

Remnant cholesterol and auditory outcomes in NHANES 1999–2016: associations with frequency-range hearing loss and tinnitus

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1 **Remnant cholesterol and auditory outcomes in NHANES 1999–2016: associations**
2 **with frequency-range hearing loss and tinnitus**

3 **Abstract**

4 **Background:** Evidence on the lipid determinants of auditory outcomes remains
5 inconsistent. ²⁷ Remnant cholesterol (RC), the cholesterol fraction contained in
6 triglyceride-rich lipoproteins, captures atherogenic and inflammatory burdens beyond
7 conventional fractions. This study assessed the associations between RC and hearing
8 loss across frequency ranges, and between RC and tinnitus, in a population-
9 representative U.S. cohort. Identifying scalable metabolic markers may help support
10 earlier recognition and prevention efforts to reduce avoidable hearing-related disability.

11 **Methods:** Participants ³⁸ aged 40 years and older with valid audiometric evaluations and
12 fasting lipid profiles were identified ²⁵ from the 1999–2016 National Health and Nutrition
13 Examination Survey (NHANES) dataset. ⁴ RC was estimated as total cholesterol minus
14 the sum of low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein
15 cholesterol (HDL-C), and was evaluated across predetermined concentration ranges.
16 The outcomes included low-, speech-, and high-frequency hearing loss defined by air-
17 conduction thresholds and self-reported tinnitus. Weighted multivariable logistic
18 regression models were applied, sequentially adjusting for demographic,
19 socioeconomic, lifestyle, and clinical covariates, followed by mutual adjustment for
20 other lipid components. Subgroup and interaction analyses evaluated effect
21 modification, including noise exposure.

22 **Results:** In fully adjusted survey-weighted logistic models, higher RC was associated
23 with hearing loss (OR 2.43, 95% CI 1.71–3.47) and with tinnitus (OR 1.64, 95% CI
24 1.31–2.06); category analyses indicated a monotonic increase (P for trend < 0.001).
25 Associations displayed a clear dose–response across RC categories and remained robust
26 in mutually adjusted models, whereas the inverse associations for HDL-C attenuated
27 and became nonsignificant once RC was included. Analyses by frequency range
28 revealed the strongest associations for high-frequency hearing loss, intermediate
29 associations for speech-frequency hearing loss, and the weakest associations for low-
30 frequency hearing loss. Subgroup findings were broadly consistent across strata, and
31 interaction testing indicated amplified RC–auditory associations among participants
32 reporting noise exposure.

33 **Conclusions:** RC was linked to adverse auditory outcomes, including hearing loss and
34 tinnitus, with clear dose–response patterns that persisted after mutual lipid adjustment.
35 As a routinely available lipid-derived measure, RC may support scalable risk
36 stratification to help prioritize earlier hearing evaluation and preventive counseling;
37 confirmation in longitudinal cohorts and trials is needed.

38

39 **Keywords:** Hearing Loss; Tinnitus; Cholesterol, VLDL; Hyperlipidemias; NHANES

40 Background

41 Worldwide, approximately 1.5 billion people are affected by hearing loss (HL),
42 and the global total is forecast to rise to about 2.4 billion by 2050 [1]. It is the third

43 highest cause of years lived with disability [2] and creates a considerable economic
44 burden through reduced productivity and increased health care costs [3]. HL is also a
45 leading risk factor for tinnitus, a condition ¹⁶ characterized by the perception of sound
46 without external stimuli [4], affecting an estimated 740 million individuals globally [5].
47 Tinnitus not only contributes to daily functional impairment but is also associated with
48 emotional distress, sleep disturbance, and heightened risks of depression and anxiety,
49 thereby imposing a significant health care and economic burden [6, 7]. Despite the
50 growing public health burden, current management of HL and tinnitus is largely focused
51 on symptomatic and rehabilitative approaches, such as hearing aids, cochlear implants,
52 sound therapy, and counseling, and there is still no universally effective curative
53 treatment—particularly for chronic tinnitus and age-related HL—so many individuals
54 continue to experience substantial residual symptoms and functional impairment [8, 9].
55 In this context, there is a need to better understand upstream mechanisms and to identify
56 modifiable risk factors that could inform preventive or disease-modifying strategies.

