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Review Article

Biomarkers of Subjective Tinnitus Presence and Clinical Burden: A Systematic Review

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ABSTRACT

Despite being common and clinically burdensome, subjective tinnitus is diagnosed and characterised primarily through subjective reporting. Objective biomarkers could transform tinnitus care by enabling reproducible identification, stratification, and monitoring, but their clinical utility for detecting tinnitus and quantifying its severity remains unclear. We conducted a PRISMA-guided systematic review of tinnitus biomarkers, critically evaluating their clinical and diagnostic relevance, methodological quality, and readiness for clinical translation. PubMed, Scopus, and Web of Science were searched for human studies reporting objective measures linked to tinnitus presence, severity, or diagnostic accuracy. Risk of bias was assessed using Joanna Briggs Institute tools, and results were synthesised narratively due to heterogeneity. We included 69 studies spanning neurophysiological, neuroimaging, cognitive-behavioural, and molecular approaches. Although many studies reported tinnitus-related group differences, convergence across studies was limited. Common limitations included small cohorts, inconsistent phenotyping, heterogenous methodologies, and inadequate adjustment for major confounders, especially hearing loss. Cognitive-behavioural paradigms, particularly attention-modulated cortical responses, showed the strongest and most consistent association with tinnitus burden and the greatest translational potential. Molecular biomarkers, notably metabolomics, showed early promise but currently lack replication and external validation. Neurophysiological and neuroimaging markers provided mechanistic insights but were constrained by reproducibility and feasibility for routine clinical use. In summary, tinnitus biomarkers are advancing, but no single measure currently supports stand-alone clinical diagnosis. Progress will require harmonised methods, large well-characterised samples, severity-stratified designs, and validated multimodal panels aligned to mechanistic models.

Systematic review registration: PROSPERO (CRD420261449639).

INTRODUCTION

Subjective tinnitus, the perception of sound in the absence of an external source, affects approximately 10–15% of adults worldwide, with 1–2% experiencing severe and persistent symptoms that substantially impair sleep, concentration, emotional well-being, and overall quality of life (De Ridder et al., 2021; Jarach et al., 2022; Lugo et al., 2019). Despite its prevalence and burden, tinnitus remains challenging to diagnose objectively. Clinical assessment continues to rely almost exclusively on subjective self-report, psychoacoustic matching, and patient-reported outcome measures, which lack biological specificity and offer limited insight into underlying neural mechanisms (Gopal et al., 2017). The absence of objective assessment tools has, in turn, constrained progress in developing targeted interventions and evaluating treatment response.

Over the past decade, considerable effort has been directed toward identifying physiological and biological markers that could provide an objective basis for characterising tinnitus presence and its clinical burden.. Neurophysiological measures such as otoacoustic emissions, auditory-evoked potentials, cortical auditory evoked potentials, and indices of brain signal variability have been proposed as indicators of altered auditory pathway activity associated with tinnitus (Cardon et al.,

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2022; Gopal et al., 2017). Neuroimaging work has similarly demonstrated atypical blood-oxygen-level–dependent responses, altered regional cerebral blood flow, and disrupted resting-state functional connectivity within auditory and non-auditory brain networks (Gopal et al., 2017). Cognitive and behavioural studies further highlight the importance of attentional modulation and higher-order perceptual processes, with attention-dependent neural responses emerging as a promising avenue for distinguishing tinnitus from non-tinnitus listeners (Cardon et al., 2022; Richardson et al., 2024). Molecular and biochemical investigations have examined circulating inflammatory proteins and plasma metabolomic signatures, yielding largely inconclusive findings for inflammatory markers (Cederroth et al., 2023) but more encouraging, though still preliminary, associations for metabolomic profiles (Zeleznik et al., 2023). Theoretical frameworks such as the Sensory Precision Model provide additional mechanistic grounding, linking altered prediction-error processing and neural gain modulation to tinnitus generation (Yukhnovich et al., 2023). An overview of the principal biomarker domains reviewed in this paper, spanning peripheral, central, cognitive–behavioural, and molecular approaches, is presented in Figure 1.

Despite rapid growth in candidate diagnostic biomarker research, the field remains at a translational bottleneck: most proposed measures are reported as group-level differences or mechanistic correlates rather than as clinically actionable markers that can reliably identify tinnitus at the individual level (De Ridder et al., 2021; Elgoyhen et al., 2015). This distinction is critical because tinnitus diagnosis still depends primarily on subjective report and psychoacoustic characterisation, approaches that lack biological specificity and offer limited leverage for stratifying patients or evaluating treatment effects in a standardised way (Langguth et al., 2013). Moreover, tinnitus is highly heterogeneous in severity, duration, and comorbidity profile (Cederroth et al., 2019). Adding to this, many candidate diagnostic biomarkers are sensitive to confounds that commonly co-occur with tinnitus - particularly hearing loss, hyperacusis, attention, mood, and medication status - making it difficult to determine what is tinnitus-specific versus what reflects broader auditory or neurocognitive dysfunction (Clarke et al., 2020; Gopal et al., 2017). At the same time, emerging approaches (e.g., cortical responses, metabolomic signatures, and data-driven classification methods) have increased the diversity of proposed diagnostic biomarkers and raised new questions about reproducibility, feasibility, and diagnostic

