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Original Research Article

Genetically Proxied Circulating C-Reactive Protein and Selected Cytokines in Relation to Register-Defined Sensorineural Hearing Loss: A Two-Sample Mendelian Randomization Study

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ABSTRACT

Background: Circulating inflammatory biomarkers are associated with sensorineural hearing loss (SNHL), but observational studies cannot establish causality.

Objective: To evaluate whether genetically proxied C-reactive protein (CRP) and eight cytokines are associated with SNHL.

Methods: We used European-ancestry GWASs for CRP (N = 575,531) and eight cytokines (maximum N = 74,783), with FinnGen R13 outcomes of 48,388 SNHL cases and 432,132 controls; sudden idiopathic hearing loss (4,082 cases) was secondary. Variants were harmonized and pruned using 1000 Genomes Finnish linkage disequilibrium (r^2 < 0.001 within 10 Mb). Random-effects inverse-variance weighting or a Wald ratio was primary. Sensitivity analyses included MR-Egger, weighted median and mode, MR-RAPS, RadialMR, Steiger directionality, cis-only estimates, source-assay filters, and false-discovery-rate correction.

Results: Of 301 unique exposure rsIDs, 279 were retrieved and 276 exposure rows passed harmonization. Finnish LD pruning left 238 CRP instruments. CRP was compatible with the null (OR per unit increase in ln[CRP mg/L], 1.005; 95% CI, 0.948–1.065; p = 0.868), consistent with weighted median, MR-Egger, weighted mode, and MR-RAPS estimates. No cytokine survived FDR correction (all q ≥ 0.393), source-assay filtering yielded no supported association, and secondary-outcome estimates were null. Steiger analyses favored the exposure-to-outcome direction.

Conclusion: Results support no material effect of lifelong genetically proxied circulating CRP on register-defined SNHL. Cytokine evidence remains less definitive because instrument sets were small, predominantly trans acting, heterogeneous, and assay sensitive. The findings neither exclude acute or cochlea-specific inflammation nor evaluate corticosteroid effectiveness. Independent replication and cis-pQTL colocalization are required before therapeutic inference.

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1. Introduction

Hearing loss is among the most prevalent chronic sensory disorders. The Global Burden of Disease analysis estimated that 1.57 billion people had hearing loss in 2019, with population aging expected to increase the absolute burden.[1] Sensorineural hearing loss (SNHL) arises from dysfunction or loss of cochlear hair cells, supporting cells, the stria vascularis, spiral ganglion neurons, central auditory pathways, or combinations of these structures. Its clinical category encompasses age-related, noise-induced, genetic, infectious, autoimmune, vascular, metabolic, and ototoxic causes. Because mature mammalian sensory hair cells have little regenerative capacity, many injuries produce permanent deficits. Identifying modifiable upstream mechanisms is therefore an important public-health and translational goal.

Observational evidence links systemic inflammation with auditory dysfunction. In a large occupational cohort with objective pure-tone testing, hearing loss was associated with elevated high-sensitivity CRP among adults older than 40 years, although the temporal and causal directions remained uncertain.[2] Similar biomarker associations may reflect direct vascular or neural injury, mediation of smoking or cardiometabolic disease, a downstream response to tissue damage, or selection into clinical testing. Conventional regression cannot fully remove residual

confounding, reverse causation, time-varying exposure, and measurement error.

Inflammation is also a biologically plausible contributor to cochlear injury. Recent experimental work has documented age-related macrophage and microglial activation in the cochlea and cochlear nucleus,[3] early strial degeneration accompanied by macrophage dysfunction in mouse and human tissue,[4] and detrimental activation of resident macrophages after acoustic trauma.[5] NLRP3 and downstream IL-1 signaling can mediate hair-cell injury in inflammatory otologic disease,[6] while human cell models show that TNF-α can disrupt blood-labyrinth-barrier integrity.[7] Experimental restoration of vascular integrity can preserve auditory function.[8] Together, these studies establish tissue-level inflammatory participation without proving that basal circulating CRP or cytokine concentrations cause population-level SNHL.

Other contemporary models reinforce this compartmental distinction. Cisplatin studies demonstrate that blood-labyrinth-barrier manipulation, pericyte injury, and inflammatory signaling can alter cochlear vulnerability.[9,10] Cochlear macrophages may have context-dependent effects, contributing to synaptic repair after acoustic injury,[11] tissue remodeling after implantation,[12] or NF-kappa-B-mediated damage after irradiation.[13] Likewise, randomized clinical studies of acute sudden SNHL evaluate short-term treatment after a defined syndrome rather than lifelong circulating biomarker exposure.[14,15] These mechanistic and therapeutic observations motivate causal inference but are not interchangeable with it.

Mendelian randomization (MR) uses germline variants associated with an exposure as instrumental variables. A prior MR study reported a nominal association between genetically predicted CRP and idiopathic sudden SNHL,[16] while a later bidirectional and multivariable analysis evaluated circulating white-cell counts in the same acute phenotype.[17] Such studies remain vulnerable to phenotype mixing, small exposure GWASs, weak aggregate instruments, horizontal pleiotropy, and reuse of overlapping outcome databases.

The available GWAS resources have expanded substantially. A CRP GWAS of 575,531 European-ancestry participants identified 266 genome-wide significant lead loci.[18] A 2025 multi-platform meta-GWAS mapped 40 circulating cytokines in as many as 74,783 participants.[19] FinnGen provides large-scale genotype and longitudinal health-register data from an isolated population.[20] More recently, a Million Veteran Program and UK Biobank meta-analysis identified extensive polygenic architecture for clinically coded and self-reported SNHL, while also demonstrating that these phenotypes are not identical.[21]

We therefore tested whether genetically proxied circulating CRP and eight mechanistically relevant cytokines were associated with register-defined SNHL. CRP was the confirmatory exposure; IL-6, TNF-α, IL-1β, IL-18, CXCL8/IL-8, CCL2/MCP-1, IL-10, and IL-1RA formed a discovery panel. The primary outcome was broad register-defined SNHL, and sudden idiopathic hearing loss was analyzed as an acute secondary phenotype. The study explicitly audited Finnish linkage disequilibrium (LD), source-assay heterogeneity, potential sample overlap, and directionality. The complete analytic sequence—from exposure selection through harmonization, LD pruning, primary MR, and sensitivity analyses—is shown in Figure 1. Reporting followed STROBE-MR and current MR investigation guidance.[22,23]

