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Lipid and C-reactive Protein Levels as Risk Factors for Hearing Loss in Older Adults

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Abstract

Objective—To determine the role of cardiovascular disease (CVD) markers, lipids and C-reactive protein, in age-related hearing loss over time.

Study Design—Prospective cohort study.

Setting—Research laboratories at an academic medical center.

Subjects and Methods—In total, 837 older adults (mean age 67.5 years) were included. Primary dependent variables were puretone thresholds (pure-tone average [PTA]), including “narrow” PTA (0.5, 1, 2, 4 kHz), “broad” PTA (0.5, 1, 2, 3, 4, 6, 8 kHz), low-frequency PTA (0.25, 0.5, 1 kHz), and high-frequency PTA (2, 3, 4, 6, 8 kHz). Repeated-measures mixed regression modeling was used to assess the relationship between C-reactive protein (CRP) and lipid levels with PTAs over time.

Results—In a cross-sectional sample of 837 subjects, modest associations were found between triglycerides and all PTAs. Weak associations were observed between the ratio of total cholesterol and high-density lipoprotein and narrow PTA, broad PTA, and high-frequency PTA. However, when assessing changes in hearing and lipids over time in a longitudinal analysis, no significant associations between hearing and lipids remained. PTAs and CRP were not statistically associated when controlling for age and sex.

Conclusion—Associations between hearing and blood lipids have been the focus of scientific inquiry for more than 50 years. The current results suggest that the association is either spurious or too small to be of consequence in the assessment and treatment of hearing loss in older adults. Inquiry into other potential risk factors for age-related hearing loss and associations with CVD may prove more fruitful.

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Keywords

age-related hearing loss; cardiovascular disease; lipid levels; C-reactive protein

It is well documented that the prevalence of both hearing loss and cardiovascular disease (CVD) increases with age.¹⁻⁵ Cardiovascular disease has been linked to elevations in the inflammatory marker C-reactive protein (CRP) and blood lipids, including levels of total cholesterol (TC), high-density lipoprotein (HDL) and low-density lipoprotein (LDL), and the ratio of TC to HDL (TC/HDL). Cardiovascular disease has also been linked to behavioral and environmental risk factors, such as smoking, and to comorbid conditions, such as hypertension, diabetes, and obesity.^{2,5} Some of these CVD risk factors have been linked to hearing loss. For example, in a population-based study of middle-age and older adults, current smokers were more likely than nonsmokers to have a hearing loss.⁶ These results led to examinations of associations between hearing loss and CVD, most often using blood lipid levels as indicators of CVD. These investigations included cross-sectional studies,^{1,7-16} a longitudinal study,¹⁷ and treatment studies examining the association between interventions to lower lipid abnormalities and the prevalence and/or change in hearing.¹⁷⁻²⁰

The association between hearing loss and coronary heart disease was first reported by Rosen and Olin in 1965.⁷ They performed an age-matched case-control study of Mabaan tribe members and urban populations in the United States, Europe, and Egypt and found a clear association between TC and hearing loss. For nearly 50 years since that study, other associations were reported among hearing loss, lipids, CVD, and various therapeutic interventions.^{1,7-19} These studies were generally small with designs and emphases that were not targeted to risk factors for age-related hearing loss.

Previous findings have been varied, with studies reporting a protective effect of TC on hearing,¹⁰ a higher risk of hearing loss with elevated TC,¹³ and protective relationships between lipid-lowering medication and/or dietary intake that lowers TC.¹⁷ Much of the evidence is from cross-sectional studies with specific design limitations, which results in an inability to support cause and effect of a CVD “exposure” risk factor on hearing loss because it is not possible to determine which event came first.^{9,11,15} Many studies, including the 1 prospective study,¹³ depended on self-report for some or all measures, which carries an additional bias.¹⁷ Lee et al,¹⁶ using the database on age-related hearing loss from the Medical University of South Carolina (MUSC) in a cross-sectional analysis, reported no significant correlation between pure-tone thresholds and TC, LDL, and HDL but found a small, but significant, protective effect of the ratio of LDL to HDL (LDL/HDL) on thresholds in older females. The current cross-sectional and longitudinal study, a follow-up to Lee et al,¹⁶ assesses associations among hearing, lipid levels, and CRP in a large, well-characterized, prospective cohort of older adults. Hearing and clinical blood chemistries were measured longitudinally, with the goal of clarifying the key measures for inclusion in any causal model of the effects of lipids and CRP on age-related hearing loss and associations with CVD. Longitudinal analyses provide a means to address the problem of risk factor to disease sequencing, which is a limitation of cross-sectional designs.

