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Original Article

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Hypercholesterolemia is Suggested to be an Independent Risk Factor of Incident Hearing Loss in Japanese Men and Women Undergoing Health Screening

Eiji Oda

Abstract

Background and Aims: Hypercholesterolemia has been suggested to be a risk factor of hearing loss. However, most of the epidemiological studies showing this were cross-sectional and controversial. The aim of this longitudinal study was to find independent risk factors of incident hearing loss.

Methods: This was an 8-year follow-up study to find risk factors of high-frequency hearing loss (HFHL) and low-frequency hearing loss (LFHL) in 2,628 and 2,775 participants, respectively. The threshold levels of HFHL and LFHL were defined at the 40dB (4,000Hz) and the 30dB (1,000Hz) for a better ear, respectively. Age and sex adjusted hazard ratios (HRs) of incident hearing loss were calculated for candidate risk factors. Then, stepwise Cox regressions were performed. Similar calculations were made excluding subjects older than 60 years.

Results: HFHL and LFHL developed in 18.4% of men and 6.5% of women and 8.7% of men and 9.5% of women, respectively. The incidence of hearing loss was markedly higher in participants older than 60 years: 53.4% in men and 20.6% in women and 28.4% in men and 26.9% in women, respectively, for HFHL and LFHL. Smoking and daily alcohol drinking were independent risk factors of HFHL while hypercholesterolemia was an independent risk factor of LFHL for all participants. Hypercholesterolemia and smoking were independent risk factors of HFHL while hypercholesterolemia and anemia were independent risk factors of LFHL after excluding subjects older than 60 years.

Conclusions: Our results suggested that hypercholesterolemia was an independent risk factor of both HFHL and LFHL after excluding subjects older than 60 years. Individuals with hypercholesterolemia should be recommended to undergo audiometry and avoid risk factors of hearing loss.

Keywords incident hearing loss, hypercholesterolemia, anemia, smoking

The World Health Organization has reported that 466 million people worldwide have disabling hearing loss (HL), and 1.1 billion young people are at risk of HL due to exposure to noise in recreational settings[1]. HL may result from genetic causes, complications at birth, chronic ear or systemic infections, certain drugs, exposure to excessive noise and ageing. Unaddressed HL poses an annual global cost of 750 billion international dollars, so interventions to prevent, identify and address HL are cost-effective and can bring great benefit to individuals with HL from early identification[1]. So, it is important to explore risk factors of HL. However, there have been conflicting reports of associations between HL and possible risk factors. Most of the studies concerning risk factors of HL have been cross-sectional[2–18].

Among longitudinal studies, one reported that hypertension, diabetes and obesity were not associated with incident HL while smoking and hypercholesterolemia had small but significant associations with incident HL in men[19]. Another study reported a significant association between hypercholesterolemia and incident sudden sensorineural HL (SSHL)[20] and yet another reported a significant association between hypertension and incident HL in women[21]. There has also been a study that reported a significant association between incident HL and diabetes and a borderline association between incident HL and prediabetes[22]. Furthermore, there have been experimental studies whose results suggested that hypercholesterolemia may be a risk factor of HL[23–27].

Medical Check-up Center, Tachikawa General Hospital
Contact : Eiji Oda, Medical Check-up Center, Tachikawa General Hospital, Asahioka 1–24, Nagaoka, Niigata 940–8621, Japan.
Tel : +81–258–36–6221 ; Fax : +81–258–34–1113 ; E-mail : ijie@venus.sannet.ne.jp

Advance Publication
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The aim of the present study was to find risk factors of incident HL in a health screening population.

The study was approved by the ethics committee of Tachikawa General Hospital and was performed in accordance with the ethical standards of the Declaration of Helsinki in 1964 and its later amendments.