57 Emerging evidence indicates that HL is related to an increased prevalence of
58 cardiovascular disease (CVD) [10]. These epidemiological links, together with data
59 showing systemic inflammatory activation and cochlear microvascular changes in
60 individuals with HL and tinnitus, suggest that these auditory disorders may share
61 common pathophysiological pathways with CVD, including vascular dysfunction and
62 chronic low-grade inflammation [11-13]. Among the cardiometabolic factors that
63 contribute to these pathways, dyslipidemia—characterized by alterations in
64 conventional lipid fractions such as total cholesterol (TC), low-density lipoprotein

65 cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C)—has attracted
66 increasing attention because of its potential involvement in auditory dysfunction [7, 14,
67 15]. Statins, the most widely prescribed lipid-lowering agents for the primary
68 prevention of CVD [16], have also been investigated as potential otoprotective agents.
69 Experimental models and several observational studies suggest that statin therapy may
70 mitigate noise-induced, age-related, metabolic-related, and ototoxic drug-induced
71 sensorineural hearing loss [17-21]. However, epidemiological evidence directly linking
72 cholesterol levels to HL is limited, and clinical findings on statin effectiveness remain
73 inconsistent [22]. Parallel evidence also suggests that dyslipidemia in individuals with
74 tinnitus, with atherogenic lipid profiles—higher TC levels, higher LDL-C levels, and
75 an unfavorable ¹ non-HDL-C to HDL-C ratio—is associated with greater tinnitus
76 incidence and symptom burden [23-25]. Findings for statin use and tinnitus remain
77 inconsistent across populations and study designs, likely reflecting differences in how
78 tinnitus is defined or measured, variation in statin dosage and duration of use, and the
79 influence of underlying health conditions that affect both statin prescription and tinnitus
80 risk [26, 27]. Collectively, these observations highlight the need to further clarify how
81 lipid abnormalities are related to HL and tinnitus.

82 In addition to conventional lipid fractions, remnant cholesterol (RC), often
83 referred to as the “forgotten lipid,” has recently attracted considerable research interest
84 [28]. RC refers to the cholesterol fraction within triglyceride-rich lipoproteins, mainly
85 intermediate-density lipoprotein (IDL) and very-low-density lipoprotein (VLDL)
86 during fasting, and chylomicron remnants in the nonfasting state [29]. Higher RC

87 concentrations have been consistently linked to greater cardiovascular risk, particularly
88 in middle-aged and older adults, and have demonstrated stronger predictive value for
89 adverse events compared with conventional lipid measures [30, 31]. Mechanistically,
90 RC contributes to systemic inflammation and microvascular injury by promoting
91 endothelial dysfunction, oxidative stress, and vascular inflammation [32, 33]. These
92 processes may compromise the cochlear microcirculation, disrupt the blood–labyrinth
93 barrier, and increase the vulnerability of sensory hair cells and auditory neurons,
94 thereby providing a plausible biological link between elevated RC levels and the
95 development of HL and tinnitus.

96 Given the shared pathophysiological pathways between the cardiovascular and
97 auditory systems, clarifying the relationship between RC and hearing outcomes may
98 have important clinical implications. Adult hearing assessment is not routinely
99 implemented in many primary care settings, and audiometric evaluation is typically
100 initiated only after noticeable symptoms arise, which may delay the detection of
101 subclinical hearing impairment. Because RC can be readily calculated from routine
102 lipid panels, it was hypothesized that higher RC levels are associated with greater odds
103 of hearing loss and tinnitus; if confirmed, RC could serve as a simple, inexpensive tool
104 to help clinicians identify individuals who may benefit from timely audiologic
105 evaluation. To clarify this unresolved issue, ¹National Health and Nutrition Examination
106 Survey (NHANES) data were analyzed to investigate the associations between RC and
107 both HL and tinnitus among U.S. adults. To the best of current knowledge, no previous
108 population-based study has systematically evaluated the relationship between RC and

109 auditory outcomes.