Methods

Subject Sample

The protocols for this study were approved by the Institutional Review Board at MUSC. In the longitudinal study of age-related hearing loss that began in 1987 at MUSC, subjects 18 years and older, in good general health, were recruited through advertisements and subject

referral. This cohort has been described previously in Lee et al,¹ Matthews et al,²¹ and Dubno et al.²² Exclusion criteria included evidence of conductive hearing loss, active otologic/neurologic disease, or significant cognitive decline. Subjects were scheduled monthly for 3 to 6 visits to complete a test battery, which included conventional and extended high-frequency pure-tone air conduction thresholds, speech recognition measures in quiet and noise, middle ear measurements, otoacoustic emissions, auditory brainstem responses, clinical blood chemistries, and health history and other questionnaires. Clinical blood chemistries included fasting lipid measurements of TC, calculated LDL, HDL, triglyceride, and high-sensitivity CRP. Conventional pure-tone thresholds were measured on each visit. After completion of the test battery, subjects were scheduled annually to obtain an updated medical history and an audiogram. The entire test battery with fasting lipids and CRP was repeated every 2 to 3 years. The initial test battery was completed by 837 subjects, 405 of whom completed 2 or more test batteries. The current analyses were conducted on data from the most recent visit when subjects were oldest. The cross-sectional results were compared with a longitudinal sample of 837 subjects, using repeated measures and mixed-effects regression modeling. The same procedures were used to evaluate longitudinal models on a subsample of 405 of these subjects who had 2 or more visits when hearing and lipids were measured, providing a means to rule out effects of selection bias in subjects who did not return for follow-up visits. Cross-sectional and longitudinal data for CRP were available for 385 subjects.

Table 1 contains demographic statistics on the sample of 837 subjects at their most recent visit. Demographic information for the 385 subjects with CRP and hearing measures was similar to the sample of 837, with the exception of a higher average age (71.8 years) in the CRP cohort. Subjects in the larger group ranged in age from 18 to 88 years (90% of subjects were 50 years and older), with a mean age of 67.5 years. Subjects completed between 1 and 7 test batteries, including clinical blood chemistries, obtained over a period of 0 to 22.8 years (mean, 3.2 years). Forty-four percent of subjects were male and 27.6% were taking lipid-lowering medication; 23.4% of subjects in the CRP analysis were taking anti-inflammatory medications.

Procedures

Conventional pure-tone thresholds were measured with either a Madsen OB822 or Madsen OB922 clinical audiometer (GN Otometrics, Schaumburg, Illinois) calibrated to appropriate ANSI standards (ANSI 1969, 1989, 1996, 2004)²³ and equipped with TDH-39 headphones (Telephonics, Huntington, New York). Pure-tone thresholds were measured using the guidelines recommended by the American Speech-Language-Hearing Association.²⁴ Blood was drawn at the laboratory facilities of the MUSC Clinical and Translational Research Center after at least 8 hours of fasting; hearing tests were conducted following a break.