Subjects and Methods

Subjects

Among 3,866 individuals who visited our Medical Check-up Center for general health screening between April 2008 and March 2009 and gave written informed consent to use their data for epidemiological studies, 3,716 individuals (37% women) aged 24–82 years completed pure tone audiometry. They were all required to fill out a questionnaire recommended by the Japanese Ministry of Health, Labor and Welfare, which includes questions on histories of coronary heart disease and stroke, smoking and drinking status, physical activity, antihypertensive, antidiabetic, and antihyperlipidemic medications. After excluding individuals with a history of coronary heart disease or stroke, 3,541 remained. Further excluding individuals with high-frequency HL (HFHL) and low-frequency HL (LFHL) at baseline left 3,204 and 3,383 participants as potential subjects for the present incident HFHL and LFHL study, respectively. Owing to drop-outs during the 8-year follow-up period, 2,628 and 2,775 participants were actually involved in the present incident HFHL and LFHL study, respectively.

Measurements

Pure tone audiometry was performed by trained technicians using an AA-46 system (RION Co. Ltd, Tokyo, Japan). LFHL and HFHL were diagnosed using a threshold level of 30 dB at 1,000 Hz and one of 40 dB at 4,000 Hz, respectively. After an overnight fast, blood samples were obtained to measure blood levels of routine health screening tests including fasting plasma glucose (FPG), triglycerides, total cholesterol, LDL cholesterol, HDL cholesterol, HbA1c, uric acid, hemoglobin, high-sensitivity C-reactive protein (hs-CRP) and creatinine. Measurements were performed at BML Nagaoka (Nagaoka, Japan) using routine laboratory methods except for hs-CRP, which was measured at BML General Laboratory (Tokyo, Japan) by nephelometry using N-latex CRP-2 (Siemens Healthcare K.K. , Tokyo, Japan). The measurement limit of hs-CRP was 0.02 mg/L and levels of hs-CRP less than the measurement limit were considered to be 0.01 mg/L. LDL cholesterol was measured using a direct surfactant method with Choletest-LDL (SEKISUI MEDICAL CO., LTD, Tokyo, Japan). HbA1c was measured by latex aggregation immunoassay using Determiner HbA1c (Kyowa Medex Co., Ltd., Tokyo, Japan) and expressed in NGSP%. Average systolic blood pressure (SBP) and diastolic blood pressure (DBP) were calculated from two automatic measurements using a MPV-3301 instrument (NIHON KOHDEN CORPORATION, Tokyo, Japan) in the sitting position after a 5 min rest. Body height and weight were automatically measured using a TBF-210 device (TANITA corporation, Tokyo, Japan) wearing light clothes provided by our center, subtracting the weight of the clothing from the measured body weight. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Respiratory function tests, including percent vital capacity (%VC) and forced expiratory volume in 1 second divided by forced vital capacity (FEV1/FVC), were performed by trained clinical technicians using the Autospirometer System 7 (Minato Medical Science, Osaka, Japan). The spirometry methods complied with the guidelines for spirometry examinations issued by the Japanese Respiratory Society. Slow vital capacity was measured several times. %VC was calculated as the maximal slow vital capacity divided by predicted vital capacity. Predicted vital capacity (PVC) was calculated using the equations recommended by the Japanese Respiratory Society in 2001: PVC = $0.045 \times \text{height (cm)}^{-0.023} \times \text{age (years)}^{-2.258}$ in men and $0.032 \times \text{height (cm)}^{-0.018} \times \text{age (years)}^{-1.178}$ in women. Estimated glomerular filtration rate (eGFR) was calculated from serum creatinine using the gender-specific equations for Japanese recommended by the Japanese Society of Nephrology[28].

Definition of candidate risk factors

Candidate risk factors were defined as below.