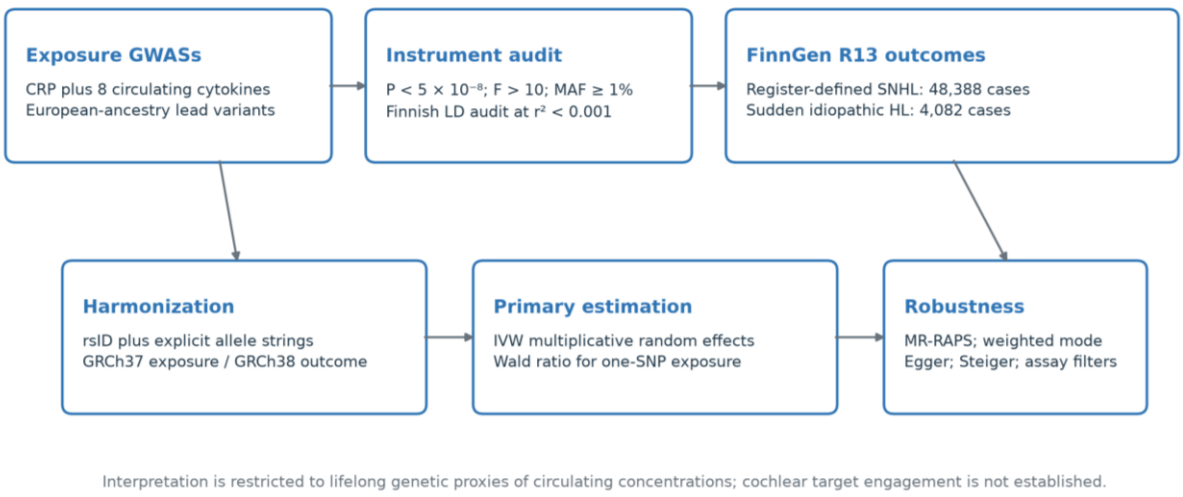

Figure 1. Two-sample Mendelian randomization workflow. CRP, C-reactive protein; FDR, false discovery rate; HL, hearing loss; IVW, inverse-variance weighted; LD, linkage disequilibrium; MAF, minor allele frequency; SNHL, sensorineural hearing loss.

2. Methods

Study Design and Reporting Framework

We conducted a two-sample MR study using publicly available summary statistics: biomarker GWASs supplied variant-exposure associations and FinnGen supplied variant-outcome associations. These were separate analytical roles, but they were not assumed to contain completely non-overlapping participants. No individual-level records were accessed. The analysis hierarchy was defined before model execution around one confirmatory exposure, eight discovery exposures, one primary outcome, and one secondary outcome; no dated external registration was available. CRP was tested at a two-sided alpha of 0.05. The eight cytokine primary estimates for the primary SNHL outcome formed one Benjamini-Hochberg FDR family, with $q < 0.05$ interpreted as statistically supported. The secondary outcome and all sensitivity estimators were exploratory and were used to evaluate robustness rather than to replace the primary estimate on the basis of significance.

The causal estimand is the change in the odds of the outcome associated with a lifelong genetically proxied increment in the circulating biomarker. For CRP, estimates were scaled per one-unit increase in natural-log-transformed CRP concentration in mg/L. For cytokines, estimates were scaled per one-standard-deviation increase in rank-based inverse-normal-transformed circulating concentration, as defined by the source meta-GWAS. These scales are not interchangeable with a short-term pharmacologic intervention, a transient acute-phase response, or a unit change in raw assay concentration.

Exposure Data Sources

CRP instruments were obtained from GCST90029070, a meta-GWAS of 575,531 participants of European ancestry.[18] CRP was measured in mg/L and natural-log transformed. The source study combined large cohorts, applied cohort-level quality control and covariate adjustment, and reported 266 genome-wide significant lead variants. We first reproduced that published lead set and then independently audited residual pairwise LD in the 1000 Genomes phase 3 Finnish population, as described below. The published lead set had minimum F statistic 29.5 and median F statistic 49.6 in our extraction. One lead variant within 1 Mb of the *CRP* gene was additionally labeled as a cis instrument for a conservative locus-specific analysis.

Cytokine instruments were obtained from accessions GCST90428399-GCST90428438 generated by the 2025 meta-GWAS.[19] The contributing data included Finnish Young Finns Study and FINRISK participants measured with multiplex immunoassays, SCALLOP consortium participants measured with Olink proximity-extension assays, and deCODE participants measured with SomaScan aptamers. Available sample size varied by cytokine from 38,868 to 74,783. Cohort cytokine phenotypes were rank inverse-normalized, and the source investigators combined evidence using sample-size-weighted z-score meta-analysis before reconstructing standardized beta coefficients and standard errors. This is not equivalent to a conventional inverse-variance fixed-effect meta-analysis of directly commensurate assays. Genetic associations were based on GRCh37 coordinates. Exposure accessions, scales, source sample sizes, and instrument attrition are detailed in Table 1.

We selected eight cytokines before model execution because they have experimental or clinical relevance to cochlear inflammation. Source-specific names were mapped as follows: IL-6; TNF-a to TNF-α; IL-1b to IL-1β; IL-18; CXCL8/IL-8; CCL2/MCP-1; IL-10; and IL-1ra to IL-1RA. For every cytokine, we retained the lowest-p-value variant within each locus identifier defined by the source meta-GWAS. All retained variants met $p < 5 \times 10^{-8}$, minor allele frequency (MAF) ≥1%, and $F > 10$. The resulting instrument counts before outcome harmonization were two for IL-6, one for TNF-α, four for IL-1β, nine for IL-18, seven for CXCL8/IL-8, five for CCL2/MCP-1, two for IL-10, and six for IL-1RA. Minimum F statistics ranged from 29.7 to 41.1. The set was predominantly trans-pQTL based; cis-only analyses were possible for IL-18 and IL-1RA.

The source supplement provided cross-cohort direction strings and Cochran heterogeneity statistics. We therefore defined three prespecified sensitivity filters without reference to FinnGen outcome effects: (1) exclusion of variants with source heterogeneity $p < 0.05$ while retaining variants for which heterogeneity was not estimable; (2) retention of variants whose observed cohort directions were concordant after ignoring unavailable cohorts denoted by "?"; and (3) a combined assay-robust filter satisfying both conditions. These filters address, but cannot eliminate, the possibility that a protein quantitative-trait association reflects platform-specific binding, epitope effects, differential normalization, or cohort-specific biology rather than a portable difference in circulating concentration.

Outcome Data Sources and Phenotypes

The primary outcome was FinnGen release 13 endpoint H8_HL_SEN_NAS, "sensorineural hearing loss," containing 48,388 cases and 432,132 controls (total N = 480,520). The endpoint definition includes ICD-10 codes H90.3, H90.4, and H90.5 and ICD-9 code 3891. It therefore represents health-register ascertainment of bilateral sensorineural loss, unilateral sensorineural loss with restricted hearing on the contralateral side, and unspecified sensorineural loss; it is not an audiometrically homogeneous phenotype. The secondary outcome was H8_HL_IDIOP, "sudden idiopathic hearing loss," containing 4,082 cases and the same 432,132 controls. FinnGen links genotype data from Finnish biobanks with longitudinal national health-register diagnoses and uses a Finnish population-specific imputation reference panel.[20] Public release 13 summary statistics were generated on GRCh38 and report the alternative allele, beta coefficient, standard error, p

value, and allele frequencies in the full sample, cases, and controls. FinnGen association analyses use regenie leave-one-chromosome-out models with age, sex, ten genetic principal components, chip version, and legacy genotyping batch as covariates, plus approximate Firth correction for variants with initial $p < 0.01$ [24]. We treated reported coefficients as log odds ratios.

The two outcomes were not pooled. H8_HL_SEN_NAS reflects clinically recorded sensorineural disease across etiologies, severities, and time courses; no pure-tone thresholds, age at onset, laterality details beyond coding, noise exposure, or etiologic adjudication were available. The sudden idiopathic endpoint represents an acute syndrome and has a much smaller case count. Separating them prevents an acute association from being presented as evidence for chronic or mixed-etiology SNHL. The 2026 Million Veteran Program GWAS provides a future replication resource with a much larger clinically diagnosed SNHL sample.[21]

Instrument Extraction and Genome-Build Harmonization

We created a union of 301 unique rsIDs across 302 exposure-variant rows; one rsID was shared by two cytokines. FinnGen R13 outcome files were streamed once per phenotype, and only records containing these rsIDs were retained. This strategy avoided downloading or storing genome-wide individual-level data while preserving exact source coefficients. We retrieved 279 unique variants from each outcome. We did not substitute missing variants with LD proxies. Missing variants were documented rather than silently replaced.