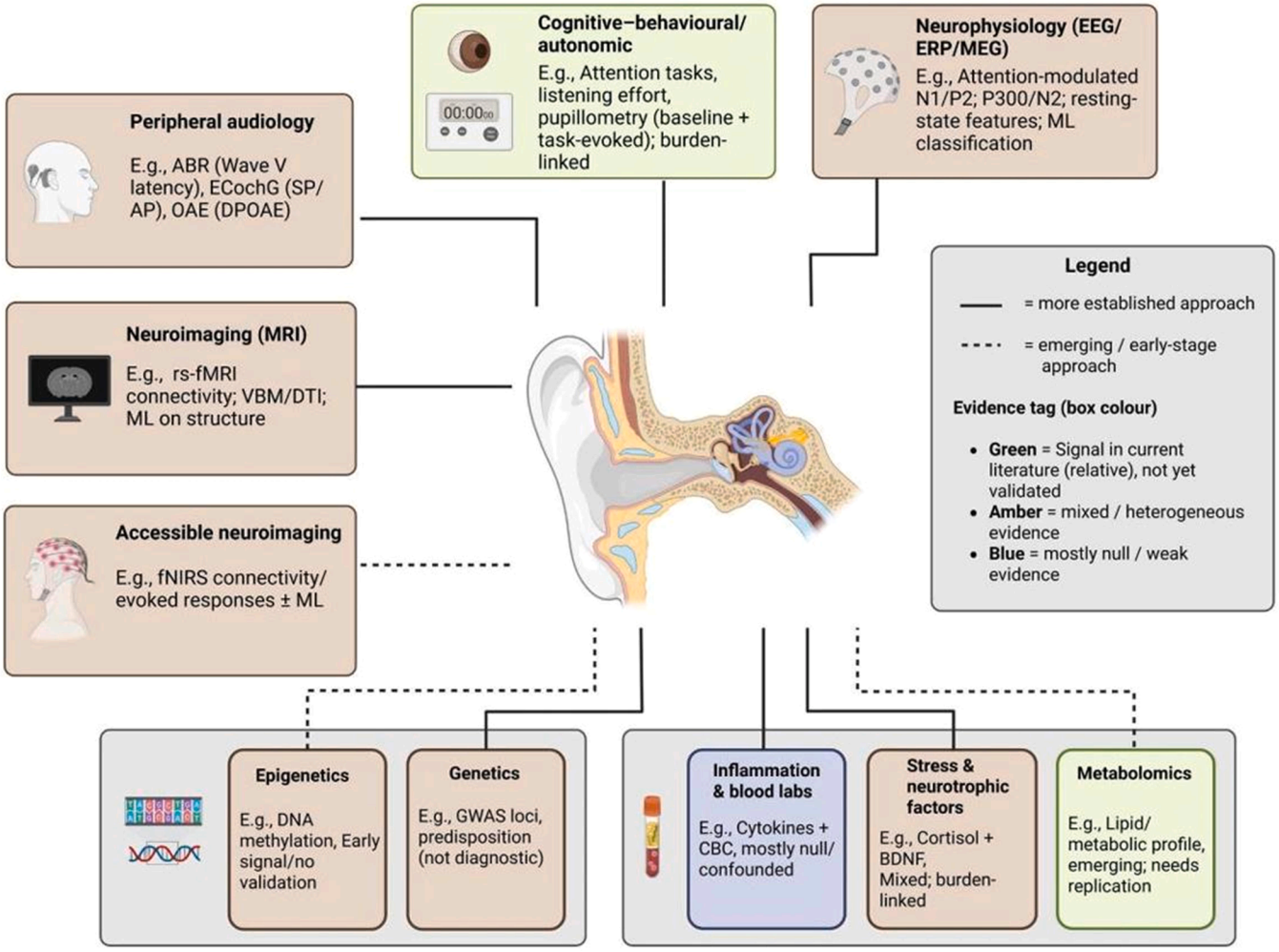

Figure 1. Overview of objective tinnitus biomarker approaches across peripheral, central, cognitive–behavioural, and molecular domains. Boxes summarise example measures within each modality; connector line style indicates approach maturity (solid = more established; dotted = emerging/early-stage). Box colour denotes an evidence tag derived from the narrative synthesis in this systematic review (green = signal in current literature, not yet validated; amber = mixed/ heterogeneous evidence; blue = mostly null/weak evidence). *Abbreviations:* ABR = auditory brainstem response; BDNF = brain-derived neurotrophic factor; CBC = complete blood count; DPOAE = distortion product otoacoustic emissions; DTI = diffusion tensor imaging; ECochG = electrocochleography; EEG = electroencephalography; ERP = event-related potential; fMRI = functional magnetic resonance imaging; fNIRS = functional near-infrared spectroscopy; GWAS = genome-wide association study; MEG = magnetoencephalography; ML = machine learning; rs-fMRI = resting-state fMRI; SP/AP = summating potential/action potential; VBM = voxel-based morphometry. Figure created with BioRender.com.

performance across domains (Vanneste and De Ridder, 2016; Woo et al., 2017).

A systematic, cross-modal synthesis is therefore needed to appraise the strength and limitations of the evidence, clarify which biomarkers show genuine promise for characterising tinnitus presence or severity (versus correlational relevance), and identify methodological priorities required to move from exploratory findings toward an objective diagnostic framework for tinnitus. Using a PRISMA-guided approach, this review evaluates the methodological quality of included studies, summarises the diagnostic performance of candidate biomarkers, identifies recurring challenges in biomarker research, and highlights areas of emerging convergence. Importantly, this review specifically focuses on biomarkers with potential utility for identifying tinnitus presence or severity, distinguishing them from neural correlates of tinnitus. The overarching aim is to clarify the current state of biomarker development and to inform future efforts toward establishing a reliable, objective assessment framework for subjective tinnitus.

METHODS

Review Framework

We conducted a systematic review with narrative synthesis, adopting a hybrid design to accommodate the methodological heterogeneity of tinnitus biomarker research. The review objectives, eligibility criteria, search strategy, screening procedures, and data extraction plan were defined a priori. The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD420261449639. All stages adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (Page et al., 2021); the completed PRISMA 2020 Checklist is provided in the Supplementary Material.

Eligibility Criteria

Studies were eligible for inclusion if they investigated any putative diagnostic biomarker for tinnitus in human participants. Subjective tinnitus of all clinical forms (acute, chronic, or persistent) was considered. Clinical objective tinnitus (i.e., objective somatosounds, such as vascular bruits or muscular myoclonus) was excluded. . No age restrictions were applied. Animal studies, narrative reviews, meta-analyses, conference abstracts without full texts, editorials, commentaries, and letters were excluded.

Eligible biomarkers spanned neurophysiological (e.g., EEG, MEG, auditory-evoked potentials), neuroimaging (e.g., fMRI, VBM, DTI), audiological (e.g., hearing thresholds, psychoacoustic measures), molecular and biochemical markers (e.g., inflammatory proteins, stress-related measures, metabolomics), and cognitive-behavioural indices. Studies with or without comparator groups were included; where present, comparators typically consisted of healthy controls, clinical controls, or tinnitus subgroups distinguished by severity or duration.

To be eligible, studies were required to report at least one of the following: associations between the biomarker and tinnitus presence or severity, biomarker-symptom correlations, or diagnostic performance metrics such as sensitivity, specificity, or ROC parameters. Observational designs including cross-sectional, cohort, and case–control studies were included. Only English-language publications were considered, and no date limits were imposed.

Search Strategy

A comprehensive search of PubMed, Scopus, and Web of Science was conducted from database inception to 3 December 2025. Search terms combined descriptors of tinnitus with biomarker-related terminology and were restricted to human studies and English-language publications where possible. Database-specific filters were applied to exclude review articles.

To ensure the reproducibility of this review, the exact, complete search syntax utilised for each database is provided below:

PubMed / MEDLINE

The PubMed search syntax was constructed as follows:

("Tinnitus"[Mesh] OR tinnitus[tiab] OR "ringing in the ears"[tiab] OR "phantom sound"[tiab]) AND ("Biomarkers"[Mesh] OR biomarker*[tiab] OR "objective marker*"[tiab] OR "objective measure*"[tiab] OR "physiological marker*"[tiab] OR "biological marker*"[tiab] OR "diagnostic marker*"[tiab] OR "inflammatory marker*"[tiab] OR "plasma marker*"[tiab] OR "serum marker*"[tiab] OR "blood marker*"[tiab] OR "peripheral marker*"[tiab] OR "metabolic marker*"[tiab] OR "biochemical marker*"[tiab] OR "acoustic marker*"[tiab] OR "clinical marker*"[tiab] OR "prognostic marker*"[tiab]) AND (human*[tiab] OR patient*[tiab] OR participant*[tiab]) NOT (Review[pt] OR "systematic review"[pt] OR meta-analysis[pt] OR "objective tinnitus"[tiab] OR "pulsatile tinnitus"[tiab])

This PubMed search initially yielded 236 results, which was refined to 224 after applying English-language limits, and ultimately to 159 after restricting to human studies.

Scopus

The Scopus search syntax was constructed as follows:

TITLE-ABS-KEY(tinnitus OR "ringing in the ears" OR "phantom sound") AND TITLE-ABS-KEY(biomarker* OR "objective marker*" OR "objective measure*" OR "physiological marker*" OR "biological marker*" OR "diagnostic marker*" OR "inflammatory marker*" OR "plasma marker*" OR "serum marker*" OR "blood marker*" OR "peripheral marker*" OR "metabolic marker*" OR "biochemical marker*" OR "acoustic marker*" OR "clinical marker*" OR "prognostic marker*") AND TITLE-ABS-KEY(human* OR patient* OR participant*) AND NOT (TITLE-ABS-KEY("objective tinnitus" OR "pulsatile tinnitus" OR "systematic review" OR "meta-analysis") OR DOCTYPE(re))

This Scopus search initially yielded 500 results, which was refined to 493 after applying English-language limits, to 468 when limited to journal sources, and ultimately to 450 after restricting to peer-reviewed articles.

Web of Science

The Web of Science search syntax was constructed as follows:

TS=((tinnitus OR "ringing in the ears" OR "phantom sound") AND (biomarker* OR "objective marker*" OR "objective measure*" OR "physiological marker*" OR "biological marker*" OR "diagnostic marker*" OR "inflammatory marker*" OR "plasma marker*" OR "serum marker*" OR "blood marker*" OR "peripheral marker*" OR "metabolic marker*" OR "biochemical marker*" OR "acoustic marker*" OR "clinical marker*" OR "prognostic marker*") AND (human* OR patient* OR participant*)) NOT (TS=("objective tinnitus" OR "pulsatile tinnitus" OR "systematic review" OR "meta-analysis") OR DT=(REVIEW))

This Web of Science search yielded 192 results.