110 ¹³ **Methods**

111 **Study design and population**

112 This cross-sectional study analyzed data from the National Health and Nutrition
113 Examination Survey (NHANES; RRID:SCR_013201) spanning 1999 to 2016.
114 NHANES is a nationwide survey designed to represent ²³ the noninstitutionalized U.S.
115 civilian population using a complex, multistage probability sampling framework. The
116 ⁵ protocol was approved by the National Center for Health Statistics (NCHS) Research
117 Ethics Review Board, and all participants provided written informed consent.
118 Participants are selected through a combination of geographic area sampling, household
119 screening, and oversampling of specific demographic groups. Data collection consists
120 of a structured household interview followed by a ¹ standardized physical examination
121 and laboratory assessments conducted in mobile examination centers. Each 2-year
122 cycle represents an independent cross-sectional sample, and NHANES is therefore not
123 a longitudinal cohort; individual participants are not followed across cycles.

124 Among 101,316 participants from the 1999–2016 cycles, the analysis was
125 restricted to adults aged ≥ 40 years. This threshold was chosen because previous
126 epidemiological studies of RC and CVD have focused primarily on middle-aged and
127 older people, in whom lipid abnormalities and vascular consequences are most relevant
128 [31, 34, 35]. Participants without complete lipid profile data (TC, LDL-C, HDL-C)
129 were further excluded.

Two analytic populations were then defined. For HL analysis, participants who reported tinnitus were excluded; thus, the hearing loss analytic sample included individuals with hearing loss but without self-reported tinnitus. For tinnitus analysis, participants with HL according to the audiometric definition described in the *Assessment of Auditory Outcomes* section were excluded, so that this sample included individuals with tinnitus but without HL. Because HL and tinnitus commonly co-occur The NHANES tinnitus item does not indicate laterality; thus, unilateral and bilateral tinnitus cannot be distinguished. A comprehensive flowchart illustrating how participants were selected is provided in Figure 1.

Assessment of auditory outcomes

Audiometric testing in NHANES was performed by trained examiners via standardized protocols in a sound-attenuated booth. Additional details regarding audiometric testing can be found in the NCHS Audiometry Procedures Manual. Pure-tone air conduction thresholds were measured at 0.5, 1, 2, 3, 4, 6, and 8 kHz for both ears. Pure-tone averages (PTA) were calculated for speech frequencies (SF-PTA: 0.5, 1, 2, and 4 kHz), low frequencies (LF-PTA: 0.5, 1, and 2 kHz), and high frequencies (HF-PTA: 3, 4, 6, and 8 kHz). In accordance with the latest WHO hearing loss grading framework [1], HL was defined as a PTA ≥ 20 dB in the better-hearing ear, consistent with the WHO/GBD-based revision of the normal-hearing threshold [36]. Accordingly, SFHL, LFHL, and HFHL were defined as SF-PTA ≥ 20 dB, LF-PTA ≥ 20 dB, and HF-PTA ≥ 20 dB, respectively. Overall HL was defined as HL in any PTA-based frequency band

151 (LFHL, SFHL, or HFHL), with each band defined as a PTA ≥ 20 dB in the better-hearing
152 ear. Tinnitus status was determined based on participants' responses to a standardized
153 questionnaire item: "During the past 12 months, have you been bothered by ringing,
154 roaring, or buzzing in your ears or head lasting for five minutes or longer?" Individuals
155 who answered "yes" were categorized as having tinnitus.

157 Lipid measurements and calculation of RC

158 During the NHANES physical examinations, venous blood was drawn after
159 participants had fasted overnight and processed in certified laboratories using
160 standardized analytic procedures. Enzymatic assays were employed to measure the
161 serum concentrations of TC and triglycerides, whereas immunoassays were used to
162 determine HDL-C levels. LDL-C was primarily calculated using the Friedewald
163 equation, which derives LDL-C values from TC, TG, and HDL-C measurements.