Data Analyses

The primary dependent variables were the pure-tone average (PTA) of 0.5, 1, 2, and 4 kHz ("narrow PTA"); PTA of 0.5, 1, 2, 3, 4, 6, and 8 kHz ("broad PTA"); low-frequency PTA of 0.25, 0.5, and 1 kHz; and high-frequency PTA of 2, 3, 4, 6, and 8 kHz (Table 1). Right and left ear pure-tone thresholds were averaged at each frequency prior to calculating PTAs. This decision was based on 2 factors: (1) effects of lipid levels and CRP would likely be the same for right and left ears, and (2) differences in thresholds between ears were very small; only 1 frequency (6 kHz) was statistically different between ears in a 2-way repeated-measures analysis of variance (ANOVA) ($t = -2.89$, $P = .004$). To test the validity of using PTAs computed from average thresholds for the left and right ears, we performed a sensitivity analysis of worse-ear high-frequency PTA for LDL at the most recent visit. Results (parameter estimate = 0.019, $P = .31$) were similar to those for high-frequency PTA

computed from the average of the left and right ears. Similarly, a sensitivity analysis of worse-ear high-frequency PTA for triglycerides resulted in a parameter estimate of 0.024 and *P* value of .0007.

The primary independent variables were TC, HDL, LDL, triglyceride, TC/HDL, LDL/HDL, and CRP (Table 1). Multivariable linear regression models were used in the cross-sectional analyses to test associations among the primary independent variables (lipid measures, lipid ratios, CRP) with the primary dependent variables (PTAs). Age, sex, and use of lipid-lowering medications (lipids) or anti-inflammatory medications (CRP) were controlled for as covariates. All analyses were performed using SAS statistical software (version 9.2; SAS Institute, Inc, Cary, North Carolina).

Findings from the cross-sectional analysis of the relationship between PTAs and lipid measures were then examined using a multivariable longitudinal analysis of the subjects examined in the cross-sectional analysis. General linear mixed models (GLMMs), with the same covariates used in the cross-sectional analyses, were completed using the Proc Mixed module in SAS. The GLMMs were used to analyze the longitudinal data as they are particularly well suited (1) to assess the change over time of an outcome when repeated measurements are irregularly timed, (2) for missing data, and (3) when there is a mixture of static covariates and time-varying covariates.²⁵ The repeated-measure regression model uses each time-paired hearing/lipid measurement in a mathematical algorithm that maps the relationship between the two for each subject for each available study visit. The subject trends are mathematically summarized over the sample to determine if the dependent variable (PTAs) is consistently varying with changes in the primary independent variable (lipids), with weighting higher for subjects having more visits. These advanced random-effects models provide a means to view the longitudinal relationships between PTA and lipid levels with appropriate adjustments for nonindependence between repeated measurements, missing data, irregular visit structure, and covariate adjustment added into the mathematical algorithm.

For each multivariable analysis, multicollinearity was assessed by computing Pearson correlation coefficients and variance inflation factors. No independent variables were highly correlated. Covariates of age, sex, and medication history were selected as factors that are known to affect hearing, lipid, or CRP levels in older adults and were used consistently across models. Statistical significance was determined at the .1 level for interaction effects and the .05 level for all other effects, using 2-sided *P* values.

Results

Demographic and Clinical Characteristics

Subjects had an average TC level of 194.8 mg/dL and HDL, LDL, and triglyceride levels of 52.5 mg/dL, 118.2 mg/dL, and 124.1 mg/dL, respectively (Table 1). Differences among the 4 PTAs reflect the effects of greater hearing loss at higher frequencies in these older adults. Mean CRP levels were 0.35 mg/dL. Mean PTAs for the smaller CRP cohort were within 1 dB of the mean PTA values for the larger group of 837 subjects in the lipid cohort.

Cross-sectional Analyses

Results from the cross-sectional analysis for relationships between lipids and hearing indicate a consistent association between PTAs and triglyceride level (Table 2). Regardless of PTA and while holding constant the confounding covariates of age, sex, and lipid-lowering medications, parameter estimates indicated a positive association between triglycerides and PTAs. This relationship equates to a 2- to 3-dB increase in PTA for every

100-mg/dL increase in triglycerides, suggesting that this small effect size, although statistically significant, may not be clinically relevant for the average older adult.