Alleles were harmonized using rsID, effect allele, other allele, FinnGen reference allele, and FinnGen alternative allele. FinnGen beta coefficients were retained when the exposure effect allele matched the FinnGen alternative allele and multiplied by -1 when it matched the reference allele. Complementary-strand matches were handled analogously. Palindromic A/T or C/G variants with MAF>0.42 or unknown frequency were excluded as ambiguous; rare palindromic variants were retained only when allele orientation was directly consistent. Indels were harmonized using their explicit allele strings. Coordinates were not used to join records and no liftover was performed: exposure rows retained their GRCh37 positions, outcome rows retained GRCh38 positions, and identity was established by rsID plus allele strings. After harmonization, 276 exposure-variant rows remained per outcome: 141 direct matches and 135 flipped matches. Twenty-two variants were unavailable in FinnGen and four palindromic rows were excluded.

We independently queried all within-exposure, same-chromosome pairs separated by no more than 10 Mb against the Ensembl REST pairwise-LD endpoint for 1000 Genomes phase 3 Finnish participants (population code 1000GENOMES:phase_3:FIN; accessed 21 July 2026). Among 236 candidate pairs, LD values were returned for six and no pairwise record was returned for 230; no request failed. All six returned pairs exceeded $r^2 = 0.001$, with maximum $r^2 = 0.306$. We applied deterministic greedy pruning ordered by the smallest exposure p value and, secondarily, the largest F statistic. Of the six flagged source pairs, three contained two CRP variants that both survived outcome harmonization; the weaker member of each was removed (rs1801272, rs7539725, and rs11711864). The CRP primary set therefore contained 238 instruments. An empty Ensembl response was recorded as "no LD record returned," not recoded as $r^2 = 0$.

Primary Mendelian Randomization Estimation

For exposures with two or more instruments, the primary estimator was IVW regression constrained through the origin, with inverse variance weights based on the outcome standard errors. We used multiplicative random-effects standard errors when Cochran heterogeneity exceeded its degrees of freedom and did not permit under-dispersion to narrow the confidence interval. This estimator combines variant-specific Wald ratios while allowing balanced heterogeneity. For TNF-α, which had one instrument, we used the Wald ratio and the first-order standard error. Effect estimates were exponentiated and reported as odds ratios with 95% confidence intervals.

The Wald ratio, its first-order variance, the IVW slope, and the per-variant strength statistic were calculated as follows:

$$\hat{\beta}_{\text{Wald,j}} = \beta_{Yj} / \beta_{Xj}$$

$$Var(\hat{\beta}_{\text{Wald,j}}) = SE(\beta_{Yj})^2 / \beta_{Xj}^2$$

$$\hat{\beta}_{IVW} = (\Sigma_j w_j \beta_{Xj} \beta_{Yj}) / (\Sigma_j w_j \beta_{Xj}^2)$$

$$F_j = \beta_{Xj}^2 / SE(\beta_{Xj})^2$$

$$N_{eff} = 4 / (1/N_{cases} + 1/N_{controls})$$

Here, β_{Xj} is the variant-biomarker association, β_{Yj} is the variant-log-odds outcome association, $SE(\beta_{Yj})$ is the outcome standard error, and $w_j = 1/SE(\beta_{Yj})^2$. We used a two-sided normal test for the primary coefficient. All retained variants exceeded $F > 10$, reducing but not eliminating weak-instrument bias.

Sensitivity and Robustness Analyses

Weighted-median MR was calculated for exposures with at least two instruments and interpreted most strongly when three or more variants were available. Its uncertainty was estimated using 5,000 parametric bootstrap draws of variant-exposure and variant-outcome coefficients. Weighted-mode MR with delta weights and 10,000 iterations was added as a robust estimator under the zero-modal-pleiotropy assumption. MR-RAPS with overdispersion and Huber loss was added to accommodate many weak or idiosyncratic instruments while providing resistance to outliers. These estimators were interpreted according to current MR guidance rather than selected by nominal significance.[23]

MR-Egger regression was calculated for exposures with at least three instruments after orienting associations to positive exposure effects. We corrected the small-sample implementation by estimating the residual multiplicative factor as max(1, Q/df), using t rather than normal inference for both slope and intercept, and preventing underdispersion from narrowing standard errors. I^2_{GX} was calculated to assess dilution from imprecisely measured variant-exposure associations. Because MR-Egger has low power and can be unstable with fewer than ten variants, estimates for small cytokine sets were treated as diagnostic rather than decisive. Horizontal pleiotropy cannot be excluded by one diagnostic alone.

Cochran Q assessed between-variant heterogeneity for the IVW model. An MR-Egger intercept $p < 0.05$ was considered evidence compatible with directional pleiotropy, recognizing limited power. Radial diagnostics were implemented with RadialMR version 1.2.4 using first-order weights and a Bonferroni threshold of $\alpha = 0.05/k$. Radial variants were reported as assumption diagnostics; deletion-based estimates were not promoted as confirmatory evidence because removal is outcome dependent. Leave-one-out IVW estimates were retained for groups with at least three variants. We did not designate a weighted-median, weighted-mode, MR-RAPS, or RadialMR result as primary merely because it crossed a nominal p-value threshold.

For CRP, IL-18, and IL-1RA, we also estimated cis-only Wald ratios. Cis-pQTLs are less likely than trans-pQTLs to act through unrelated proteins, although LD, neighboring-gene regulation, and reverse molecular causation remain possible. Because each cis-only analysis used one lead variant, it could not support heterogeneity or pleiotropy tests and was interpreted as triangulation. Colocalization was not undertaken because the public extraction used published lead-variant supplements rather than complete dense regional exposure statistics. Multi-signal colocalization requires regional association evidence and should precede target-specific inference.[25]

Steiger directionality testing was implemented with TwoSampleMR version 0.7.9. Variant-exposure correlations were derived from F statistics and exposure sample sizes. Binary-outcome correlations were approximated on the liability scale from log odds ratios, outcome allele frequencies, case-control counts, and plausible population-prevalence scenarios. We used prevalence values of 5%, 10%, and 20% for broad SNHL and 0.05%, 0.1%, and 0.5% for sudden idiopathic loss. Because liability conversion is prevalence dependent and the phenotypes are register defined, the Steiger analysis was interpreted as a directional sensitivity check rather than proof against reverse causation.

Multiple Testing and Approximate Power

CRP was the confirmatory exposure evaluated at $\alpha = 0.05$. The eight cytokine primary estimates for register-defined SNHL constituted one discovery family, and Benjamini-Hochberg q values were calculated from those eight p values. FDR controls the expected proportion of false discoveries among rejected cytokine hypotheses; it is not family-wise error-rate control. The sudden idiopathic outcome, assay-quality subsets, and robust estimators were exploratory and were not given additional confirmatory thresholds. We emphasized effect sizes, confidence intervals, consistency, and assumption diagnostics rather than dichotomizing every analysis by $p < 0.05$.