164 RC was estimated indirectly as follows:

$$166 \quad RC = TC - LDL-C - HDL-C$$

167 RC was examined as a continuous measure and in categories defined by cutoffs of
168 <0.50 , $0.50-0.99$, $1.00-1.49$, and ≥ 1.50 mmol/L. This concentration-based
169 classification has been commonly applied in recent studies, including investigations of
170 RC and cardiovascular risk [37, 38].

171 **Covariates**

172 Sociodemographic variables, including age, sex, race/ethnicity, educational
173 attainment, marital status, and family poverty-income ratio (PIR)—were collected
174 through standardized NHANES interviews. Educational attainment was dichotomized
175 as high school or less versus college or higher, while marital status was categorized as
176 cohabiting (married or cohabiting) or alone (never married, widowed, divorced, or
177 separated). The PIR was stratified into three levels: $\leq 130\%$, $>130\text{--}350\%$, and $>350\%$.
178 Lifestyle factors, including smoking status, alcohol use, and noise exposure, were
179 obtained from standardized NHANES questionnaires. Smoking status was ascertained
180 from two standardized NHANES questions: “Have you smoked at least 100 cigarettes
181 in your entire life?” and “Do you now smoke cigarettes?” Participants were grouped
182 into never smokers (<100 lifetime cigarettes), former smokers (≥ 100 lifetime cigarettes
183 but not currently smoking), or current smokers (≥ 100 lifetime cigarettes and currently
184 smoking). Alcohol consumption was classified as nondrinking, moderate drinking
185 (women: $0\text{--}15$ g/day; men: $0\text{--}30$ g/day), or heavy drinking (women: ≥ 15 g/day; men:
186 ≥ 30 g/day). Environmental exposure included noise exposure, which was defined as
187 any affirmative report of occupational, nonoccupational, or firearm-related noise [39].
188 Clinical conditions previously reported to be closely related to HL and tinnitus,
189 including hypertension, diabetes, and CVD, were also considered [40-44].
190 Hypertension was identified using any of the following criteria: (1) self-reported
191 physician diagnosis, (2) current antihypertensive medication use, or (3) a measured
192 mean blood pressure of $\geq 140/90$ mmHg during the examination. Diabetes was defined

193 as (1) self-reported physician diagnosis, (2) use of insulin or oral hypoglycemic agents,
194 (3) a fasting plasma glucose concentration ≥ 7.0 mmol/L, or (4) an HbA1c concentration
195 $\geq 6.5\%$. CVD was defined based on self-reported physician diagnosis of congestive
196 heart failure, coronary heart disease, angina, myocardial infarction, or stroke.

197 Statistical analysis

198 Baseline characteristics were described using weighted means (with standard
199 errors reported for continuous variables) and unweighted counts with weighted
200 percentages for categorical variables. Comparisons between groups were performed
201 using weighted *t* tests for continuous variables, whereas Rao–Scott chi-square tests
202 were used for categorical variables. Because NHANES uses a multistage, stratified
203 cluster sampling design, all analyses were performed using survey-weighted methods
204 to ensure the results were representative of the U.S. civilian, noninstitutionalized
205 population. For each 2-year survey cycle, we applied the examination (subsample)
206 weights provided by NHANES for participants with complete data on both exposure
207 and outcome. When multiple cycles (1999–2016) were combined, multicycle weights
208 were created dividing the 2-year weights by the number of included cycles, in
209 accordance with the NHANES analytic guidelines. In the survey design specification,
210 the sample weights were included together with the masked variance strata and primary
211 sampling units (PSUs), thereby accounting for unequal sampling probabilities,
212 differential nonresponse, and poststratification. Associations between lipid parameters
213 and auditory outcomes (overall HL, SFHL, LFHL, HFHL, and tinnitus) were examined