Obesity-25: BMI ≥ 25 kg/m^2.
Obesity-30: BMI ≥ 30 kg/m^2.
Hypertension: SBP ≥ 140 mmHg or DBP ≤ 90 mmHg or use of antihypertensive drugs.
Diabetes: FPG ≥ 7.0 mmol/L or HbA1c ≥ 6.5% or use of antidiabetic drugs.
Prediabetes: FPG ≥ 5.6 mmol/L or HbA1c ≥ 5.7% excluding diabetes.
Hypercholesterolemia: total cholesterol ≥ 6.2 mmol/L or use of antihyperlipidemic drugs.
Hyper-LDL cholesterolemia-1: LDL cholesterol ≥ 3.6 mmol/L or use of antihyperlipidemic drugs.
Hyper-LDL cholesterolemia-2: LDL cholesterol ≥ 4.1 mmol/L or use of antihyperlipidemic drugs.
Hypertriglyceridemia: triglycerides ≥ 1.7 mmol/L.
Hypo-HDL cholesterolemia: HDL cholesterol < 1.0 mmol/L in men and < 1.3 mmol/L in women.
Hyperuricemia: ≥ 400 μmol/L in men and ≥ 360 μmol/L in women.
Anemia: hemoglobin < 130 g/L in men and < 120 g/L in women.
Low-grade inflammation: hs-CRP ≥ 1.00 mg/L.
Renal dysfunction (RD): eGFR < 60 mL/min/1.73m^2.

Advance Publication
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Restrictive lung disease (RLD): %VC < 80%.
Obstructive lung disease (OLD): FEV1/FVC < 70%.

Obesity-25 includes Obesity-30. Hypo-HDL cholesterolemia was defined differently by sex according to the international definition[29] although the definition is the same for both sexes in Japan. Detailed information about antihyperlipidemic drugs was not available but most of the antihyperlipidemic drugs were considered to have been prescribed for hypercholesterolemia. Therefore, antihyperlipidemic drugs were all considered to be antihypercholesterolemic drugs in this study. This assumption is not exactly scientific but was a practical way of dealing with the limited information.

Detailed quantitative information was not obtained regarding alcohol consumption in this study.

Statistical analysis

Baseline variables were compared between participants who developed HFHL or LFHL during the follow-up period and their normal counterparts. Physical activity was defined as walking for one hour or longer per day or exercising for 30 minutes or longer twice or more per week. Means were compared by *t*-tests and percentages were compared by *chi*-squared tests.

Calculated incidences of HFHL and LFHL were stratified by age groups (decades) and sex.

Hazard ratios (HRs) of LFHL and HFHL were calculated adjusting for sex and age using Cox regression models, in which years were used as the unit of the survival variable, the first diagnosis with hearing loss by annual audiometry was ascertained as the outcome and subjects without the outcome were censored at their last annual health screening visit. Then, stepwise Cox regressions were performed using $p < 0.05$ as the inclusion criterion and $p \geq 0.1$ as the exclusion criterion adopting age, male sex, current smoking, daily alcohol drinking, physical activity and all the candidate risk factors defined above as the initial covariates. The above calculations of HRs were repeated excluding participants older than 60 years.

Statistical analyses were performed using Dr SPSS-2 (IBM Japan, Tokyo, Japan). *p* values of lower than 0.05 were considered significant.

Results

Baseline data stratified by development of HL are presented in **Table 1**. Male sex, age, obesity-25, hypertension, diabetes, prediabetes, hypercholesterolemia, low-grade inflammation, RD, OLD, current smoking, daily alcohol drinking and physical activity were significantly associated with incident HFHL while age, hypertension, diabetes, prediabetes, hypercholesterolemia, hyper-LDL cholesterolemia-1, hyper-LDL cholesterolemia-2, low-grade inflammation, RD, OLD and physical activity were significantly associated with incident LFHL.

Incidences of HFHL and LFHL are shown in **Table 2** stratified by age groups (decade) and sex. HFHL developed in 303 men (18.4%) and 64 women (6.5%) while LFHL developed in 153 men (8.7%) and 32 women (9.4%) during the 8 years of follow-up. The mean follow-up duration was 5.7 years in the HFHL study and 5.9 years in the LFHL study. The incidences of HFHL and LFHL were markedly higher in the age groups with subjects older than 60 years.