We recalculated variance explained for the actual retained independent set rather than transferring the full source-GWAS R^2. For each variant, R^2 was approximated as $F/(F + N - 2)$, then summed under the post-pruning independence assumption. Minimum detectable odds ratios for 80% power used the case-control effective sample size N_{eff} defined in the equation block, with two-sided $\alpha = 0.05$. The primary-outcome effective N was approximately 174,061. Retained-set R^2 was 0.0440 for CRP and ranged from 0.00100 for IL-6 to 0.0146 for IL-1RA. Corresponding optimistic minimum detectable ORs ranged from 1.033 for CRP to 1.236 for IL-6. These calculations do not incorporate pleiotropy, phenotype misclassification, or uncertainty in R^2 and therefore remain approximations.

Software, Reproducibility, and Data Quality Controls

Data processing and core MR estimation were implemented in Python 3.12.13 with NumPy 2.5.1, pandas 2.2.3, and SciPy 1.18.0 using deterministic seeds. Robust methods were implemented in R 4.5.3 with RadialMR 1.2.4, mr.raps 0.4.3, MendelianRandomization 0.10.0, and TwoSampleMR 0.7.9. The workflow preserved source accession, sample size, scale, rsID, alleles, beta, standard error, p value, allele frequency, F statistic, instrument scope, source heterogeneity, cohort direction, Finnish LD audit status, and pruning decision. Numerical results, tables, and figures were regenerated from the same derived instrument tables used to populate this manuscript.

Quality controls included: verifying the FinnGen header and alternative-allele convention; preserving rather than conflating GRCh37 and GRCh38 coordinates; matching by rsID and allele strings rather than coordinate; excluding ambiguous palindromes; retaining only MAF ≥ 1%, genome-wide significant, F > 10 instruments; querying Finnish pairwise LD; applying pruning without outcome coefficients; auditing cytokine source heterogeneity and observed cohort direction; comparing extracted records across both outcomes; constraining MR-Egger underdispersion; and reproducing confidence intervals from the exact inferential distribution used by each estimator. No FinnGen outcome result was inspected when selecting the biomarker panel or source-assay filters.

The cytokine source meta-GWAS included up to 8,293 participants from YFS/FINRISK. Exact participant overlap with FinnGen was not reported and could not be identified from public summary data. As a conservative bound, 8,293 would represent 11.1%-21.3% of the cytokine GWAS sample, depending on exposure. This is a maximum possible contribution of the named Finnish cohorts, not an estimate of actual overlap. We therefore retained sample overlap as a limitation rather than asserting complete two-sample independence.

Ethical Considerations

This study used only publicly released, aggregate GWAS summary statistics and involved no contact with participants, no identifiable data, and no new recruitment. Ethical approvals and informed consent were obtained by the original FinnGen and contributing exposure studies as described in their publications. Under commonly applied institutional policies, secondary analysis of de-identified public summary data does not constitute new human-subject research requiring additional participant consent.

3. Results

Instrument Availability, Strength, and Harmonization

The exposure inventory contained 266 CRP lead variants and 36 cytokine exposure-variant rows, representing 301 unique rsIDs because rs1329424 instrumented both TNF-α and IL-10. All variants satisfied the p-value, MAF, and F-statistic criteria defined before modeling. CRP had the largest and strongest source set: minimum F = 29.5, median F = 49.6, and maximum F = 1,535.9. The cytokine minimum F statistics ranged from 29.7 to 41.1. Thus, no retained variant met the conventional definition of an individually weak instrument, although small aggregate R^2 still limited power for several cytokines. The exposure sources, measurement scales, and sequential instrument counts are summarized in Table 1.

Table 1. Exposure GWAS sources, scales, and instrument counts.

Exposure	GWAS accession	N	Scale	Selected k	Harmonized k	Primary k	Assay-robust k
C-reactive protein	GCST90029070	575,531	ln[mg/L]	266	241	238	–
IL-6	GCST90428418	74,679	1 SD	2	2	2	1
TNF-α	GCST90428435	39,013	1 SD	1	1	1	0
IL-1β	GCST90428412	38,868	1 SD	4	4	4	2
IL-18	GCST90428411	70,126	1 SD	9	9	9	7
CXCL8/IL-8	GCST90428420	70,016	1 SD	7	7	7	3
CCL2/MCP-1	GCST90428424	74,783	1 SD	5	5	5	2
IL-10	GCST90428407	43,240	1 SD	2	2	2	0
IL-1RA	GCST90428413	70,128	1 SD	6	5	5	3

Primary k is the Finnish-LD-pruned count used in the primary models. Assay-robust k applies the combined source-heterogeneity and cohort-direction filter to cytokines. CRP is scaled per one-unit increase in ln(mg/L); cytokines are scaled per SD.

Streaming extraction from each FinnGen R13 outcome identified 279 of the 301 unique rsIDs. At the exposure-row level, 22 records per outcome were unavailable, four were excluded as palindromic with intermediate or unknown frequency, 141 aligned directly, and 135 required effect reversal. Before Finnish LD pruning, the harmonized SNHL analysis used 241 variants for CRP, five for CCL2/MCP-1, seven for CXCL8/IL-8, four for IL-1β, five for IL-1RA, two for IL-10, nine for IL-18, two for IL-6, and one for TNF-α. The same counts applied to the secondary endpoint. Finnish LD auditing identified six source CRP pairs with returned r^2 values above 0.001. Three weaker variants belonged to pairs in which both members were harmonized and were removed, yielding 238 CRP instruments for the primary analyses. No cytokine pair violated the Finnish LD threshold.

Among the 35 unique cytokine instruments that survived outcome harmonization, 14 had source cross-cohort heterogeneity $p < 0.05$, 17 had $p < 0.10$, and nine had discordant directions among cohorts with reported effects. Eighteen variants met the combined assay-robust definition. No IL-10 or TNF-α instrument met both criteria; consequently, those two exposures could not be estimated in the combined filtered analysis.

Primary Outcome: C-Reactive Protein

The primary random-effects IVW estimate was compatible with no material CRP effect on register-defined SNHL. The OR per one-unit increase in ln(CRP mg/L) was 1.005 (95% CI, 0.948-1.065; p = 0.868; 238 variants). Cochran Q was 455.0 on 237 degrees of freedom ($p = 7.43 \times 10^{-16}$), indicating substantial between-variant heterogeneity and justifying the random-effects standard error.

Robust estimators did not reveal a concealed CRP association. The weighted-median OR was 1.014 (95% CI, 0.936-1.099; p = 0.729), corrected MR-Egger OR was 0.985 (95% CI, 0.894-1.086; t-based p = 0.767), weighted-mode OR was 0.971 (95% CI, 0.902-1.045; p = 0.425), and MR-RAPS OR was 1.002 (95% CI, 0.945-1.062; p = 0.950). MR-Egger I^2_{GX} was 97.1%, and the

underdispersion-constrained intercept test was null (p = 0.622). Validated RadialMR flagged five CRP variants at the Bonferroni threshold, but these were treated as diagnostics rather than a basis for selecting a deletion-corrected causal estimate. The cis-only CRP variant remained null (OR, 1.031; 95% CI, 0.851-1.248; p = 0.758). Across estimators with different assumptions, CRP point estimates were compatible with no material effect.