Another consistently significant association seen in the cross-sectional analysis was among narrow, broad, and high-frequency PTA and TC/HDL, with parameter estimates of 0.74 ($P = .04$), 0.86 ($P = .03$), and 1.21 ($P < .01$), respectively. The latter finding reveals, on average, a 1.2-dB increase in PTA for each 1-unit increase in TC/HDL. This ratio generally ranges from 0 to 8.0, with >4.0 to 5.0 (depending on the source) as the generally accepted normal ceiling for a higher risk of CVD.²⁶ Thus, a 1-unit change in this ratio would be considered large, whereas a 1.2-dB increase in PTA would generally not be considered clinically significant. This result is another indication that, although there are statistically significant effects of higher lipid values on hearing, they likely have little or no effect on clinical measurements of hearing for the average older adult. All other cross-sectional models examining the effects of TC, HDL, LDL, and LDL/HDL on PTA were not statistically significant (Table 2).

In a similar cross-sectional analysis in 385 subjects examining the association between CRP and hearing, weak correlations were found between CRP, narrow PTA, and low-frequency PTA. A series of multivariable linear regression analyses was performed on CRP regressed on multiple PTAs, considering age, sex, anti-inflammatory medication history, and smoking history as covariates. The relationship between PTA (all types) and CRP was not statistically associated when controlling for age and sex. Medication and smoking history did not significantly contribute to the regression models.

Longitudinal Analyses

The longitudinal analysis provides a means to model the extent to which changes in hearing as subjects age are coincident with variations in lipid levels; the predictive value of lipid levels for changes in hearing was not addressed. To limit the effects of the confounding variables of age, sex, and lipid-lowering medication, these variables were included in each model, regardless of whether they improved the predictive ability of the model. Repeated-measures longitudinal analyses, whereby subjects act as their own controls, increase precision and permit more power for assessment of effects with fewer subjects.²⁷ In contrast, when effects of age are assessed on groups of different individuals in a cross-sectional design, changes brought about by the time effect may be masked by the variability between subjects and uncontrolled factors such as noise history, nutrition, comorbid conditions, and occupation. Thus, longitudinal designs provide an analytical tool for studying the effect of lipid levels on age-related hearing loss in humans, with fewer potentially confounding factors.

All models used in the cross-sectional analyses were repeated in the longitudinal analysis, with special emphasis on examining significant measures identified in the cross-sectional results. Longitudinal mixed models were estimated on the full sample of 837 and a subsample of 405 of these subjects with 2 or more hearing and lipid measurements. Neither approach identified significant associations between hearing and lipid levels (Table 3).

Discussion

The findings from the cross-sectional analyses that elevated triglyceride levels were associated with small increases in pure-tone thresholds are consistent with results of Evans et al¹¹; this study included 40 middle-aged to older adults and found that triglyceride levels were associated with increased hearing loss, but LDL and HDL were not statistically significant predictors of mean pure-tone thresholds or pure-tone thresholds measured in each ear. The magnitude of the association between PTA and triglycerides is smaller in the

current study, which may be due to its homogeneous sample of primarily older adults with less variation in lipid profiles, the irregular timing of the measurements, and the use of lipid-lowering medications not controlled for in the Evans et al study.

Jerger et al²⁸ reviewed large-scale hearing surveys over 50 years and reported that males showed more hearing loss above 1 kHz, whereas females showed more loss below 1 kHz, suggesting that hearing loss in females was mostly due to “metabolic presbycusis” associated with CVD. Gates et al,⁹ in a cross-sectional analysis of the Framingham study cohort, reported an inverse relationship between age-adjusted HDL level and PTAs below 1 kHz in females. Lee et al,^{1,16} in a longitudinal analysis of pure-tone thresholds from the MUSC cohort, showed no low-frequency sex difference. Moreover, Lee et al,¹⁶ in a cross-sectional study using an earlier MUSC cohort, reported no significant association between pure-tone thresholds and TC, LDL, and HDL.

Using self-reported measures of lipids and hearing, Shargorodsky et al¹³ analyzed data from 26,917 middle-aged to older men enrolled in the Health Professionals Follow-up Study and identified a 10% increase in risk of hearing loss in those having elevated cholesterol, with a 28% increased risk of hearing loss in those with elevated cholesterol in a subgroup of men younger than 55 years. Helzner et al¹⁵ analyzed data from the National Health and Nutrition Survey (NHANES) using multivariable modeling and identified an association between higher triglyceride levels and poorer low- and mid-frequency pure-tone thresholds in males. Differences in findings between these 2 studies and the current study may relate to the use of retrospective self-report surveys rather than measured values and a sample of middle-age to older men rather than older men and women.