214 via weighted multivariable logistic regression models. HL outcomes were analyzed as
215 binary endpoints (presence vs. absence) using logistic regression, consistent with the
216 threshold-based definition of HL. Three hierarchical survey-weighted logistic
217 regression ¹models were established. Model 1 accounted for age, sex, and race/ethnicity;
218 Model 2 incorporated further adjustment for socioeconomic and lifestyle variables,
219 including educational ¹level, marital status, and household PIR, smoking status, alcohol
220 intake, and noise exposure; and Model 3 further accounted for clinical comorbidities
221 such as hypertension, diabetes, and CVD. To evaluate the independence of lipid
222 parameters, supplementary models were fitted in which each lipid fraction was further
223 adjusted for the remaining lipid measures. RC was examined both as a continuous
224 variable and across predefined concentration categories (<0.50, 0.50–0.99, 1.00–1.49,
225 and ≥1.50 mmol/L). Linear trends ²²were evaluated by assigning the median value of
226 each RC category as a continuous term in ³¹regression models. Restricted cubic spline
227 (RCS) analyses models were additionally fitted to examine whether RC showed
228 nonlinear relationships with HL (overall and frequency-specific) and tinnitus. In
229 addition, subgroup analyses were ¹⁷performed to assess potential effect modification
230 across demographic, lifestyle, and clinical factors. Multiple interaction terms were add
231 to the regression models. In addition, dose–response curves stratified by noise exposure
232 were generated to visualize the RC–auditory outcome relationships. The incorporation
233 of survey weights, strata, and clusters allows appropriate variance estimation under this
234 sampling structure. In NHANES, survey weights reflect the inverse probability of
235 selection and incorporate adjustments for oversampling, survey nonresponse, and

236 poststratification, ensuring that analyses yield nationally representative estimates.
237 Strata refer to the masked variance strata constructed³⁴ by the National Center for Health
238 Statistics (NCHS) to support accurate variance estimation, whereas clusters correspond
239 to PSUs representing sampled geographic areas. Incorporating survey weights, strata,
240 and PSUs is therefore necessary to obtain unbiased population estimates and valid
241 standard errors under a complex sampling design.²⁰ All statistical analyses were carried
242 out in R (v4.3.1; R Foundation for Statistical Computing, Vienna, Austria) via the
243 survey package.¹ Multivariate imputation via chained equations (MICE) was performed
244 to handle missing covariate data, generating 100 complete using the R package “mice”.
245 Combined estimates across imputations were obtained via Rubin’s methodology [45,
246 46] to accommodate the complex survey design, yielding averaged point estimates and
247 appropriately incorporating both within- and between-imputation variance components.
248¹ Statistical significance was defined as a two-sided $P < 0.05$.

249 Results

250 Baseline characteristics of the study population

251 In total, 3,169 participants were evaluated for HL, and 4,922 were assessed for
252 tinnitus. The weighted prevalence rates of HL and tinnitus were 44.9% and 22.4%,
253 respectively. The participants with HL were older; more often male and non-Hispanic
254 White; had lower educational attainment and PIRs; were more likely to be former
255 smokers; reported noise exposure; and had hypertension, diabetes, and CVD. The
256 tinnitus participants were also older, more often non-Hispanic White, had lower

257 education and income, had a higher prevalence of smoking, were more likely to report
258 noise exposure, and more commonly had cardiometabolic conditions, although the sex
259 distribution did not significantly differ.

260 Regarding lipid profiles, the HL and tinnitus groups exhibited elevated RC
261 concentrations and reduced HDL-C levels. In addition, compared with participants
262 without HL, participants with HL had decreased TC and LDL-C levels, whereas no
263 significant differences in TC or LDL-C were observed between tinnitus and nontinnitus
264 participants (Table 1).

265 Associations of lipid parameters with HL and tinnitus

266 As shown in Table 2, RC was positively associated with both HL and tinnitus.
267 According to the fully adjusted models (Model 3), RC was linked to increased odds of
268 having HL (OR=2.43, 95% CI (Confidence interval): 1.71–3.47) and tinnitus (OR=1.64,
269 95% CI: 1.31–2.06). RC was consistently associated with frequency-specific outcomes,
270 including HFHL (OR=2.21, 95% CI: 1.43–3.41), SFHL (OR=1.77, 95% CI: 1.09–2.88),
271 and LFHL (OR=3.45, 95% CI: 1.20–9.91). In contrast, HDL-C was inversely associated
272 with HL (OR=0.69, 95% CI: 0.49–0.99) and tinnitus (OR=0.72, 95% CI: 0.55–0.93),
273 which was most evident for HFHL (OR=0.60, 95% CI: 0.39–0.92). TC and LDL-C did
274 not display consistent associations. To further evaluate the independence of these
275 findings, each lipid parameter was additionally modeled with mutual adjustment for the
276 other lipid fractions (Supplementary Table S1). RC remained positively associated
277 with HL and tinnitus after adjustment for each of the other lipid parameters, whereas

the inverse associations of HDL-C were attenuated and became nonsignificant once RC was included in the model (Model 6).