Primary Outcome: Cytokine Panel

None of the eight cytokines met the primary-outcome FDR threshold. The smallest primary p value was observed for IL-1RA, but its IVW estimate remained nonsignificant after multiplicative random-effects correction (OR per SD, 0.899; 95% CI, 0.794-1.019; p = 0.0948; q = 0.393; five variants). The weighted-median estimate was nominally protective (OR, 0.905; 95% CI, 0.841-0.973; p = 0.00732), and weighted mode (OR, 0.904; p = 0.00528) and MR-RAPS (OR, 0.898; p = 0.0310) pointed in the same direction, whereas corrected MR-Egger was imprecise and null (OR, 0.935; 95% CI, 0.632-1.382; t-based p = 0.622). Heterogeneity was present (Q p = 0.00902), and RadialMR flagged rs9937053. The cis-only IL-1RA estimate was null (OR, 0.934; 95% CI, 0.846-1.032; p = 0.178). After combined source-assay filtering, three variants remained and the IVW estimate was OR 0.834 (95% CI, 0.482-1.443; p = 0.517), with persistent heterogeneity (Q p = 0.00214). These results are insufficient to establish protection.

For IL-1β, the primary IVW OR was 1.162 (95% CI, 0.914-1.476; p = 0.221; q = 0.441; four variants), with heterogeneity (Q p = 0.00918). Weighted median (OR, 1.183; p = 0.0269) and weighted mode (OR, 1.293; p = 0.000639) were nominally positive, whereas MR-RAPS (OR, 1.235; p = 0.159) and corrected MR-Egger (OR, 1.234; 95% CI, 0.555-2.743; t-based p = 0.375) were not. RadialMR flagged rs56836833, but deletion-based re-estimation was not used to overturn the primary result. Two of four source instruments had heterogeneity p < 0.05 and two had discordant cohort directions. The combined assay-robust subset retained only two variants and yielded OR 0.875 (95% CI, 0.524-1.461; p = 0.610), reversing the unfiltered point direction. This instability argues against a target-level causal conclusion.

IL-18 was null by IVW (OR, 1.009; 95% CI, 0.881-1.155; p = 0.896; q = 0.896; nine variants) despite heterogeneity (Q p = 0.00295). The weighted-median OR was 0.990 (p = 0.868), corrected MR-Egger OR was 0.781 (t-based p = 0.446), and cis-only OR was 0.887 (p = 0.441). RadialMR flagged rs72927001. Source heterogeneity was not estimable for the IL-18 variants because not all cohorts contributed; the seven direction-concordant variants yielded a combined-filter OR of 1.068 (95% CI, 0.925-1.233; p = 0.369).

CXCL8/IL-8 likewise showed no primary association (OR, 1.059; 95% CI, 0.785-1.428; p = 0.708; q = 0.896; seven variants) and substantial heterogeneity (Q p = 6.64×10^{-6}). Weighted median, corrected MR-Egger, weighted mode, and MR-RAPS were all null. RadialMR flagged rs9277379. Three instruments had source heterogeneity p < 0.05 and two had discordant observed directions; the three-variant combined assay-robust result remained imprecise (OR, 1.213; 95% CI, 0.509-2.893; p = 0.663) with residual heterogeneity. This pattern illustrates why heterogeneous trans-pQTL results require caution.

The remaining cytokines were also null. IL-6 had an IVW OR of 1.131 (95% CI, 0.872-1.468; p = 0.354; q = 0.566; two variants). The single TNF-α variant produced OR 0.796 (95% CI, 0.588-1.077; p = 0.138; q = 0.393). CCL2/MCP-1 yielded OR 1.015 (95% CI, 0.878-1.174; p = 0.841; q = 0.896; five variants), without IVW heterogeneity (Q p = 0.486). IL-10 yielded OR 0.868 (95% CI, 0.717-1.051; p = 0.148; q = 0.393; two variants). None of the available MR-Egger intercept tests for cytokines was significant. The complete primary estimates and heterogeneity statistics are detailed in Table 2, while their effect sizes and 95% confidence intervals are visualized in Figure 2.

Table 2. Primary Mendelian randomization estimates for sensorineural hearing loss.

Exposure	k	Estimator	OR	95% CI	p	FDR q	Q p
CRP	238	IVW-RE	1.005	0.948–1.065	0.868	–	7.43 × 10⁻16
IL-6	2	IVW-RE	1.131	0.872–1.468	0.354	0.566	0.614
TNF-α	1	Wald	0.796	0.588–1.077	0.138	0.393	–
IL-1β	4	IVW-RE	1.162	0.914–1.476	0.221	0.441	0.009
IL-18	9	IVW-RE	1.009	0.881–1.155	0.896	0.896	0.003
CXCL8/IL-8	7	IVW-RE	1.059	0.785–1.428	0.708	0.896	6.64 × 10⁻06
CCL2/MCP-1	5	IVW-RE	1.015	0.878–1.174	0.841	0.896	0.486
IL-10	2	IVW-RE	0.868	0.717–1.051	0.148	0.393	0.448
IL-1RA	5	IVW-RE	0.899	0.794–1.019	0.095	0.393	0.009

IVW-RE, inverse-variance weighted multiplicative random effects; FDR, false discovery rate. Instruments were Finnish-LD-pruned. CRP was confirmatory and therefore has no FDR q value. Q p is unavailable for the single-variant Wald ratio.

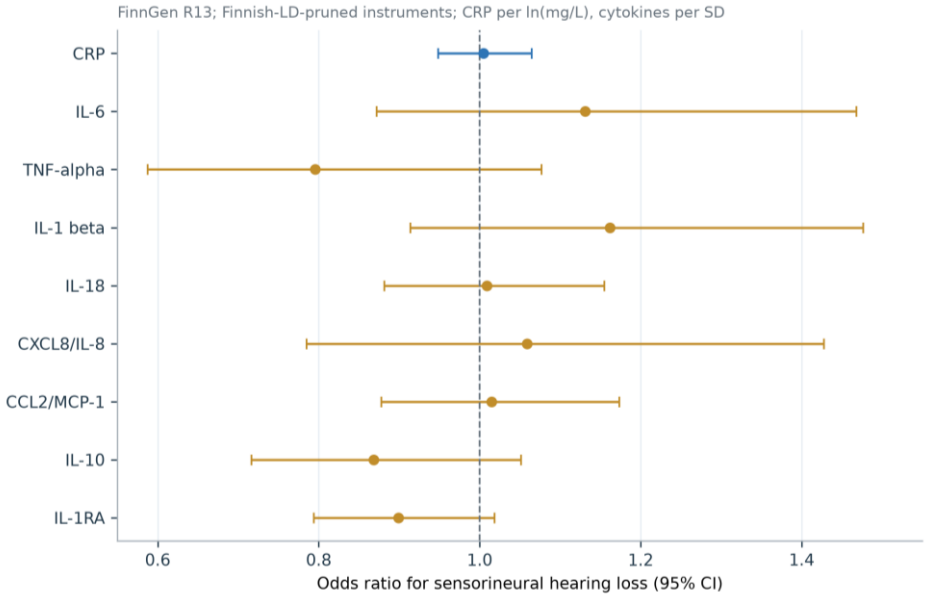

Figure 2. Primary Mendelian randomization estimates for register-defined sensorineural hearing loss. Estimates are multiplicative random-effects IVW except TNF-α, which uses a Wald ratio. The dashed line indicates OR = 1.