The HRs (95% confidence intervals (CIs)) of HFHL and LFHL for candidate risk factors are shown in **Table 3**. There were no significant associations between incident HFHL and obesity-25, hypertension, diabetes, prediabetes, hypercholesterolemia, low-grade inflammation, RD, OLD or physical activity after adjustment for sex and age. Only current smoking and daily alcohol drinking were significantly associated with incident HFHL after adjustment for sex and age. There were no significant associations between incident LFHL and hypertension, diabetes, prediabetes, hyper-LDL cholesterolemia-1, hyper-LDL cholesterolemia-2, low-grade inflammation, RD, OLD or physical activity after adjustment for sex and age. Only hypercholesterolemia was significantly associated with incident LFHL after adjustment for sex and age. Age, male sex, current smoking and daily alcohol drinking were significantly associated with incident HFHL in the final step of the stepwise regressions while age and hypercholesterolemia were significantly associated with incident LFHL in the final step of the stepwise regressions.

The HRs (95% CIs) of HFHL and LFHL for candidate risk factors calculated excluding participants older than 60 years are shown in **Table 4**. Among the 2,259 (63.2% men) participants, 218 (9.7%) subjects developed HFHL and among the 2,380 (63.7% men) participants, 138 (5.8%) subjects developed LFHL. There were significant associations between incident HFHL and hypercholesterolemia, hyper-LDL cholesterolemia-1 and current smoking after adjustment for sex and age. Only hypercholesterolemia was significantly associated with incident LFHL after adjustment for sex and age. There were significant associations between incident HFHL and age, male sex, hypercholesterolemia and current smoking in the final step of the stepwise regressions while age, hypercholesterolemia and anemia were significantly associated with incident LFHL in the final step of the stepwise regressions.

Discussion

In the present 8-year follow-up study, current smoking and daily alcohol drinking were independently associated with incident HFHL while hypercholesterolemia was independently associated with incident LFHL, in a health screening population. After excluding indi-

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Table 1. Baseline Variables Stratified by Incident Hearing Loss