Few studies have examined associations among hearing and another known CVD risk factor, the inflammatory marker, CRP. Using data from the Hertfordshire Ageing Study, Verschuur et al²⁹ found a partial correlation between CRP and average hearing thresholds ($r = 0.1$, $P = .01$) after controlling for age, sex, smoking status, and noise exposure but not for anti-inflammatory medications. In the current study, no statistical association between PTA (all types) and CRP was found when controlling for age and sex, with medication and smoking history not significantly contributing to the regression models.

The most important findings of the current study relate to the inability to identify a durable longitudinal association between measures of hearing and lipids. This study is the first to assess this relationship in a prospective cohort where both hearing and lipid measures were collected under strict protocol specifications repeatedly in a subject sample that was not a convenience sample or a consecutive clinical cohort of patients. As noted earlier, this design strengthens the validity of the findings; however, limitations related to observational studies remain, such as the inability to control for potentially biasing unmeasured factors that can only be controlled for in a randomized study design.

Several studies examined associations between lipid-lowering drug therapy and/or diet and hearing loss. Olzowy et al¹⁹ reported no difference in hearing between 60- to 75-year-old subjects taking atorvastatin over a relatively brief 7- to 13-month period and those not taking atorvastatin. Gopinath et al,¹⁷ in a longitudinal study, assessed associations between age-related hearing loss and dietary intake of cholesterol, as well as the use of cholesterol-lowering drugs, and reported that high dietary intake of cholesterol, but not blood TC, was associated with increased likelihood of hearing loss. Similarly, Spankovich et al²⁰ reported an association between a cholesterol-rich diet and poorer pure-tone thresholds in older adults. These findings are consistent with the lack of predictive ability of cross-sectional models examining the effects of TC, HDL, LDL, LDL/HDL, and triglycerides on hearing. The results suggest that the use of lipid measures (and CRP) may not be of value in future

studies assessing associations between hearing loss, blood chemistries, and CVD because of their documented inability to identify the very small associations that do not remain when examined longitudinally.

In conclusion, the association between hearing and blood lipids has been the focus of scientific inquiry for nearly 50 years. We and others have identified small cross-sectional associations with triglycerides, which may be too small to be of consequence in the assessment and treatment of hearing loss in older adults; the cost of including triglyceride measurements in a hearing test battery outweighs any significant clinical benefit. Moreover, the cross-sectional association observed between hearing loss and lipid levels did not persist when examined in a well-controlled longitudinal analysis. Thus, the association is either spurious or mediated by other factors, which are yet to be identified. Recent reports of the effects of diet and lipid-lowering therapy, as well as smoking, suggest that the exploration of the association between hearing and dietary factors^{17,20} and environmental factors⁶ may prove to be more fruitful than a continuing focus on lipid levels.

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Table 1

Descriptive Characteristics of the Subjects

	Total No.	Most Recent Visit
Demographics		No. (%)
Male sex	837	368 (44.0)
Taking lipid-lowering medication	837	231 (27.6)
Taking anti-inflammatory medication	385	90 (23.4)
		Mean (95% CI)
Age	837	67.5 (66.5–68.5)
Years of follow-up	837	3.2 (2.9–3.5)
Blood chemistry measures		
Total cholesterol, mg/dL	837	194.8 (192.0–197.6)
HDL, mg/dL	831	52.5 (51.3–53.6)
LDL, mg/dL	824	118.2 (115.8–120.5)
Triglyceride, mg/dL	834	124.1 (117.6–130.5)
Total cholesterol/HDL ratio	831	4.0 (3.9–4.1)
LDL/HDL ratio	824	2.5 (2.4–2.5)
CRP, mg/dL	385	0.35 (0.28–0.42)
Pure-tone thresholds, dB HL		
Narrow PTA (0.5, 1, 2, 4 kHz)	837	28.5 (27.4–29.7)
Broad PTA (0.5, 1, 2, 3, 4, 6, 8 kHz)	837	37.5 (36.2–38.8)
Low-frequency PTA (0.25, 0.5, 1 kHz)	837	18.4 (17.5–19.2)
High-frequency PTA (2, 3, 4, 6, 8 kHz)	837	45.1 (45.5–46.6)

Abbreviations: CI, confidence interval; CRP, C-reactive protein; HDL, high-density lipoprotein; HL, hearing level; LDL, low-density lipoprotein; PTA, pure-tone average.