The combined search strategy yielded a total of 801 records across all databases. Detailed screening and inclusion counts are reported in the Results section of this review and summarised in the PRISMA flow diagram (Figure 2). Reference lists of included studies and relevant review articles were also manually screened to identify additional eligible records.

Study Selection

All search results were imported into EndNote (Clarivate Analytics) for deduplication and screening. Screening proceeded in two stages: an initial title and abstract review followed by full-text assessment. Initial screening was conducted via a primary-reviewer model, with secondary reviewers participating in verification and consensus checks, and a senior author resolving final eligibility queries. Reasons for full-text

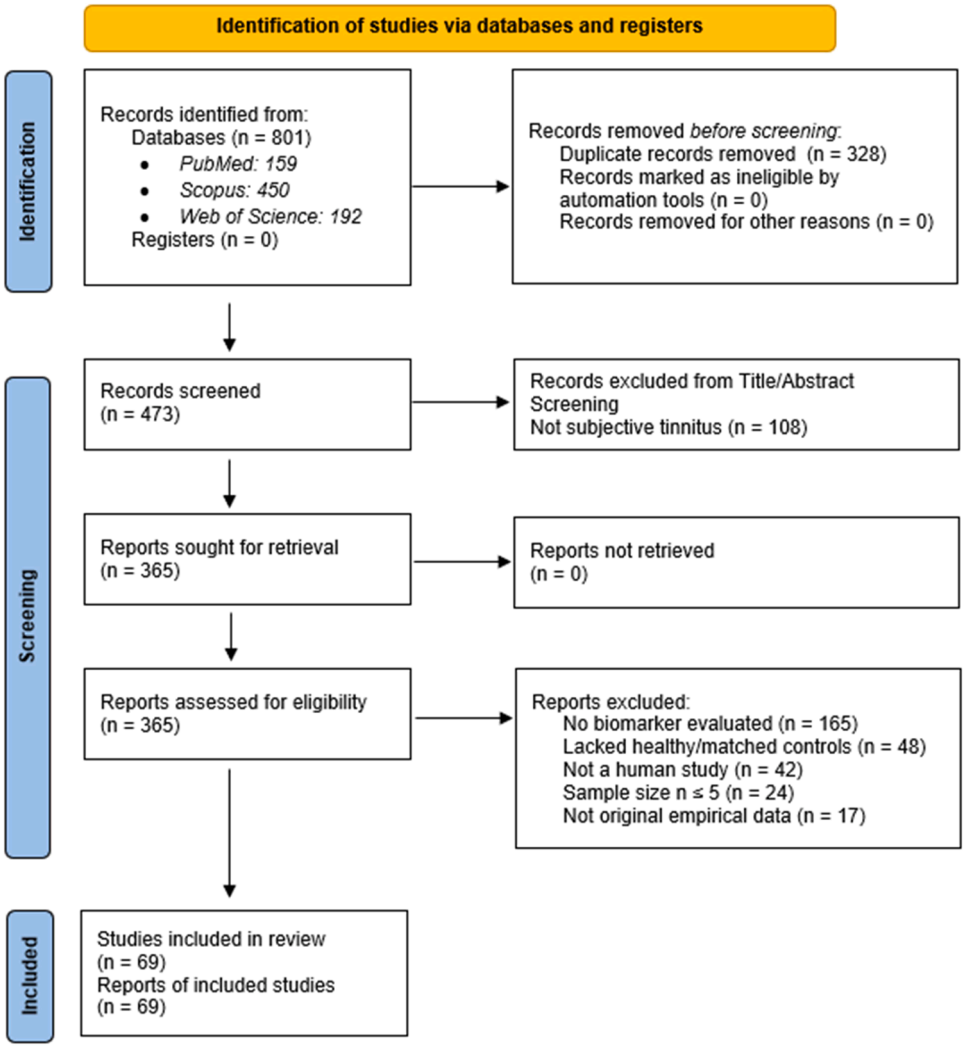

Figure 2. PRISMA flow diagram summarising the literature search and study selection process. PRISMA flow diagram summarising the literature search and study selection process. A total of 801 records were identified through database searches, with 473 records screened after the removal of duplicates. Following full-text assessment, 69 studies met eligibility criteria and were included in the review.

exclusion were documented in accordance with PRISMA 2020 recommendations.

Data Extraction

Data extraction was structured around a primary-led workflow using a pre-piloted extraction template, supported by secondary verification and consensus checks by co-authors to ensure overall consistency. Extracted information included study design; participant characteristics; tinnitus features such as duration, severity, or subtype; biomarker modality and measurement methodology; primary results relating to diagnostic relevance; and statistical indicators such as effect sizes, correlations, or diagnostic accuracy metrics. To ensure consistency, extracted data were cross-checked during synthesis and any uncertainties were resolved through re-examination of the source articles and consensus with a senior author.

Risk of Bias Assessment

Risk of bias was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Tools appropriate to each study design (Hilton et al., 2024). Each study was evaluated for sampling and selection methods, measurement validity and reliability, control of confounding variables, analytical transparency, and overall reporting quality. Assessments were conducted by a single reviewer and cross-checked against original study reports to ensure consistency of judgements. Individual study checklists, grouped by study design, were tabulated to determine item-by-item risk of bias (Supplementary Tables 1-3). Domain-level risk profiles (low, high, or unclear risk) were visually aggregated to synthesise overall study quality (Supplementary Figures 4-6).

Data Synthesis

Given the substantial heterogeneity in biomarker modalities, study designs, outcome measures, and analytical approaches, findings were synthesised narratively. Studies were grouped according to biomarker domain, and results were compared with attention to methodological strengths, limitations, and areas of convergence or divergence across the evidence base. Quantitative meta-analysis was not undertaken due to heterogeneity in study design, biomarker definitions, and outcome reporting, which precluded meaningful statistical pooling.

RESULTS

Study Selection

The systematic search identified a total of 801 records across databases, including 159 from PubMed, 450 from Scopus, and 192 from Web of Science. Following deduplication, 328 duplicate records were removed, leaving 473 unique records for screening.

Title and abstract screening excluded 108 records that did not evaluate subjective tinnitus, leaving 365 records sought for full-text retrieval. All 365 reports were successfully retrieved and assessed for eligibility. Following full-text assessment, 296 reports were excluded for specific reasons: 165 did not evaluate a biomarker, 48 lacked healthy or matched controls, 42 were not human studies, 24 had a sample size of $n \leq 5$, and 17 did not present original empirical data. Ultimately, 69 studies met the predefined inclusion criteria and were included in the final qualitative synthesis. The study selection process is summarised in the PRISMA flow diagram (Figure 2).

Study Characteristics

The included studies demonstrated substantial heterogeneity in methodology, biomarker modality, and sample size (Table 1). Electrophysiological investigations, particularly those examining auditory evoked potentials and cortical auditory responses, typically relied on relatively small cohorts, whereas molecular and epidemiological studies were generally larger, including population-based designs with matched tinnitus and control groups (Altıntaş et al., 2023; Cardon et al., 2022; Cederroth et al., 2023; Richardson et al., 2024).

Neuroimaging studies most commonly employed functional MRI paradigms in adults with chronic tinnitus and frequently matched groups on demographic variables and audiometric thresholds (Gopal et al., 2017). Definitions of tinnitus varied across studies, although most focused on chronic or persistent symptoms. Across modalities, many investigations attempted to account for confounders such as age, sex, smoking status, and hearing loss, particularly within molecular and epidemiological designs (Cederroth et al., 2023). Overall, the literature spanned electrophysiological, neuroimaging, behavioural, psychoacoustic, and biochemical approaches.