	high-frequency audiometry			low-frequency audiometry		
	normal	impaired	*p*	normal	impaired	*p*
n	2261	367		2527	248	
men (%)	59.6	82.6	<0.001	63.4	61.3	0.512
age (years)	50.0 (8.7)	59.4 (8.4)	<0.001	50.6 (8.9)	59.7 (9.0)	<0.001
obesity-25 [a] (%)	19.4	25.9	0.004	19.9	24.2	0.109
obesity-30 [b] (%)	2.1	2.5	0.646	2.1	2.0	0.932
hypertension (%)	21.5	35.1	<0.001	23.0	33.1	<0.001
diabetes (%)	3.6	8.7	<0.001	4.1	6.9	0.040
prediabetes (%)	22.6	32.2	<0.001	23.2	33.9	<0.001
hypercholesterolemia [c] (%)	19.5	24.5	0.026	19.4	31.0	<0.001
hyper-LDLC-1 [d] (%)	30.9	35.1	0.102	31.0	39.5	0.006
hyper-LDLC-2 [e] (%)	16.5	20.2	0.079	16.4	24.2	0.002
hypertriglyceridemia (%)	16.5	19.9	0.108	16.9	17.3	0.872
hypo-HDLC [f] (%)	8.0	7.6	0.805	7.9	8.1	0.934
hyperuricemia (%)	20.5	19.1	0.535	20.3	16.5	0.157
low-grade inflammation [g] (%)	12.1	16.9	0.010	12.4	18.1	0.010
anemia (%)	8.4	6.3	0.172	7.8	10.5	0.131
renal dysfunction (%)	4.6	9.0	<0.001	4.8	11.7	<0.001
restrictive lung disease (%)	4.1	4.9	0.484	4.0	5.6	0.201
obstructive lung disease (%)	2.1	5.7	<0.001	2.5	4.8	0.030
current smoking (%)	23.1	29.4	0.008	24.7	19.8	0.084
daily alcohol drinking (%)	36.0	51.0	<0.001	37.8	41.1	0.308
physical activity [h] (%)	34.9	41.1	0.020	34.9	41.9	0.028
antihypertensives (%)	12.5	24.0	<0.001	13.5	22.6	<0.001
antidiabetics (%)	1.8	5.2	<0.001	2.2	4.0	0.073
antihyperlipidemics (%)	7.4	12.8	<0.001	7.6	16.9	<0.001
body mass index (kg/m^2)	22.5 (3.0)	23.2 (3.0)	<0.001	22.6 (3.0)	23.1 (3.0)	0.025
SBP [i] (mmHg)	117.4 (17.6)	123.0 (18.3)	<0.001	118.1 (17.8)	121.2 (18.1)	0.010
DBP [j] (mmHg)	74.2 (11.0)	77.6 (11.1)	<0.001	74.6 (11.1)	76.2 (11.2)	0.041
FPG [k] (mmol/L)	5.15 (0.73)	5.44 (1.09)	<0.001	5.18 (0.78)	5.36 (0.91)	0.001
hemoglobin A1c (%)	5.4 (0.5)	5.6 (0.6)	<0.001	5.4 (0.5)	5.6 (0.5)	<0.001
total cholesterol (mmol/L)	5.29 (0.82)	5.27 (0.79)	0.612	5.29 (0.80)	5.38 (0.84)	0.088
LDL cholesterol (mmol/L)	3.15 (0.75)	3.11 (0.74)	0.411	3.14 (0.75)	3.20 (0.74)	0.215
HDL cholesterol (mmol/L)	1.60 (0.40)	1.53 (0.40)	0.004	1.59 (0.40)	1.56 (0.39)	0.286
triglycerides (mmol/L)	1.19 (0.76)	1.31 (0.88)	0.006	1.20 (0.78)	1.23 (0.64)	0.602
uric acid (μ mol/L)	327 (83)	339 (83)	0.012	327 (83)	321 (77)	0.108
hs-CRP [l] (mg/L)	0.55 (1.00)	0.97 (3.61)	<0.001	0.59 (1.45)	0.70 (1.17)	0.239
hemoglobin (g/L)	141 (15)	144 (12)	<0.001	142 (15)	141 (14)	0.276
eGFR [m] (mL/min/1.73m^2)	79.1 (12.8)	75.9 (13.0)	<0.001	79.1 (12.8)	74.8 (14.3)	<0.001
percent vital capacity (%)	96.5 (11.3)	96.9 (11.5)	0.508	96.8 (11.3)	97.0 (12.3)	0.712
FEV1/FVC [n] (%)	81.6 (5.9)	78.8 (6.8)	<0.001	81.3 (6.1)	79.9 (6.6)	0.001

mean (SD) or %, [a] BMI ≥ 25kg/m^2, [b] BMI ≥ 30kg/m^2, [c] total cholesterol ≥ 6.2mmol/L or use of antihyperlipidemic drugs, [d] LDL cholesterol ≥ 3.6mmol/L or use of antihyperlipidemic drugs, [e] LDL cholesterol ≥ 4.1mmol/L or use of antihyperlipidemic drugs, [f] hypo-HDL cholesterolemia, [g] hs-CRP ≥ 1 mg/dL, [h] defined as walking for one hour or longer per day or exercising for 30 minutes or longer twice or more per week, [i] systolic blood pressure, [j] diastolic blood pressure, [k] fasting plasma glucose, [l] high-sensitivity CRP, [m] estimated glomerular filtration rate, [n] forced expiratory volume in 1 second divided by forced vital capacity, *t*-tests for means and chi-squared tests for percentages

viduals older than 60 years, hypercholesterolemia and current smoking were independently associated with incident HFHL and hypercholesterolemia and anemia were independently associated with incident LFHL in the stepwise regressions. However, anemia might be questionable as an independent risk factor because sex was excluded from the covariates by the stepwise regression in the LFHL study. The present study suggests that old age may confound associations between risk factors and HL because it is a very strong risk factor of HL as shown in **Table 2**.