Secondary Outcome: Sudden Idiopathic Hearing Loss

All Finnish-LD-pruned primary estimates for sudden idiopathic hearing loss were null, as detailed in Table 3. The CRP IVW OR was 1.031 (95% CI, 0.902-1.177; p = 0.656; 238 variants), with no statistically detectable heterogeneity (Q p = 0.373). Cytokine estimates were: IL-6 OR 1.321 (95% CI, 0.452-3.856; p = 0.611); TNF-α OR 0.804 (95% CI, 0.311-2.076; p = 0.652); IL-1β OR 0.892 (95% CI, 0.614-1.296; p = 0.549); IL-18 OR 1.070 (95% CI, 0.813-1.408; p = 0.628); CXCL8/IL-8 OR 1.279 (95% CI, 0.729-2.245; p = 0.391); CCL2/MCP-1 OR 0.733 (95% CI, 0.398-1.350; p = 0.319); IL-10 OR 1.079 (95% CI, 0.592-1.966; p = 0.805); and IL-1RA OR 0.944 (95% CI, 0.708-1.258; p = 0.694). This endpoint and its sensitivity analyses were treated as exploratory rather than as a second FDR-controlled discovery family. Cis-only estimates for CRP, IL-18, and IL-1RA were also null.

The smaller acute endpoint generated wider confidence intervals than the primary SNHL endpoint, especially for one- or two-variant exposures. Nevertheless, the CRP point estimate was much closer to unity than the OR 1.23 reported in an earlier FinnGen-based study.[16] The current interval overlapped small protective and harmful effects and did not reproduce a nominal positive CRP association.

Table 3. Primary estimates for sudden idiopathic hearing loss.

Exposure	k	Estimator	OR	95% CI	p	Q p
CRP	238	IVW-RE	1.031	0.902–1.177	0.656	0.373
IL-6	2	IVW-RE	1.321	0.452–3.856	0.611	0.190
TNF-α	1	Wald	0.804	0.311–2.076	0.652	–
IL-1β	4	IVW-RE	0.892	0.614–1.296	0.549	0.818
IL-18	9	IVW-RE	1.070	0.813–1.408	0.628	0.282
CXCL8/IL-8	7	IVW-RE	1.279	0.729–2.245	0.391	0.057
CCL2/MCP-1	5	IVW-RE	0.733	0.398–1.350	0.319	0.126
IL-10	2	IVW-RE	1.079	0.592–1.966	0.805	0.450
IL-1RA	5	IVW-RE	0.944	0.708–1.258	0.694	0.120

The secondary phenotype included 4,082 cases and 432,132 controls. Instruments were Finnish-LD-pruned. This outcome was exploratory and was not treated as a second FDR-controlled discovery family.

Sensitivity Synthesis and Approximate Power

The sensitivity pattern, summarized in Figure 3, was strongest for CRP: IVW, weighted median, corrected MR-Egger, weighted mode, MR-RAPS, and the cis-only instrument all had confidence intervals spanning unity. For the cytokines, no exposure combined a statistically supported primary result, FDR support, low heterogeneity, assay-robust stability, and supportive cis evidence. Nominal weighted-median and weighted-mode results for IL-1β and IL-1RA pointed in opposite risk directions and occurred in small heterogeneous sets. Validated radial flags identified influential observations but did not justify outcome-dependent promotion of deletion estimates.

Retained-set R^2 was 0.0440 for CRP, corresponding to an approximate 80%-power minimum detectable OR of 1.033 for the primary outcome. Cytokine retained-set R^2 ranged from 0.00100 to 0.0146, with approximate minimum detectable ORs of 1.057 for IL-1RA, 1.067 for IL-1β, 1.100 for IL-18, 1.107 for CXCL8/IL-8, 1.126 for CCL2/MCP-1, 1.139 for IL-10, 1.232 for TNF-α, and 1.236 for IL-6. Thus, the data constrain moderate CRP effects more strongly than cytokine effects and do not exclude smaller cytokine effects.

Steiger testing favored the biomarker-to-outcome direction for every exposure in both outcomes across all three assumed prevalence scenarios; the largest p value across the primary-outcome tests was 2.79×10^{-8}. This result reduces concern that stronger genetic prediction of the outcome than exposure drove the estimates, but it does not remove pleiotropy and is conditional on liability-scale approximations. The potential contribution of YFS/FINRISK participants ranged from a maximum of 11.1% to 21.3% of each cytokine exposure GWAS. Actual overlap with FinnGen was unknown, so no numerical overlap-bias correction was attempted.

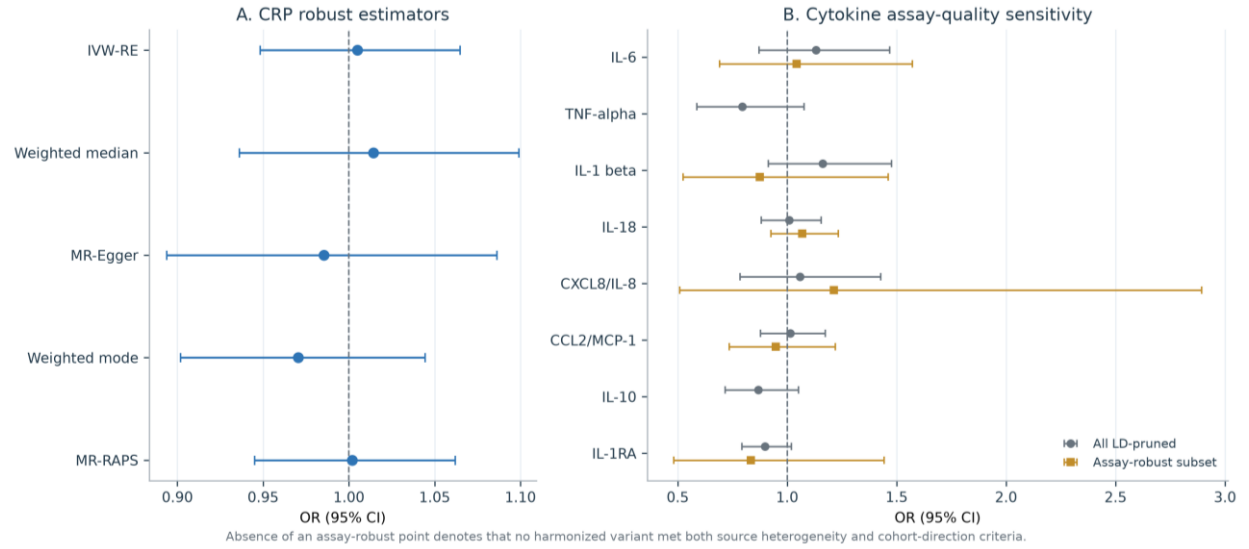

Figure 3. Sensitivity analyses for circulating inflammatory biomarkers. Missing assay-robust points indicate that no harmonized variant met both source-heterogeneity and cohort-direction criteria.

4. Discussion

Principal Findings

In this two-sample MR study using FinnGen R13, genetically proxied circulating CRP was compatible with no material effect on register-defined SNHL after Finnish LD pruning, and none of eight selected cytokines was supported after FDR correction. CRP, the confirmatory exposure with the strongest and most numerous instruments, had a primary OR of 1.005 and concordant weighted-median, corrected MR-Egger, weighted-mode, MR-RAPS, and cis estimates. Cytokine findings were less definitive: instrument counts were small, heterogeneity was frequent, most instruments were trans acting, and almost half of the harmonized variants failed at least one source-assay quality criterion. A separate exploratory analysis of sudden idiopathic hearing loss was also null.