RC categories and dose-response analyses

When RC was divided into four categories (<0.50 , 0.50 – 0.99 , 1.00 – 1.49 , and ≥ 1.50 mmol/L), progressively higher levels were linked to a greater likelihood of HL and tinnitus. In the fully adjusted models, the odds of having HL were 1.57 (95% CI: 1.16–2.13), 2.33 (95% CI: 1.53–3.55), and 2.79 (95% CI: 1.55–5.04) across successive categories, whereas the corresponding odds of having tinnitus were 1.34 (95% CI: 1.10–1.63), 1.45 (95% CI: 1.11–1.90), and 1.95 (95% CI: 1.30–2.92) compared with the <0.50 mmol/L group.

For frequency-specific outcomes, the strongest associations were observed for HFHL, where the odds increased to 1.56 (95% CI: 1.15–2.12), 2.21 (95% CI: 1.43–3.41), and 2.87 (95% CI: 1.58–5.19) across the 0.50 – 0.99 , 1.00 – 1.49 , and ≥ 1.50 mmol/L groups, respectively. Associations with SFHL were slightly weaker, with odds of 1.50 (95% CI: 1.04–2.15), 1.77 (95% CI: 1.09–2.88), and 2.41 (95% CI: 1.10–5.26), respectively. LFHL showed the weakest associations, with odds ratios (OR) of 1.48 (95% CI: 0.99–2.21), 1.61 (95% CI: 0.96–2.69), and 3.45 (95% CI: 1.20–9.91), respectively.

Tests for linear trends were statistically significant for both overall HL and tinnitus, as were tests for HFHL, SFHL, and LFHL (all P values for trends <0.05) (Table 3). RCS analyses further supported these findings, showing positive and approximately linear associations between RC and both HL and tinnitus, with frequency-specific

299 analyses indicating the strongest relationships for HFHL, followed by SFHL, and the
300 weakest for LFHL (**Figure 2**). These ⁵ results indicate that higher RC levels are
301 associated with progressively greater odds of HL and tinnitus. The frequency-specific
302 gradient suggests that high-frequency hearing thresholds have the strongest association
303 with RC, followed by speech-frequency thresholds, whereas the association is weakest
304 for low-frequency thresholds.

305

306 **Subgroup and interaction analyses**

307 Across various demographic, socioeconomic, lifestyle, and clinical subgroups, the
308 subgroup analyses revealed that the relationships between RC and both HL and tinnitus
309 remained largely consistent, reinforcing the robustness of the results (**Figure 3**; detailed
310 estimates in **Supplementary Table S2**). Significant associations were observed
311 regardless of ⁶ age, sex, Body mass index (BMI), smoking status and drinking status,
312 marital status, education status, PIR, hypertension status, and diabetes status.

313 Interaction analyses, however, demonstrated heterogeneity due to noise exposure.
314 For HL, the association with RC was significantly stronger among participants with
315 self-reported noise exposure (OR=4.21, 95% CI: 2.37–7.47; P for interaction <0.001).
316 Similarly, for tinnitus, stronger associations were also observed in noise-exposed
317 individuals (OR=2.31, 95% CI: 1.61–3.32; P for interaction <0.05). RCS analyses
318 stratified by noise exposure further confirmed this effect modification, showing steeper
319 dose–response relationships in exposed participants (**Supplementary Figure S1**). No

320 significant interaction effects were observed for the remaining covariates.