Associations between HL and risk factors are controversial and most of the epidemiological studies have been cross-sectional[2–18]. Hyperlipidemia was thought to be a risk factor of HL in animal experiments [23–27].

Among longitudinal studies, one evaluated associations between hypertension, diabetes, hypercholesterolemia, smoking and BMI and incident HL in 26,917

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Table 2. Incidence of Hearing Loss Stratified by Sex and Age Groups (Decades)

	high-frequency hearing loss				low-frequency hearing loss			
	men		women		men		women	
age (years)	n	incidence (%)	n	incidence (%)	n	incidence (%)	n	incidence (%)
–30	9	0.0	4	0.0	9	0.0	4	0.0
31–40	221	2.3	134	1.5	232	0.9	135	3.0
41–50	551	8.0	311	1.9	579	3.6	321	3.4
51–60	646	20.9	383	6.8	695	8.8	405	9.6
subtotal	1427	12.9	832	4.1	1515	5.6	865	6.2
61–70	185	48.6	120	20.8	197	26.9	127	25.2
71–80	34	79.4	25	20.0	38	36.8	28	35.7
81–	4	50.0	1	0.0	4	25.0	1	0.0
subtotal	223	53.4	146	20.6	239	28.4	156	26.9
total	1650	18.4	978	6.5	1754	8.7	1021	9.4

Table 3. Hazard Ratios of Hearing Loss

	high-frequency hearing loss		low-frequency hearing loss	
	hazard ratio (95% CI [h])	*p*	hazard ratio (95% CI [h])	*p*
adjusted for sex and age				
obesity-25 [a]	1.169 (0.925–1.479)	0.191	1.198 (0.895–1.605)	0.225
obesity-30 [b]	1.661 (0.855–3.226)	0.134	1.210 (0.498–2.941)	0.674
hypertension	0.921 (0.737–1.152)	0.472	0.978 (0.742–1.288)	0.872
diabetes	1.194 (0.828–1.722)	0.342	1.121 (0.681–1.847)	0.653
prediabetes	1.078 (0.864–1.344)	0.507	1.089 (0.834–1.422)	0.533
hypercholesterolemia [c]	1.159 (0.911–1.476)	0.230	1.334 (1.013–1.785)	0.041
hyper-LDLC-1 [d]	1.105 (0.891–1.371)	0.364	1.190 (0.919–1.540)	0.186
hyper-LDLC-2 [e]	1.166 (0.901–1.510)	0.242	1.205 (0.895–1.623)	0.218
hypertriglyceridemia	1.101 (0.849–1.428)	0.468	1.140 (0.816–1.594)	0.443
hypo-HDL cholesterolemia	1.010 (0.687–1.485)	0.960	1.098 (0.695–1.735)	0.688
hyperuricemia	0.872 (0.669–1.136)	0.309	0.957 (0.678–1.349)	0.801
low-grade inflammation [f]	1.204 (0.915–1.583)	0.185	1.322 (0.955–1.831)	0.092
anemia	0.957 (0.624–1.470)	0.842	1.226 (0.811–1.853)	0.333
renal dysfunction	0.928 (0.644–1.337)	0.688	1.190 (0.799–1.771)	0.392
restrictive lung disease	0.847 (0.525–1.365)	0.494	1.033 (0.600–1.780)	0.906
obstructive lung disease	0.921 (0.587–1.444)	0.719	1.071 (0.594–1.931)	0.820
current smoking	1.461 (1.153–1.850)	0.002	1.083 (0.778–1.507)	0.637
daily alcohol drinking	1.345 (1.082–1.671)	0.008	1.277 (0.965–1.691)	0.087
physical activity [g]	1.090 (0.884–1.344)	0.419	1.112 (0.863–1.434)	0.411
final step of stepwise regressions [i]				
age (years)	1.115 (1.103–1.128)	<0.001	1.105 (1.091–1.120)	<0.001
male sex	2.739 (2.055–3.651)	<0.001		
current smoking	1.402 (1.104–1.781)	0.006		
daily alcohol drinking	1.289 (1.035–1.606)	0.024	1.244 (0.962–1.608)	0.096
hypercholesterolemia [c]			1.384 (1.054–1.818)	0.019
low-grade inflammation [f]			1.330 (0.961–1.840)	0.086