The most defensible interpretation is not that inflammation is irrelevant to cochlear disease. Rather, the present evidence does not support a detectable effect of lifelong differences in the measured circulating biomarkers on the risk of receiving an SNHL diagnosis. Local cochlear inflammation can be central to injury while circulating biomarker concentrations remain noncausal, downstream, or too coarse to represent the relevant pathway. This distinction matters clinically: association of a blood marker with hearing thresholds does not by itself justify targeting that marker to prevent common SNHL.

Comparison With Previous Mendelian Randomization Evidence

Our CRP result does not reproduce the earlier nominal association with idiopathic sudden SNHL reported using 53 variants and an earlier FinnGen dataset.[16] Several differences may explain the discrepancy. First, the present CRP source GWAS was much larger and the current analysis retained 238 harmonized, Finnish-LD-pruned instruments, changing precision and the balance of loci. Second, FinnGen R13 contained more participants and used a later analysis pipeline. Third, the previous p value of 0.03 was modest and could reflect sampling variation, phenotype definition, or analytic choices. Fourth, acute sudden hearing loss is not equivalent to broad register-defined SNHL. Finally, the earlier weighted-median confidence interval as printed in that publication appears internally inconsistent with its

point estimate, illustrating the importance of reproducible numerical checks.

The current sudden idiopathic hearing-loss estimate for CRP was 1.031, with a 95% CI of 0.902-1.177. Although it cannot exclude a small effect, it is incompatible with treating the previous OR of 1.23 as a stable, well-replicated causal magnitude. The result also reinforces a general MR principle: nominal significance from one database release should be considered provisional until replicated with updated instruments, independent outcomes, and sensitivity analyses.

Other recent MR studies have tested mitochondrial proteins,[26] circulating lipids in age-related hearing loss,[27] and bidirectional lipid associations with sudden SNHL.[28] Direct comparison is difficult because the outcomes range from self-reported difficulty to ICD-coded disease and acute syndromes. The 2026 Million Veteran Program and UK Biobank meta-analysis identified 108 genome-wide significant loci in its multi-ancestry analysis and demonstrated substantial, but incomplete, genetic overlap across differently ascertained hearing phenotypes.[21] Future replication should preserve phenotype specificity rather than treating all hearing outcomes as equivalent.

Biological Interpretation: Systemic Versus Cochlear Inflammation

Experimental evidence for inflammatory involvement in hearing loss is compelling. Aging, acoustic overstimulation, infection, ototoxic injury, and irradiation can activate cochlear macrophages, barrier cells, and cytokine signaling.[3-13] Macrophages are present across primate cochlear development,[29] and inflammatory electrical stimulation can activate macrophages and fibroblasts relevant to intracochlear remodeling.[30] In specific contexts, inhibiting inflammatory signaling reduces histologic injury or auditory threshold shifts, whereas in others macrophages support repair. These findings establish that inflammatory responses can participate in cochlear damage; they do not establish that basal circulating concentrations of the same proteins drive population-level SNHL.

Circulating cytokines are influenced by many tissues, cell populations, infections, and technical assay features. A trans-pQTL may alter a receptor, clearance pathway, blood-cell composition, or upstream signaling node rather than biologically active cytokine at the cochlear target. The 2025 cytokine GWAS itself demonstrated extensive cross-cytokine regulation and identified upstream "mega-regulator" effects, underscoring the possibility of horizontal pleiotropy.[19] Measurements from Luminex, Olink, and SomaScan can also capture different epitopes or molecular forms. Meta-analysis increases statistical power but the resulting standardized exposure is an average across platforms, matrices, and populations.

The cochlea is protected by a blood-labyrinth barrier and contains specialized resident immune cells. Local autocrine or paracrine signaling may be only weakly correlated with plasma concentration. Timing is equally important. MR estimates the consequence of lifelong genetically influenced exposure, whereas acute inflammatory bursts after noise trauma or viral infection can have nonlinear, thresholded, and time-limited effects. A null lifelong average does not rule out a causal acute response within hours of cochlear injury. Conversely, a circulating biomarker measured after hearing loss may reflect tissue damage or comorbidity rather than the upstream event.

These distinctions are analogous to CRP in cardiovascular research. CRP is a strong risk marker, but cis-focused genetic studies have often separated the marker from upstream inflammatory pathways that are therapeutically causal. In our analysis, a large genome-wide CRP instrument and a cis-only CRP variant were both null for SNHL. This pattern is more consistent with CRP being a nonspecific indicator of inflammatory state than a direct cochlear toxin. It does not exclude causal upstream pathways such as IL-6 signaling, innate immune activation, or vascular inflammation, but our two-variant circulating IL-6 instrument was insufficiently precise to exclude small effects.

Interpretation of IL-1 Beta and IL-1RA Signals

IL-1 biology deserves particular caution because exploratory results could be overinterpreted. The unfiltered primary IL-1β estimate was positive but nonsignificant and heterogeneous; weighted median and weighted mode were nominally positive, whereas MR-RAPS and corrected MR-Egger were not. Two instruments were heterogeneous across source cohorts and two had discordant cohort directions. The two-variant assay-robust subset pointed below unity. There was no independent cis-IL-1β instrument in the selected source set and no colocalization analysis. These limitations prevent a causal claim.

IL-1RA showed a mirror-image pattern: the primary point estimate was protective but nonsignificant; weighted median was nominally protective; and heterogeneity and one radial outlier were present. The cis-only IL-1RA estimate did not confirm protection. Because IL-1RA is an endogenous antagonist and therapeutic analogues modify IL-1 signaling, a true protective effect would be biologically plausible. Nevertheless, plausibility cannot substitute for a stable genetic estimate. The combination of small k, trans effects, heterogeneity, and discordant estimators is more appropriately labeled a prioritization signal for replication.

The paired IL-1β and IL-1RA patterns could motivate a future pathway-level study using independent cis instruments for ligand, receptor, antagonist, and inflammasome components. Such a study should use dense regional summary statistics, conditional signals, ancestry-matched LD, and colocalization. It should also test audiometric phenotypes and clearly separate chronic presbycusis, acute sudden loss, autoimmune inner-ear disease, and noise-induced loss. Until those

data exist, the present analysis supports uncertainty rather than an IL-1 therapeutic recommendation.

Clinical and Translational Implications

The findings have three practical implications. First, circulating CRP and selected cytokines should not be presented to patients as proven causes of SNHL on the basis of cross-sectional associations. CRP may remain useful for general cardiovascular or inflammatory risk assessment, but this study provides no genetic support for using CRP reduction specifically to prevent register-defined SNHL. Second, corticosteroid effectiveness for sudden idiopathic SNHL is not tested by this MR study. Acute treatment modifies immune signaling over hours or days after a specific clinical event, whereas the genetic estimand represents lifelong average differences in circulating concentration across a heterogeneous population. Treatment decisions must remain based on syndrome-specific randomized and comparative evidence.[14,15] Third, null or unstable circulating-marker MR can refine target selection by redirecting attention toward tissue-relevant immune mechanisms, vascular integrity, oxidative stress, and gene-environment interactions.

The results do not argue against healthy behaviors that reduce systemic inflammation. Smoking cessation, noise protection, diabetes control, blood-pressure management, and physical activity have multiple established benefits and may influence hearing through pathways not captured by a single biomarker. MR evaluates a defined molecular proxy, not the full effect of a complex lifestyle intervention. Similarly, corticosteroids and other anti-inflammatory drugs have pharmacologic actions, doses, timing, tissue penetration, and patient selection that differ from germline proxies; a selected acute subgroup could benefit even when population MR is compatible with the null.