321 **Discussion**

322 In this population-based analysis of U.S. adults, higher RC levels were
323 significantly associated with both HL and tinnitus. These associations were independent
324 of demographic, socioeconomic, behavioral, and clinical factors and remained robust
325 after mutual adjustment for other lipid fractions. Importantly, the strength of the
326 association varied across frequency-specific outcomes, being most pronounced for
327 HFHL, followed by SFHL, and weakest for LFHL. The associations were also
328 ¹⁷ consistent across most population subgroups, with stronger effects observed among
329 individuals exposed to noise. To date, population-based evidence linking RC to auditory
330 outcomes has been limited; this work offers the first population-based, comprehensive
331 assessment of RC in relation to auditory outcomes, offering new evidence that RC may
332 contribute to the development of auditory dysfunction.

333 The evidence regarding conventional lipid fractions and auditory outcomes has
334 been inconsistent. Although several studies have suggested that higher ³⁷ TC and LDL-C
335 levels are associated with a greater likelihood of HL [10, 32], others have not confirmed
336 these relationships [14, 47]. In this study, none of these conventional lipid parameters
337 were significantly associated with HL or tinnitus. In contrast, higher HDL-C
338 concentrations have been more consistently linked to a reduced risk of HL [14, 15, 47],
339 although in the mutually adjusted models, the protective effect of HDL-C disappeared
340 after adjustment for RC, suggesting that its association requires further confirmation.

341 ¹ Taken together, these findings indicate that the relevance of traditional lipid fractions
342 to auditory health may be limited, whereas RC provides a more specific marker of
343 atherogenic burden and vascular risk. Importantly, RC directly quantifies the
344 cholesterol carried in triglyceride-rich remnants, thereby offering a more
345 mechanistically grounded indicator of vascular and inflammatory stress. RC reflects the
346 cholesterol content of triglyceride-rich remnants, thereby indicating the residual
347 cholesterol burden that is mechanistically linked to systemic inflammation and
348 microvascular dysfunction [33, 37, 38].

349 ³⁰ Several biological pathways may underlie the observed associations between RC
350 and auditory outcomes. First, elevated RC promotes endothelial dysfunction and
351 atherosclerosis, which can compromise the cochlear microcirculation and lead to
352 ischemic injury to sensory hair cells [48-50]. Second, triglyceride-rich remnants are
353 highly atherogenic and can trigger chronic inflammation and oxidative stress through
354 macrophage activation, thereby exacerbating cochlear damage [20, 51]. Third, RC is
355 strongly linked to metabolic dysregulation, including insulin resistance ³³ and type 2
356 diabetes, both of which have been linked to an increased likelihood of HL [52]. These
357 multifactorial pathways should be viewed as potential explanations rather than
358 confirmed mechanisms, and they may help illustrate why RC could relate more strongly
359 to auditory dysfunction than conventional lipid measures, reinforcing their relevance as
360 a potential clinical indicator.

361 Notably, the associations between RC and HL varied across frequency ranges. The
362 effects were most pronounced for HFHL, followed by those for SFHL, whereas

363 significant associations with LFHL were observed only at the highest RC levels. This
364 pattern is biologically plausible, as the basal turn of the cochlea, which encodes high
365 frequencies, is more vulnerable to vascular insufficiency and oxidative stress [51, 53].
366 Both mechanisms are strongly influenced by RC, which promotes endothelial
367 dysfunction and chronic inflammation [49]. In addition, RC-mediated vascular injury
368 may impair the blood–labyrinth barrier, further exacerbating cochlear ischemia and hair
369 cell vulnerability, an area that deserves exploration in future mechanistic studies.
370 Furthermore, interaction analyses revealed that the associations of RC with HL and
371 tinnitus were amplified among individuals with noise exposure. Given that noise
372 primarily damages outer hair cells in high-frequency regions [54], elevated RCs may
373 exacerbate cochlear injury through synergistic pathways involving microvascular
374 dysfunction and inflammation. These results emphasize the importance of jointly
375 considering metabolic and environmental risk factors when evaluating auditory
376 impairment.