[a] BMI ≥ 25kg/m^2, [b] BMI ≥ 30kg/m^2, [c] total cholesterol ≥ 6.2mmol/L or use of antihyperlipidemic drugs, [d] LDL cholesterol ≥ 3.6mmol/L or use of antihyperlipidemic drugs, [e] LDL cholesterol ≥ 4.1mmol/L or use of antihyperlipidemic drugs, [f] hs-CRP ≥ 1 mg/dL, g defined as walking for one hour or longer per day or exercising for 30 minutes or longer twice or more per week, [h] confidence interval, [i] using age, sex, current smoking, daily alcohol drinking, physical activity, obesity-25, obesity-30, hypertension, diabetes, prediabetes, hypercholesterolemia, hyper-LDLC-1, hyper-LDLC-2, hypertriglyceridemia, hypo-HDL cholesterolemia, hyperuricemia, low-grade inflammation, anemia, chronic kidney disease, restrictive lung disease, obstructive lung disease as the initial covariates, Blank cells in the table indicate that p for the covariate in the left column was higher than 0.1.

men and reported that hypertension, diabetes and obesity were not associated with incident HL while smoking and hypercholesterolemia had a small but significant association with incident HL[19]. A longitudinal case-control study in Taiwan suggested a significant association between hypercholesterolemia and incident SSHL[20]. The present study observed a significant association between hypercholesterolemia and both HFHL

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Table 4. Hazard Ratios of Hearing Loss Excluding Subjects Older than 60 Years

	high-frequency hearing loss		low-frequency hearing loss	
	hazard ratio (95% CI [h])	*p*	hazard ratio (95% CI [h])	*p*
adjusted for sex and age				
obesity-25 [a]	1.233 (0.916–1.659)	0.168	1.198 (0.895–1.605)	0.225
obesity-30 [b]	1.749 (0.823–3.718)	0.146	1.210 (0.498–2.941)	0.674
hypertension	0.921 (0.681–1.246)	0.594	0.978 (0.742–1.288)	0.872
diabetes	1.162 (0.685–1.973)	0.577	1.121 (0.681–1.847)	0.653
prediabetes	1.222 (0.914–1.634)	0.175	1.089 (0.834–1.422)	0.533
hypercholesterolemia [c]	1.457 (1.071–1.980)	0.016	1.334 (1.013–1.758)	0.041
hyper-LDLC-1 [d]	1.373 (1.044–1.805)	0.023	1.190 (0.919–1.540)	0.186
hyper-LDLC-2 [e]	1.361 (0.982–1.884)	0.064	1.205 (0.895–1.623)	0.218
hypertriglyceridemia	1.162 (0.844–1.601)	0.357	1.140 (0.816–1.594)	0.443
hypo-HDL cholesterolemia	1.173 (0.740–1.859)	0.496	1.098 (0.695–1.735)	0.688
hyperuricemia	0.908 (0.659–1.253)	0.558	0.957 (0.678–1.349)	0.801
low-grade inflammation [f]	1.119 (0.752–1.664)	0.580	1.322 (0.955–1.831)	0.092
anemia	0.916 (0.466–1.802)	0.800	1.226 (0.811–1.853)	0.333
renal dysfunction	1.122 (0.640–1.969)	0.688	1.190 (0.799–1.771)	0.392
restrictive lung disease	1.111 (0.570–2.167)	0.757	1.033 (0.600–1.780)	0.906
obstructive lung disease	1.431 (0.706–2.904)	0.320	1.071 (0.594–1.931)	0.820
current smoking	1.692 (1.278–2.241)	<0.001	1.083 (0.778–1.507)	0.637
daily alcohol drinking	1.081 (0.817–1.430)	0.587	1.277 (0.965–1.691)	0.087
physical activity [g]	1.036 (0.782–1.373)	0.806	1.112 (0.863–1.434)	0.411
final step of stepwise regressions [i]				
age (years)	1.154 (1.125–1.184)	<0.001	1.124 (1.090–1.159)	<0.001
male sex	3.015 (2.054–4.426)	<0.001		
hypercholesterolemia c	1.524 (1.120–2.075)	0.007	1.644 (1.146–2.361)	0.007
anemia			1.775 (1.036–3.042)	0.037
current smoking	1.739 (1.312–2.305)	<0.001		