Strengths

This study has several strengths. It used an outcome resource with 48,388 register-defined SNHL cases, substantially larger than many earlier hearing MR analyses. It separated broad SNHL from sudden idiopathic hearing loss rather than merging etiologically different outcomes. Exposure instruments came from large contemporary GWASs, including CRP data from more than half a million participants and a multi-platform cytokine meta-GWAS published in 2025. Published lead loci were independently audited against Finnish LD, and all retained instruments were genome-wide significant, common, and strong by the F-statistic criterion.

The harmonization process preserved genome-build provenance, matched by rsID and allele strings, documented missing variants, and excluded ambiguous palindromes. An independent Finnish LD audit changed the CRP primary set. The analysis retained a full audit trail from source accession through pruning and final estimate. Random-effects IVW and corrected MR-Egger prevented underdispersion from narrowing confidence intervals. Weighted median, weighted mode, MR-RAPS, validated RadialMR, Steiger directionality, source-assay filters, leave-one-out, and cis-only analyses were interpreted as complementary diagnostics. The manuscript preserves the primary results and does not promote the most significant estimator or an outcome-defined deletion analysis.

Limitations

Several limitations constrain interpretation. The first is instrument and assay biology. Most cytokine instruments were trans-pQTLs, which are prone to horizontal pleiotropy and may represent assay binding, epitope accessibility, clearance, cell composition, or upstream networks. Fourteen of 35 harmonized cytokine instruments had source heterogeneity $p < 0.05$ and nine had discordant observed cohort directions. Filtering reduced but did not resolve outcome heterogeneity and sometimes left too few variants to estimate an exposure. MR-Egger intercept tests were null, but they have low power with small sets and do not detect all pleiotropy. Cis-only estimates were based on single lead variants and lacked dense-regional colocalization, so they cannot distinguish a shared causal variant from linkage disequilibrium.

Second, the number of cytokine instruments was small. TNF-α had one variant, and IL-6 and IL-10 had two. Weighted median and MR-Egger are not reliable pleiotropy solutions when k is very small. Power calculations indicated that moderate effects could remain undetected for these exposures. The null findings are strongest for CRP and for more strongly instrumented cytokines; they are less definitive for TNF-α, IL-6, and IL-10.

Third, the source cytokine meta-GWAS included up to 8,293 Finnish YFS and FINRISK participants. This represents 11.1%-21.3% of the exposure sample depending on cytokine, but it is only a conservative upper bound on possible contribution, not actual overlap with FinnGen. Exact shared-participant counts were unavailable. Sample overlap can bias two-sample MR toward a confounded observational association, particularly for weak instruments. Individual F statistics were strong, but aggregate instrument strength was modest for some cytokines; independent non-Finnish replication remains preferable.

Fourth, FinnGen is a population isolate with distinctive allele frequencies, linkage disequilibrium, healthcare registers, and biobank recruitment. Genetic effects and diagnosis capture may not generalize to other ancestries or health systems. Hospital-based recruitment and age distribution can enrich disease endpoints but also influence selection. The broad SNHL code does not provide hearing thresholds, frequencies, laterality, severity, age at onset, noise dose, medication exposure, or etiology. Misclassification generally reduces power and can blur mechanism-specific effects.

Fifth, genetic exposures represent lifelong average differences and may not model short, high-amplitude inflammatory episodes. Nonlinear effects, developmental windows, interactions with noise or infection, and threshold responses are not identifiable from summary-data linear MR. The estimates also cannot distinguish peripheral blood concentration from local cochlear production. Tissue-specific pQTL resources for the human inner ear remain limited.

Sixth, 22 of 301 unique rsIDs were unavailable in FinnGen, four palindromic exposure rows were excluded, and three additional harmonized CRP variants were pruned after Finnish LD auditing. No proxies were used. Retained-set R^2 was recalculated, but the resulting power remains approximate. Ensembl returned explicit LD values for only six of 236 queried pairs; absence of a record was not proof of $r^2 = 0$. Finally, we did not conduct multivariable MR for adiposity, smoking, glycemia, lipids, or blood pressure. Such analyses could help separate inflammatory pathways from cardiometabolic pleiotropy, but they require compatible instruments, exposure covariance, and additional assumptions; they are extensions rather than repairs for invalid univariable instruments.

Future Research

The next phase should replicate these results in the Million Veteran Program clinical SNHL GWAS and in cohorts with objective pure-tone audiometry. Because the MVP cohort is predominantly male and has substantial military noise exposure, replication should be stratified or complemented by population-based samples. Cross-ancestry analyses can test transportability and exploit different LD patterns while maintaining ancestry-matched instruments and references.

Molecular follow-up should prioritize cis-pQTLs for cytokine genes and receptors, use conditional signals, and require colocalization before target-level inference.[25] When a region contains multiple causal variants, SuSiE-based colocalization or other multi-signal approaches are preferable to a single-causal-variant model. Integration with eQTLs from vascular, immune, neuronal, and inner-ear-relevant tissues could clarify whether plasma pQTLs reflect the compartment that matters for hearing.

Phenotype refinement is equally important. Age-related SNHL, noise-induced loss, autoimmune inner-ear disease, ototoxicity, congenital infection, and sudden idiopathic loss should be analyzed separately, then compared. Time-to-event GWASs and age-at-onset data may be more informative than prevalent case-control coding. Gene-environment MR or factorial designs could test whether inflammatory pathways modify vulnerability to acoustic trauma, diabetes, or smoking. Finally, randomized trials of anti-inflammatory strategies should use biological target engagement and audiometric endpoints; MR can prioritize mechanisms but cannot replace clinical experimentation.

5. Conclusion

Using contemporary CRP and cytokine GWASs and FinnGen R13, the estimates were compatible with no material effect of lifelong genetically proxied circulating CRP on register-defined SNHL. No selected cytokine survived FDR correction, but those null estimates are less definitive because instrument sets were small, heterogeneous, mostly trans acting, and partly sensitive to source-assay filtering. The results do not determine whether local cochlear inflammation contributes to disease, whether short acute inflammatory episodes matter, or whether corticosteroids benefit sudden SNHL. Claims about specific cytokine targets should await independent replication, audiometrically defined outcomes, tissue-relevant cis instruments, and colocalization.

Declarations

Ethics Approval and Consent to Participate

Only public, aggregate, de-identified GWAS summary statistics were analyzed. No new participant recruitment or individual-level data access occurred. Original studies obtained their respective ethics approvals and participant consent. No additional approval was required for this secondary analysis of publicly available, de-identified summary data.

Consent for Publication

Not applicable. The manuscript contains no individual participant data, images, or case descriptions.

Availability of Data and Materials

FinnGen release 13 summary statistics and endpoint metadata are publicly available through the FinnGen results portal. The primary outcome code is H8_HL_SEN_NAS and the secondary code is H8_HL_IDIOP. CRP summary statistics are available through the NHGRI-EBI GWAS Catalog under GCST90029070. Cytokine summary statistics are available under GCST90428399-GCST90428438; the eight accessions used here are reported in Table 1. The source studies and their supplementary lead-variant tables are cited in references 18 and 19.

Competing Interests

The authors declare no competing interests.

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Author Contributions

All authors contributed to study conceptualization, methodology, interpretation, manuscript drafting, and critical revision, and approved the final manuscript.

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