Table 2

Associations between PTA and Lipid Levels

Dependent Variable	Independent Variable	Cross-Sectional Multivariable Models ^a (n = 837)	
		Parameter Estimate (SE)	P Value
Narrow PTA (0.5, 1, 2, 4 kHz)	TC	0.012 (0.012)	.34
	HDL	−0.044 (0.031)	.16
	LDL	0.005 (0.005)	.73
	Triglycerides	0.020 (0.006)	.003
	TC/HDL ratio	0.743 (0.365)	.042
	LDL/HDL ratio	0.600 (0.482)	.21
Broad PTA (0.5, 1, 2, 4, 6, 8 kHz)	TC	0.018 (0.013)	.17
	HDL	−0.040 (0.033)	.22
	LDL	0.010 (0.016)	.53
	Triglycerides	0.022 (0.006)	<.001
	TC/HDL ratio	0.859 (0.385)	.03
	LDL/HDL ratio	0.727 (0.508)	.15
Low-frequency PTA (0.25, 0.5, 1 kHz)	TC	0.002 (0.010)	.85
	HDL	−0.021 (0.026)	.42
	LDL	−0.004 (0.012)	.76
	Triglycerides	0.015 (0.005)	.002
	TC/HDL ratio	0.307 (0.309)	.32
	LDL/HDL ratio	0.163 (0.407)	.69
High-frequency PTA (2, 4, 6, 8 kHz)	TC	0.028 (0.015)	.058
	HDL	−0.050 (0.038)	.19
	LDL	0.021 (0.018)	.25
	Triglycerides	0.026 (0.007)	<.001
	TC/HDL ratio	1.207 (0.446)	.007
	LDL/HDL ratio	1.107 (0.590)	.06

Bolding indicates significant results.

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; PTA, pure-tone average; TC, total cholesterol.

^a All cross-sectional models controlled for age, sex, and use of lipid-lowering medications.

Table 3
Longitudinal Association between PTA and Lipid Levels for the Significant Cross-Sectional Parameter Estimates

Dependent Variable	Independent Variable	Cross-Sectional Multivariable Models ^a (n = 837)		Longitudinal Multivariable Models ^b (n = 837)	
		Parameter Estimate (SE)	P Value	Parameter Estimate (SE)	P Value
Narrow PTA (0.5, 1, 2, 4 kHz)	Triglycerides	0.020 (0.006)	.003	0.0002 (0.0003)	.47
	TC/HDL ratio	0.743 (0.365)	.042	-0.0136 (0.022)	.53
Broad PTA (0.5, 1, 2, 4, 6, 8 kHz)	Triglycerides	0.022 (0.006)	<.001	0.00007 (0.0004)	.86
	TC/HDL ratio	0.859 (0.385)	.03	0.0117 (0.024)	.62
Low-frequency PTA (0.25, 0.5, 1 kHz)	Triglycerides	0.015 (0.005)	.002	0.0002 (0.0004)	.54
High-frequency PTA (2, 4, 6, 8 kHz)	Triglycerides	0.026 (0.007)	<.001	-0.0001 (0.0004)	.78
	TC/HDL ratio	1.207 (0.446)	.007	-0.0143 (0.025)	.57

Abbreviations: HDL, high-density lipoprotein; PTA, pure-tone average; TC, total cholesterol.

^a All cross-sectional models controlled for age, sex, and use of lipid-lowering medications.

^b All longitudinal models controlled for baseline age, sex, use of lipid-lowering medications, years of follow-up, and years of follow-up by primary independent variable interaction. Longitudinal model results are for the independent variable by years of follow-up interaction term.