Quality and Risk of Bias Assessment

Risk-of-bias assessment revealed substantial variation in methodological quality across studies. Individual per-study JBI scores are compiled in Supplementary Tables 2-4, and aggregated domain-level risk profiles are illustrated in Supplementary Figures 4-6.

For the 35 case-control designs (Supplementary Table 2; Supplementary Figure 4), overall quality was moderate-to-high, with 22 studies scoring $\geq 9/10$. However, a notable domain-level vulnerability was a lack of explicit reporting of matching strategies between cohorts (Q2: ~50% unclear or high risk) and inconsistent reporting of control strategies for potential confounding variables (Q6 & Q7: ~20% unclear or high risk). Among the 30 analytical cross-sectional studies (Supplementary Table 3; Supplementary Figure 5), overall reporting quality was high, with 27 studies scoring $\geq 7/8$. Confounder identification and management remained the primary domain of concern, with ~35% of studies failing to explicitly state strategies to deal with confounding factors (Q6). The four quasi-experimental studies (Supplementary Table 4; Supplementary Figure 6) demonstrated moderate-to-high quality (scores ranging from 7/9 to 8/9), though they were primarily limited by the inherent lack of concurrent control groups (Q4) and incomplete details regarding statistical assumptions or follow-up assessments (Q9).

Methodological heterogeneity was particularly pronounced in sample sizing and hardware configuration. Small sample sizes were a recurrent limitation in electrophysiological and neuroimaging research, constraining statistical power (Cardon et al., 2022; Richardson et al., 2024). Heterogeneity in experimental paradigms, signal preprocessing, analytic pipelines, and participant selection contributed to inconsistency in reported findings, particularly within auditory evoked potential and functional MRI studies.

Several molecular investigations were limited by incomplete reporting or control of medication use, lifestyle factors, or comorbidities, which may influence circulating biomarker levels (Cederroth et al., 2023). Neuroimaging studies additionally varied in scanner hardware, acquisition protocols, and post-processing workflows. At least one electrophysiological study reported no significant group differences across multiple auditory measures, including auditory brainstem responses and event-related potentials (Altıntaş et al., 2023).

Neurophysiological and Audiological Biomarkers

Neurophysiological and audiological biomarkers represent the largest and most heterogeneous body of tinnitus research, spanning peripheral auditory function, auditory brainstem responses, cortical electrophysiology, and haemodynamic imaging. At the brainstem level, altered auditory brainstem responses (most consistently increased Wave V latency) have been reported in individuals with chronic, persistent tinnitus, defined specifically in some cohorts to distinguish it from occasional tinnitus, after controlling for hearing thresholds, suggesting central auditory alterations beyond peripheral hearing loss (Edvall et al., 2022; Gopal et al., 2017). Cortical auditory evoked potential studies have demonstrated reduced P300 amplitudes and increased neural signal variability in tinnitus participants relative to controls, findings commonly interpreted as reflecting altered attentional or cognitive processing rather than primary sensory deficits (Cardon et al., 2022).

Beyond conventional evoked responses, advanced EEG analyses have explored resting-state and task-based features as candidate biomarkers. Nonlinear dynamic features derived from resting-state EEG have demonstrated heterogeneous but potentially discriminative patterns between tinnitus and control groups, suggesting that higher-order temporal dynamics may encode diagnostically relevant information not captured by traditional spectral measures (Naghdabadi et al., 2024). Task-based ERP studies have identified P2 latency and P2–N2 amplitude measures associated with tinnitus severity and responsiveness to intervention, indicating greater sensitivity to symptom burden and treatment-related plasticity than to tinnitus presence alone (Caldwell et al., 2024). Similarly, sleep electrophysiology has been leveraged to index thalamocortical loop integrity; Park et al. (2026) conducted an exploratory analysis of sleep spindles in unilaterally deaf adults, noting a dual trend of lower spindle density and higher amplitude in those with tinnitus compared to controls, suggesting a possible avenue for probing auditory thalamic reticular nucleus (TRN) dysfunction in larger cohorts.

Recent studies have increasingly combined electrophysiological features with machine-learning approaches. Auditory oddball paradigms have revealed reduced P3 amplitudes and delayed N2 latencies in chronic tinnitus, alongside altered source-level activity. When combined within support vector machine classifiers, these features achieved an internally validated (5-fold cross-validation) classification accuracy of 85.42%, with a sensitivity of 87.50% and a specificity of 83.33% in distinguishing tinnitus patients from healthy controls (J. Kim et al., 2025). EEG connectivity features have further demonstrated objective classification of tinnitus laterality; specifically, support vector machine (SVM) and multi-layer perceptron (MLP) models reached average accuracies of 99.42% and 99.10%, respectively, utilising internal leave-one-out and 10-fold cross-validation (Li et al., 2022). Furthermore, representation-learning approaches applied to resting-state EEG have demonstrated improved cross-subject generalisability; for example, a multi-band EEG contrastive representation learning framework achieved a cross-subject (internal cross-validation) classification accuracy of 90.34% (CD Wang et al., 2023). Similarly, Allgaier et al. (2021) demonstrated the utility of an end-to-end deep learning

Table 1

Study characteristics of objective and physiological biomarker studies in subjective tinnitus. Comprehensive overview of objective and physiological biomarker studies in subjective tinnitus, spanning electrophysiological, neuroimaging, audiological, molecular, and behavioural modalities. The table summarises study design, participant numbers (tinnitus and control groups), modality (e.g., EEG, fMRI, blood-based, audiological), outcome measures, and specific neurophysiological or biomarker components assessed.

Titles	First Author (Year)	Journal	Participants (Tinnitus)	Participants (Control)	Modality	Outcome Measurement	Component(s)
A Correlational Study of Tinnitus Handicap Inventory (THI) Scores and Otoacoustic Emissions (OAE) Among Tinnitus Patients	Aishwarya, N. (2025)	Indian Journal of Otolaryngology and Head and Neck Surgery	52	0	Audiological (OAE)	OAE result (Pass vs Refer) correlated with THI score	OHC dysfunction (binary OAE outcome); THI severity association
Deep Learning End-to-End Approach for the Prediction of Tinnitus based on EEG Data	Allgaier, J. (2021)	IEEE Engineering in Medicine and Biology	29	13	EEG	Machine learning classification accuracy (tinnitus vs. control) based on end-to-end convolutional neural networks processing raw resting-state EEG.	Resting-state EEG (62 channels), noise reduction performance (Autoreject true/false), down-sampling vs. up-sampling balancing approaches, and classification test accuracy (75.6%).
An Exploratory Investigation of Pupillometry As a Measure of Tinnitus Intrusiveness on a Test of Auditory Short-Term Memory	Barrett, DJK. (2022)	Ear and Hearing	12	12	Pupillometry	Baseline pupil diameter changes; TEPR amplitude; correlation with THI	Baseline dilation; maximum TEPR; tinnitus severity (THI)
Psychological Treatment Effects Unrelated to Hair-Cortisol and Hair-BDNF Levels in Chronic Tinnitus	Basso, L. (2022)	Frontiers in Psychiatry	80	0	Hair-Cortisol	Tinnitus Questionnaire (TQ), Perceived Stress Questionnaire (PSQ-20), Hair cortisol concentration, Hair BDNF concentration, Linear mixed-effects models, Cross-lagged panel model	Hair cortisol levels, Hair BDNF levels, TQ total score, PSQ-20 total score, Compact multimodal tinnitus-specific cognitive behavioral therapy
Effects of serum zinc level on tinnitus	Berkiten, G. (2015)	American Journal of Otolaryngology	100	0	Blood	Tinnitus presence (± severity and/or pre-post treatment comparison)	Serum zinc concentration
DNA Methylation Patterns Associated with Tinnitus in Young Adults-A Pilot Study	Bhatt, I.S. (2024)	Journal of the Association for Research in Otolaryngology	24	24	Epigenetic	Tinnitus presence (case-control differential methylation analysis)	Differential CpG sites; differentially methylated genes; pathway enrichment signatures
Limited Link of Common Blood Parameters with Tinnitus	Bulla, J. (2023)	Journal of Clinical Medicine	200	0	Blood	Between-group comparison of common blood parameters in tinnitus vs controls	Hemoglobin, hematocrit, RBC, WBC, platelet count (routine laboratory indices)
Electrophysiological auditory measures to identify potential cortical markers of tinnitus	Caldwell, J. (2024)	Brain Research	10	10	EEG	Peak amplitude, latency, MMN AUC, GFP, questionnaire correlations (THI, TRQ)	P1, N1, P2, N2, MMN, P300
Cortical auditory evoked potentials, brain signal variability and cognition as biomarkers to detect the presence of chronic tinnitus	Cardon, E. (2022)	Hearing Research	20	20	EEG	Tinnitus presence (case vs control classification)	P300 amplitude; source activity (temporal/insula/ parahippocampus); multiscale entropy; RBANS-H delayed memory
On the evidence of auditory evoked magnetic fields as an objective measure of tinnitus	Colding-Jørgensen, E. (1992)	Electroencephalography and Clinical Neurophysiology	14	14	MEG	Amplitude / latency of auditory evoked magnetic responses, source strength of N1 / P2 components, group differences	N1m, ± P2m, Auditory cortex source localisation
Cognitive speed as an objective measure of tinnitus	Das, S.K. (2012)	The Laryngoscope	92	0	Behavioural / Neurocognitive	Tinnitus severity (THI ± TFI); correlation and multivariate regression	BST z-score (auditory processing speed); Composite Psychiatric State
Does inflammation play a role in the pathophysiology of tinnitus	Demir, M. (2021)	Nigerian Journal of Clinical Practice	159	57	Blood	Tinnitus presence (case–control) with subgroup hearing comparisons	NLR; PLR; MPV
Listening effort and stress in tinnitus: a multidimensional approach	Giliberto, G. (2025)	Frontiers in Neuroscience	24	23	Multimodal psychophysiological assessment	Listening effort performance and physiological stress response in tinnitus vs controls	Salivary cortisol; heart rate; heart rate variability; reaction time/ accuracy