377 Importantly, statins—widely used for lowering lipids—reduce LDL-C and can
378 also lower RC, although the degree of RC reduction is generally less pronounced than
379 that of LDL-C [55] and may differ across statin types [56]. RC has been shown to
380 predict cardiovascular risk beyond LDL-C and ApoB [35] and to be independently
381 associated with incident cardiovascular events [34]. Previous clinical studies on statins
382 and HL have yielded inconsistent results, with some reporting protective effects,
383 particularly against drug-induced ototoxicity, while others reporting no significant
384 benefit [17, 57]. Large cardiovascular trials have also demonstrated that even with

385 maximal statin therapy or combination lipid-lowering regimens, considerable residual
386 risk persists, and this residual risk is strongly related to RC [33, 37]. Similarly, residual
387 risk may influence auditory outcomes, suggesting that targeted RC reduction strategies
388 should be considered in future clinical studies on HL and tinnitus.

389 From a clinical and public health perspective, RC may serve as an easily
390 obtainable indicator of an increased likelihood of HL and tinnitus. Because RC is
391 already incorporated into routine lipid assessments for cardiovascular risk management,
392 its use may provide complementary value for identifying individuals who warrant
393 closer monitoring of hearing health. Notably, the associations between RC and auditory
394 outcomes were stronger among individuals with noise exposure, underscoring the
395 combined influence of metabolic and environmental stressors. However, this study
396 neither establishes a specific RC threshold that should prompt referral for audiologic
397 evaluation, nor assesses whether incorporating RC improves the predictive
398 performance beyond conventional demographic and clinical factors. Thus, RC should
399 be interpreted as a preliminary risk indicator rather than a standalone decision-making
400 tool. Given its simplicity and low cost, RC may nonetheless represent an efficient
401 marker for population-level risk assessment in both general and occupational health
402 contexts, and future work should determine clinically actionable cutoff values and
403 evaluate its incremental predictive utility.

404 **Strengths and limitations**

405 This study has several notable strengths, including a large, population-

406 representative sample, standardized audiometric assessments, and comprehensive lipid
407 profiling, which enhance both the validity and generalizability of the findings. In
408 addition, the application of mutually adjusted models and subgroup analyses increases
409 the robustness of the observed associations.

410 Several limitations should also be noted in considering these findings. Because HL
411 and tinnitus commonly co-occur, excluding individuals with both conditions may limit
412 generalizability and could introduce selection bias. Accordingly, the findings primarily
413 characterize associations with isolated HL or isolated tinnitus rather than the comorbid
414 phenotype. Because of the cross-sectional study design, causal inference is not possible,
415 highlighting the need for longitudinal research to validate the temporal associations
416 between RC and auditory outcomes. The analyses operationalized HL as a binary
417 endpoint; therefore, associations with hearing loss severity (e.g., PTA as a continuous
418 measure or graded severity categories) could not be evaluated. Tinnitus was assessed
419 using a single self-report questionnaire item that referred to bothersome tinnitus during
420 the past 12 months. This approach captures only the presence or absence of tinnitus and
421 does not provide information on its laterality, severity, or functional impact, and
422 reliance on a 12-month recall window may lead to misclassification, particularly among
423 older adults. Moreover, RC was estimated via a calculation formula rather than direct
424 measurement, which may increase the potential for measurement error. Overall, while
425 these limitations warrant cautious interpretation, this study provides novel population-
426 based evidence linking RC to HL and tinnitus and highlights the need for future
427 prospective and mechanistic studies to clarify the underlying pathways involved.

428 **Conclusion**

429 This study provides the first population-based evidence that elevated RC is
430 independently associated with HL and tinnitus. These associations were particularly
431 evident at higher frequencies and among individuals with noise exposure, underscoring
432 the combined influence of metabolic and environmental risk factors. Because RC can
433 be readily calculated from routine lipid panels, it may serve as a practical marker to
434 help identify individuals who may benefit from earlier audiologic evaluation and
435 reinforced hearing-conservation counseling, particularly where access to audiometry is
436 limited, with potential to reduce avoidable disability and preserve communication and
437 quality of life. Prospective studies are needed to establish temporality and to evaluate
438 whether RC-lowering strategies are associated with improved auditory outcomes,
439 including HL severity.

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