[a] BMI ≥ 25kg/m^2, [b] BMI ≥ 30kg/m^2, [c] total cholesterol ≥ 6.2mmol/L or use of antihyperlipidemic drugs, [d] LDL cholesterol ≥ 3.6mmol/L or use of antihyperlipidemic drugs, [e] LDL cholesterol ≥ 4.1mmol/L or use of antihyperlipidemic drugs, [f] hs-CRP ≥ 1 mg/dL, [g] defined as walking for one hour or longer per day or exercising for 30 minutes or longer twice or more per week, [h] confidence interval, [i] using age, sex, current smoking, daily alcohol drinking, physical activity, obesity-25, obesity-30, hypertension, diabetes, prediabetes, hypercholesterolemia, hyper-LDLC-1, hyper-LDLC-2, hypertriglyceridemia, hypo-HDL cholesterolemia, hyperuricemia, low-grade inflammation, anemia, chronic kidney disease, restrictive lung disease, obstructive lung disease as the initial covariates, Blank cells in the table indicate that p for the covariate in the left column was higher than 0.1.

and LFHL after excluding individuals older than 60 years. Smoking was also significantly associated with HFHL after adjustment for confounders in the present study. Another study reported a small but significant association between hypertension and incident HL[21] and yet another reported a borderline association of incident HL with prediabetes and a significant association with diabetes as compared with normoglycemia[22]. However, there was no significant association between incident HL and hypertension, prediabetes or diabetes in the present study even after excluding participants older than 60 years.

Cholesterol stabilizes the cell membrane and modulates lipid and protein translocation across it. In the cochlea, the lipid composition, fluidity, and stiffness of the outer hair cell lateral wall membrane have been shown to be important to its function[25,26]. Ultrastructural analysis of cochleas from hypercholesterolemic chinchillas has revealed alterations in both the stria vascularis and outer hair cells and these alterations suggested that chronic hypercholesterolemia metabolically stresses inner ear tissue[27]. Hypercholesterolemia may also decrease cochlear vascularity and contribute to HL.

The present study suggested that hypercholesterolemia, but not hyper-LDL cholesterolemia, was a significant risk factor of HL after excluding subjects older than 60 years. Thus, cholesterol in lipoproteins other than LDL may contribute to the development of HL. Our results suggested that hypercholesterolemia was a significant risk factor of LFHL, not HFHL, in all subjects. The incidence of HFHL in men was 2–3 times higher than that in women while the incidence of LFHL was almost equal in men and women, as shown in **Table 2**. The influence of hypercholesterolemia on HL may be stronger in women than men.

Limitations

The participants of the present study were not recruited from a general population and detailed information regarding history of otological diseases, noise exposure, demographic backgrounds and medications

Advance Publication
Ningen Dock International
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was not available. Therefore, residual confounders might have influenced the present results. The number of participants may have been too small to detect significant associations between incident HL and hyper-LDL cholesterolemia. Also, exclusion of antihypercholesterolemic drug users may have left an insufficient number of participants for detecting significant associations between incident HL and hypercholesterolemia (data not shown).

Conclusions

The present 8-year follow-up study suggested that hypercholesterolemia was significantly associated with both incident HFHL and incident LFHL after adjusting for confounders in a health screening population excluding subjects older than 60 years. Individuals with hypercholesterolemia should be recommended to undergo audiometry for early detection of hearing loss and to avoid risk factors of hearing loss such as exposure to noise.

Conflict of Interest

The author has no conflict of interest.

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