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Table 1 (*continued*)

Titles	First Author (Year)	Journal	Participants (Tinnitus)	Participants (Control)	Modality	Outcome Measurement	Component(s)
A comparison of reaction times to tinnitus and non-tinnitus frequencies	Goodwin, P.E. (1980)	Ear and Hearing	9	9	Behavioural	Reaction time (ms) to pure tones across 1–60 dB SL	Frequency-specific RT comparison (tinnitus vs non-tinnitus); RT–intensity function; loudness recruitment derivation
Potential audiological and MRI markers of tinnitus	Gopal, K.V (2017)	Journal of the American Academy of Audiology	10	10	MRI	Tinnitus vs control classification (LASSO model)	N1 amplitude growth; Frontal cortex BOLD activity to tinnitus-pitch tones
Various levels of plasma brain-derived neurotrophic factor in patients with tinnitus	Goto, F. (2012)	Neuroscience Letters	43	30	Plasma	Plasma BDNF levels; THI score; HADS score	BDNF concentration; tinnitus severity (THI); depression/anxiety (HADS)
Audiological biomarkers of tinnitus in an older Portuguese population	Haider, H.F. (2022)	Frontiers in Aging Neuroscience	92	30	Audiological/ Electrophysiological	Tinnitus presence (binary) and severity (THI-based); logistic regression; ROC/AUC	PTA; HF PTA; DPOAE amplitude (500-8000 Hz); ABR wave I amplitude; wave I latency; I-III interwave interval; V/I ratio
Biomarkers of Presbycusis and Tinnitus in a Portuguese Older Population	Haider, H.F. (2017)	Frontiers in Aging Neuroscience	24	54	Audiological/ Electrophysiological	Tinnitus presence (binary) and severity (THI); logistic regression; ROC/AUC	PTA; HF PTA; DPOAE amplitude (500-8000 Hz); ABR wave I amplitude; wave I latency; interpeak intervals (I-III, III-V, I-V); V/I ratio
Objective measurement of subjective tinnitus using the acoustic change complex	Han, J.H. (2017)	PLOS One	33 (ears)	63 (ears)	EEG	Normalised ACC amplitude (naACC); ROC AUC	N1-P2 (onset), N1′-P2′ (change response)
Corticostriatal functional connectivity of bothersome tinnitus in single-sided deafness	Henderson-Sabes, J. (2019)	Scientific Reports	15	15	fMRI	Functional connectivity strength; TFI total & subscale correlations	Caudate nucleus-auditory cortex connectivity (corticostriatal), caudate-non-auditory network connectivity
Evaluating psychoacoustic measures for establishing presence of tinnitus	Henry, J.A. (2013)	Journal of Rehabilitation Research and Development	80	87	Psychoacoustic	Presence vs absence of tinnitus (ROC-based diagnostic classification)	Low-frequency loudness match (dB SL); Median pitch match
The Cortisol Awakening Response: A Feasibility Study Investigating the Use of the Area Under the Curve With Respect to Increase as an Effective Objective Measure of Tinnitus Distress	Jackson, J.G. (2019)	American Journal of Audiology	20	10	Salivary cortisol	CAR (AUC, AUCi); tinnitus distress scores	Cortisol levels; AUCi; AUC
Machine Learning-Based Diagnosis of Chronic Subjective Tinnitus with Altered Cognitive Function: An Event-Related Potential Study	Kim, J. (2025)	Ear & Hearing	24	24	EEG	P3 amplitude; N2 latency; N2 source activity; classification accuracy (tinnitus vs HC); correlation with HADS	N2; P3; source activity (insula, temporal gyrus, fusiform, cuneus)
Resting state EEG reveals no reliable biomarkers of tinnitus laterality	Kim, S.J. (2025)	Scientific Reports	110	0	qEEG	Tinnitus laterality classification (4-group + binary); ML accuracy	Spectral power (delta-gamma); functional connectivity; hemispheric asymmetry indices; PTA-adjusted models
An IoT-enabled EEG headphones with customized music for chronic tinnitus assessment and symptom management	Lam, N.N.H. (2024)	Internet of Things	6	6	EEG	Resting-state and music-evoked EEG spectral features; classification accuracy; symptom change	Band power metrics; stimulation-induced changes; ML-derived EEG features; wearable acquisition metrics
Electrocochleography in Chronic Tinnitus: Correlations with Audiological Profiles and Psychological Distress	Lee, H.Y. (2024)	American Journal of Otolaryngology	256	0	ECochG	Association of SP/AP ratio with clinical and psychological phenotype in chronic tinnitus	SP/AP ratio; low-frequency PTA; LDL; DPOAE amplitude; BDI
Objective Recognition of Tinnitus Location Using Electroencephalography Connectivity Features	Li, Z. (2022)	Frontiers in Neuroscience	32	10	EEG	Classification of tinnitus laterality (ACC, SENS, SPEC, AUC)	Phase-based connectivity (PLI/ wPLI) across delta-gamma bands

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Table 1 (*continued*)

