices, HDL-C level has a linear inverse association with the risk of HF-HL in Korean population, even after considering the wide range of covariates including cardiovascular risk factors and noise exposure. Provided the known protective role of HDL-C against atherosclerotic change this finding seems to support the impaired microcirculation in the inner ear as a mechanism for HF-HL.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.4082/kjfm.21.0148. Supplement 1. Multivariable adjusted association between serum lipid levels and frequency-specific hearing loss after excluding those study subjects who reported taking lipid lowering agents (N=9,257). Supplement 2. Stratified analysis for the association between serum HDL-C levels and HF-HL after excluding those study subjects who reported taking lipid lowering agents (N=9,257).

ORCID

Wonyoung Jung: https://orcid.org/0000-0003-4749-4637
Jiyoung Kim: https://orcid.org/0000-0002-6739-3545
In Young Cho: https://orcid.org/0000-0002-6240-9026
Keun Hye Jeon: https://orcid.org/0000-0003-2294-0637
Yun-Mi Song: https://orcid.org/0000-0001-9232-5563

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