Titles	First Author (Year)	Journal	Participants (Tinnitus)	Participants (Control)	Modality	Outcome Measurement	Component(s)
Multi-tasking deep network for tinnitus classification and severity prediction from multimodal structural MR images	Lin, C.T. (2023)	Journal of Neural Engineering	183	196	sMRI	Tinnitus vs control classification (ACC, SENS, SPEC, PPV, NPV); TFI severity prediction (r^2)	Whole brain; Grey matter; White matter; CSF
Morphological Neuroimaging Biomarkers for Tinnitus: Evidence Obtained by Applying Machine Learning	Liu, Y. (2019)	Neural Plasticity	46	56	sMRI	Classification of tinnitus vs controls using structural brain features	Grey matter volume; cortical thickness; regional morphometric features
Exploring How Blood Cell Levels Influence Subjective Tinnitus: A Cross-Sectional Case-Control Study	Maihoub, S. (2025)	Audiology research	439	274	Molecular / Blood-based	Tinnitus presence (case-control); THI severity; laterality; onset/duration; intensity	WBC, RBC, haemoglobin (Hb), haematocrit (Hct), platelet count
Tinnitus and Cognition: Linked?	Majhi, S.K. (2019)	Indian Journal of Otolaryngology and Head Neck Surgery	55	51	EEG	P300 latency and amplitude; correlation with tinnitus severity and hearing loss	P300
Lateralized tinnitus studied with functional magnetic resonance imaging: Abnormal inferior colliculus activation	Melcher, J.R. (2000)	Journal of Neurophysiology	6	6	fMRI	Abnormal and lateralized inferior colliculus BOLD activation in tinnitus vs controls	Inferior colliculus BOLD signal; hemispheric asymmetry
Cross-sectional screening for inflammation in tinnitus with near-normal hearing	Mennink, L.M. (2024)	Hearing Research	50	50	Blood (inflammatory protein profiling)	Tinnitus presence (case-control comparison)	Multiplex inflammatory cytokine panel (no FDR-significant markers)
Association between atherogenic index of plasma and tinnitus: evidence from NHANES and the mediating role of hypertension	Miao, W. (2025)	Lipids in Health and Disease	2,464	0	Molecular / Blood-based	Self-reported tinnitus (binary) associated with AIP; multivariable logistic regression; mediation analysis	AIP (log10 TG/HDL-C); triglycerides; HDL-C; quartile-based dose-response; hypertension mediation
Predisposition to domain-wide maladaptive changes in predictive coding in auditory phantom perception	Mohan, A. (2022)	Neuroimage	10	10	EEG	Tinnitus vs control classification; correlation with loudness & distress	P300 amplitude; pre-stimulus theta; gamma activity; alpha activity; alpha & theta functional connectivity (auditory cortex, parahippocampus, dACC, PCC)
Hidden or subclinical cochleopathy in idiopathic subjective tinnitus: extended high frequency audiometry and otoacoustic emission	Morgan, A.E. (2022)	Hearing, Balance and Communication	27	20	Audiological/ Electrophysiological	Reduced Wave I amplitude and altered Wave I/V ratio in tinnitus vs controls	ABR Wave I amplitude (primary); Wave V amplitude; Wave I/V ratio; interpeak latencies
Heterogeneous correlate and potential diagnostic biomarker of tinnitus based on nonlinear dynamics of resting-state EEG recordings	Naghdabadi, Z. (2024)	PLOS One	7	7	EEG	Tinnitus presence (classification accuracy, sensitivity, specificity)	Nonlinear dynamic features: entropy measures, fractal dimension, signal complexity metrics
Tinnitus and otoacoustic emissions: Is there a link?	Norton, S.J. (1990)	Ear and Hearing	5	3	Otoacoustic emissions (TEOAE/DPOAE)	OAE amplitude, SNR, presence/absence, group differences	Peripheral auditory system (outer hair cell function)
Neutrophil-to-lymphocyte ratio in patients with severe tinnitus: prospective, controlled clinical study	Ozbay, I. (2015)	The Journal of Laryngology & Otology	107	107	Molecular / Blood-based	Comparison of systemic inflammatory blood markers (specifically the Neutrophil-to-Lymphocyte Ratio) between severe chronic tinnitus patients and healthy control subjects.	Neutrophil-to-lymphocyte ratio (NLR), white blood cell (WBC) count, absolute neutrophils, absolute lymphocytes, platelet count, mean platelet volume (MPV), and hemoglobin.
Tinnitus and distress: an electroencephalography classification study	, Naghdabadi Z. (2024)	Brain Communications	129	142	EEG	Classification accuracy (tinnitus vs control; low vs high distress), Machine Learning	EEG spectral power, connectivity features, frequency-band activity patterns
Whole scalp resting state EEG of oscillatory brain activity shows no parametric relationship with psychoacoustic and psychosocial	Pierzycki, R.H. (2016)	Hearing Research	42	0	EEG	Whole-scalp EEG band power (delta-gamma); correlation with THI/TFI/THQ/QoL; ICC test–retest reliability	Oscillatory frequency bands (delta, theta, alpha, beta, gamma)

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Table 1 (*continued*)

Titles	First Author (Year)	Journal	Participants (Tinnitus)	Participants (Control)	Modality	Outcome Measurement	Component(s)
assessment of tinnitus: A repeated measures study							
Elevation of Serum Prestin in Patients With Tinnitus: Pathophysiological Implications and Biomarker Potential Relationship Between Serum Levels of Brain-Derived Neurotrophic Factor (BDNF) and Hearing Loss and Tinnitus	Prakash P, P. (2026) Ranjbar, N. (2023)	Otology & Neurotology Indian Journal of Otolaryngology and Head & Neck Surgery	49 40	40 40	Molecular / Blood-based Blood	Serum prestin levels compared between tinnitus vs controls, correlated with noise exposure Serum BDNF levels (group comparison + correlations)	97 kDa prestin isoform, 140 kDa prestin isoform, OHC dysfunction BDNF concentration, hearing threshold, tinnitus pitch/loudness, THI, BDI
Attention-Modulated Cortical Responses as a Biomarker for Tinnitus	Richardson, M.L. (2024)	Brain Sciences	16	13	EEG	Attention-modulated ERP amplitude (Attended - Unattended); ROC discrimination (AUC 0.81)	P1, N1, P2 peaks; N1 modulation at 5 kHz; P2 modulation at 500 Hz; frequency-specific attention contrast
Tinnitus alters resting state functional connectivity (RSFC) in human auditory and non-auditory brain regions as measured by functional near-infrared spectroscopy (fNIRS)	San Juan, J. (2017)	PLOS One	10	8	fNIRS	Functional connectivity strength (RSFC), hemodynamic activity	Auditory cortex connectivity, non-auditory cortical connectivity, stimulus-induced connectivity modulation
Increased mean platelet volume in patients with idiopathic subjective tinnitus	Sarıkaya, Y. (2016)	European Archives of Oto-Rhino-Laryngology	101	54	Blood	Elevated mean platelet volume (MPV) in tinnitus vs controls	Mean Platelet Volume (MPV)
Connectivity of precuneus to the default mode and dorsal attention networks: A possible invariant marker of long-term tinnitus	Schmidt, S.A. (2017)	NeuroImage Clinica	57	28	fMRI	Seed-to-voxel functional connectivity (Fisher z-transformed correlations), especially DMN-precuneus and DAN-precuneus connectivity	Precuneus connectivity with DMN (mPFC, PCC) and DAN (FEF, IPS)
Exposing Pathological Sensory Predictions in Tinnitus Using Auditory Intensity Deviant Evoked Responses	Sedley, W. (2019)	The Journal of Neuroscience	26	26	EEG	MMN amplitude asymmetry to upward vs downward intensity deviants (Intensity Mismatch Asymmetry; ROC AUC = 0.77)	MMN (200-450 ms); secondary: P50, N100
Multimodal assessment of tinnitus using functional near-infrared spectroscopy and psychophysiological measures	Shoushtarian, M. (2025)	International Journal of Audiology	27	21	fNIRS	HbO/HbR changes; autonomic stress markers; group discrimination	HbO, HbR; PFC activation; HR; HRV; SCR
Objective measurement of tinnitus using functional near-infrared spectroscopy and machine learning	Shoushtarian, M. (2020)	PLOS One	25	21	fNIRS	Tinnitus vs control classification (ACC, SENS, SPEC, AUC)	HbO, HbR; functional connectivity features
Abnormal Slow Electroencephalography Activity in Eyes-Open and Eyes-Closed Conditions as an Optimal Marker for Tinnitus	Sobhany, M. (2025)	Auditory and Vestibular Research	46	0	EEG	Spectral power analysis (eyes-open and eyes-closed)	Delta-band power; slow-wave activity; EO-EC contrast; scalp distribution
Association of organic solvents and occupational noise on hearing loss and tinnitus among adults in the U.S., 1999-2004 Assessment of Macular Choroidal Thickness via Enhanced Depth Imaging Optical Coherence Tomography in Patients With Chronic Tinnitus	Staudt, A.M. (2019) Sung, Y.C. (2026)	International Archives of Occupational and Environmental Health Journal of Ophthalmology	Range (1085-2471) 93	0 245	Epidemiological Ocular Neuroimaging (EDI-OCT)	Self-reported tinnitus (binary); adjusted ORs Macular choroidal thickness (CT) at the central fovea and 2 mm surrounding	Organic solvent exposure; occupational noise exposure; combined exposure categories Macular choroidal thickness (CT), subfoveal choroidal thickness (SFCT), choroidal perfusion
Biological correlates of tinnitus-related distress: an exploratory study	Szczepek, A.J. (2014)	Hearing Research	30	0	Molecular/ Psychobiological	Tinnitus-related distress (questionnaire-based); high vs low distress comparison	Circulating cytokines; stress-related immune markers; plasma protein levels
Inflammatory Biomarkers and Tinnitus in Older Adults	Tanaka, L.S. (2024)	Noise & Health	50	47	Blood	Serum cytokine levels compared between tinnitus vs controls; correlations with VAS, THI, and MML	IL-2, IL-4, IL-6, IL-10, TNF-α, IFN-γ

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Table 1 (*continued*)

Titles	First Author (Year)	Journal	Participants (Tinnitus)	Participants (Control)	Modality	Outcome Measurement	Component(s)
Auditory Brainstem Response Wave I Amplitude Has Limited Clinical Utility in Diagnosing Tinnitus in Humans	Turner, K. (2022)	Brain Sciences	21	22	Electrophysiological (ABR)	Wave I amplitude (μV) and amplitude growth slope (μV/dB); tinnitus vs control comparison	Wave I peak-to-trough amplitude; wave I growth slope; click and 1, 4, 8 kHz tone bursts
Investigation of neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio and mean platelet volume in patients with tinnitus	Ulusoy, B. (2018)	The Journal of Laryngology & Otology	64	64	Blood	Between-group comparison (tinnitus vs healthy controls) of platelet activation and inflammatory indices	MPV, PDW, NLR, PLR
Genetic predisposition to tinnitus in the UK Biobank population	Urbanek, M.E. (2021)	Scientific Reports	19047	526	Genetic	Tinnitus presence (genome-wide SNP association; case-control)	SNP variants; genome-wide significant loci; SNP-based heritability
Cross-Subject Tinnitus Diagnosis Based on Multi-Band EEG Contrastive Representation Learning	Wang, C.D. (2023)	IEEE Journal of Biomedical and Health Informatics	187	80	EEG	Tinnitus presence (cross-subject classification performance)	Multi-band EEG spectral features; contrastive representation embeddings; connectivity/spatial-spectral features
Characteristic alterations of gut microbiota and serum metabolites in patients with chronic tinnitus: a multi-omics analysis	Wang, J. (2025)	Microbiology Spectrum	70	30	Metabolomics	Tinnitus presence (case-control); differential abundance and multivariate metabolomic modelling	Altered gut microbial taxa; differential serum metabolites (lipid and amino acid pathways)
Neural mechanisms of tinnitus: An exploration from the perspective of varying severity levels	Xie, J. (2025)	Brain Research Bulletin	62	31	Rs-fMRI	ReHo, ALFF, fALFF, seed-based FC; correlation with THI	Local spontaneous activity (ReHo, ALFF, fALFF) + Functional connectivity (FC)
Plasma brain-derived neurotrophic factor levels are increased in patients with tinnitus and correlated with therapeutic effects	Xiong, H. (2016)	Neuroscience Letters	82	32	Blood	Tinnitus presence; Tinnitus severity; Treatment response	Plasma BDNF levels; THI score; Pre/post-treatment change
The characteristic and changes of the event-related potentials (ERP) and brain topographic maps before and after treatment with rTMS in subjective tinnitus patients	Yang, H. (2013)	PLOS One	20	16	EEG	N1 amplitude, MMN amplitude, LDN amplitude, hemispheric asymmetry (pre vs. post rTMS; vs. controls)	N1, MMN, LDN
A comparison of P-300 study in subjective tinnitus with normal hearing patients and normal hearing adults	Yodthong, N. (2025)	Asia-Pacific Journal of Science and Technology	18	18	EEG	Comparison of auditory P300 characteristics (latency and amplitude) between normal-hearing subjective tinnitus patients and healthy controls, stratified by age subgroups.	P300 latency (ms) and P300 amplitude (μV) across age subgroups (18–40 and 41–60 years); correlation with Tinnitus Handicap Inventory (THI) score.
Tinnitus severity is related to changes in functional connectivity between precuneus and inferior temporal gyrus	Yu, C. (2025)	Brain research Bulletin	60	53	fMRI	DFC-SD, Mean Dwell Time, correlation with TQ	Precuneus-ITG connectivity variability and state dynamics
Nuances in intensity deviant asymmetric responses as a biomarker for tinnitus	Yukhnovich, E.A. (2023)	PLOS One	14	14	EEG	MMN amplitude asymmetry (Upward vs Downward intensity deviants)	MMN (primary), P50, N100
Can Platelet Indices Be New Biomarkers for Subjective Tinnitus?	Yüksel, F. (2016)	Journal of Craniofacial Surgery	100	100	Blood	Tinnitus presence (case-control comparison) ± severity correlation	MPV, PDW, platelet count
Proteasome Activity in the Plasma as a Novel Biomarker in Mild Cognitive Impairment with Chronic Tinnitus	Yun, Y. (2020)	Journal of Alzheimer's Disease	55	0	Blood	MCI vs non-MCI within tinnitus; correlation with cognition	Circulating proteasome activity (20S); proteasome concentration; Aβ40; Aβ42
Association of Plasma Metabolomic Biomarkers With Persistent Tinnitus: A Population-Based Case-Control Study	Zeleznik, O.A. (2023)	JAMA Otolaryngology Head Neck Surgery	488	5989	Molecular / Blood-based	Persistent tinnitus (binary); multivariable logistic regression (OR per 1 SD metabolite); FDR-controlled enrichment analysis	466 plasma metabolites; lipid classes (TAGs, PEs, DAGs, LPCs, CEs); homocitrulline; α-keto-β-methylvalerate; levulinate

Note. THI = Tinnitus Handicap Inventory; TFI = Tinnitus Functional Index; ABR = auditory brainstem response; OAE = otoacoustic emissions; EEG = electroencephalography; MEG = magnetoencephalography; fMRI = functional magnetic resonance imaging; fNIRS = functional near-infrared spectroscopy; ACC = acoustic change complex; TEPR = task-evoked pupillary response. Participant counts reflect tinnitus vs control groups as reported; '0' indicates no control group reported in the study entry.

framework using convolutional neural networks on resting-state EEG data (62 channels). By combining automated artifact rejection (using the Autoreject library) with a down-sampling balancing approach, their model achieved a maximum binary classification accuracy of 75.6% on a test set of 5,140 samples, highlighting the viability of deep learning models in detecting difficult-to-recognise EEG patterns. It is important to note, the exceptionally high accuracies reported in several of these pilot models—including the 85.42% accuracy in J. Kim et al. (2025) and near-perfect rates in Li et al., 2022—should be interpreted with caution. These metrics are frequently constrained by high feature-to-sample ratios (such as using 18 distinct sensor- and source-level features for only 48 participants in J. Kim et al., 2025) and a vulnerability to overestimating performance through localised internal validation. Consequently, across these electrophysiological studies, modest sample sizes, potential confounds from unmatched subclinical hearing thresholds, and a near-exclusive reliance on internal cross-validation rather than independent, external cohorts currently limit immediate clinical applicability. Despite these advances, evidence across electrophysiological modalities remains mixed. Several studies have reported no significant group differences in auditory evoked potentials, auditory ERPs, or mismatch negativity responses, when tinnitus is treated as a binary construct (Altıntaş et al., 2023; Pierzycki et al., 2016; Turner et al., 2022). In contrast, asymmetric intensity-deviant responses in auditory oddball paradigms have been proposed as mechanistically informative markers of altered auditory prediction-error processing (Yukhnovich et al., 2023). Machine-learning analyses have further demonstrated that perceptual presence and distress severity can be independently classified using largely non-overlapping EEG feature sets, with internal 5-fold cross-validation yielding an accuracy of 94.6% for distinguishing tinnitus patients from controls, suggesting partially distinct neural substrates (Piarulli et al., 2023).

Peripheral auditory measures have yielded similarly heterogeneous results. Evidence of subclinical cochleopathy in idiopathic tinnitus suggests potential synaptopathic damage despite normal audiometric thresholds (Morgan et al., 2021), yet human studies assessing auditory brainstem response Wave I amplitude have failed to demonstrate reliable tinnitus–control differences, highlighting translational challenges from animal models (Turner et al., 2022). Other stimulus-locked measures, including the acoustic change complex, have been proposed as potential markers of tinnitus-related perceptual differences (Han et al., 2017), while magnetoencephalography studies offer improved spatial specificity for mapping tinnitus-related cortical dynamics, findings remain sparse and methodologically mixed. For instance, Colding-Jørgensen et al. (1992) utilised MEG to map the equivalent current dipoles of auditory evoked magnetic fields (specifically the N100m and P200m) but found no significant differences in latencies, amplitudes, or dipole locations between tinnitus patients and matched controls, underscoring the reproducibility challenges present even in spatially precise modalities. Electrocochleography has been revisited as a peripheral phenotyping tool, with elevated summating potential/action potential ratios reported in subsets of individuals with chronic tinnitus and associated with low-frequency hearing loss, reduced loudness discomfort levels, aural fullness, and increased psychological distress (Lee et al., 2024). These findings suggest that ECochG metrics may reflect peripheral dysfunction linked to symptom burden and comorbidity profiles rather than tinnitus presence.

Resting-state EEG spectral analyses have also produced inconsistent findings. Early whole-scalp analyses reported mixed frequency-band alterations (Pierzycki et al., 2016), whereas more recent large-scale studies employing stringent correction and cross-validation reported no reliable qEEG markers of tinnitus laterality after controlling for hearing asymmetry (S. J. Kim et al., 2025). In contrast, severity-focused analyses linked elevated delta power, reduced alpha power, and increased delta–alpha ratios to higher Tinnitus Handicap Inventory scores (Sobhany et al., 2025).

Otoacoustic emission studies have likewise yielded inconclusive

results. Reduced distortion product otoacoustic emissions have been reported in some tinnitus cohorts, particularly following noise exposure, although findings remain inconsistent (Haider et al., 2022). More recent evidence suggests closer associations with tinnitus severity or distress than with tinnitus presence, with abnormal OAE outcomes linked to higher handicap scores in observational cohorts lacking non-tinnitus controls (Aishwarya et al., 2025). Psychoacoustic measures such as pitch and loudness matching remain clinically useful for percept characterisation but are limited by poor reliability and specificity, reinforcing the need for objective physiological biomarkers to support diagnosis and stratification (Henry, 2013).

Neuroimaging Biomarkers

Neuroimaging studies, predominantly employing functional magnetic resonance imaging (fMRI), have identified tinnitus-related alterations across both auditory and non-auditory brain regions, supporting a distributed network account rather than a focal auditory pathology. Task-based fMRI studies have shown increased frontal cortical activation in response to tones matched to an individual's tinnitus pitch, differentiating tinnitus participants from controls and implicating higher-order cognitive and attentional systems in tinnitus perception (Gopal et al., 2017). Across resting-state and stimulus-evoked paradigms, fMRI investigations have reported atypical activation patterns and altered functional connectivity within auditory cortex, the inferior colliculus, and frontoparietal networks involved in attention and executive control (Melcher et al., 2000; Schmidt et al., 2017; San Juan et al., 2017; Yu et al., 2025).

Resting-state analyses have further demonstrated abnormal coupling between the precuneus and large-scale networks, including the default-mode and dorsal attention networks, suggesting a stable network-level signature associated with chronic tinnitus (Schmidt et al., 2017). Subcortical contributions have also been reported, with lateralised tinnitus linked to asymmetric inferior colliculus activation, providing evidence for subcortical involvement in tinnitus-related perceptual asymmetry (Melcher et al., 2000). In individuals with single-sided deafness, altered corticostriatal connectivity has been observed in those experiencing bothersome tinnitus, implicating striatal–cortical circuits associated with salience and affective processing rather than auditory processing alone (Henderson-Sabes et al., 2019).

Despite the strengths of fMRI for characterising distributed neural activity, reproducibility challenges remain substantial. Variability in scanner hardware, acquisition parameters, preprocessing pipelines, and analytic strategies has contributed to inconsistent findings across studies, complicating synthesis and limiting immediate clinical translation (Melcher et al., 2000). Emerging evidence suggests that some inconsistencies may reflect inadequate consideration of tinnitus severity (Yu et al., 2025; Xie et al., 2025; Majhi et al., 2019). Severity-stratified analyses have demonstrated graded neuroimaging and electrophysiological alterations across tinnitus populations, supporting the development of severity-specific biomarker profiles rather than binary diagnostic contrasts (Yu et al., 2025).

Consistent with this framework, studies explicitly examining tinnitus across graded levels of clinical burden have shown that neural alterations scale with symptom severity. More severe tinnitus is associated with progressively greater engagement of non-auditory networks, including limbic, attentional, and default-mode systems, alongside auditory cortical changes, whereas milder tinnitus is characterised by more spatially restricted neural alterations (Xie et al., 2025).

Structural MRI studies have also identified tinnitus-associated morphological differences using machine learning. Machine-learning analyses of grey matter volume across cortical and subcortical regions differentiated individuals with idiopathic tinnitus from healthy controls with an internally validated area under the receiver operating characteristic curve (AUC) of approximately 0.86, with discriminative regions extending beyond auditory cortex to include insular, cingulate, hypothalamic, and frontal areas (Liu et al., 2019). Deep-learning frameworks applied to multimodal structural imaging have further improved joint classification of tinnitus presence and prediction of symptom severity by integrating T1- and T2-weighted MRI features across grey matter, white matter, and cerebrospinal fluid compartments (Lin et al., 2023). Notably, this multi-tasking convolutional network achieved an internally validated 5-fold cross-validation accuracy of approximately 80% during training, and successfully maintained a classification accuracy of 70% when evaluated on an independent, external validation dataset (Lin et al., 2023). While this represents a promising step toward external validation, overall, morphological neuroimaging approaches are still constrained by modest developmental sample sizes. In parallel with MRI-based methods, functional near-infrared spectroscopy (fNIRS) has been explored as a more accessible, portable, and low-cost neuroimaging modality that remains unaffected by the acoustic and electrical artifacts common to fMRI and EEG. Early studies combining resting-state and stimulus-evoked paradigms reported altered fronto-temporal and temporo-occipital connectivity in chronic tinnitus, alongside reduced baseline auditory connectivity, exaggerated post-stimulation coupling, and reduced auditory- and visual-evoked haemodynamic responses (San Juan et al., 2017; Shoushtarian et al., 2020). More recent multimodal studies combining fNIRS with psychophysiological measures demonstrated altered haemodynamic responses in prefrontal and temporal regions alongside changes in autonomic indices related to affective and attentional processing, supporting fNIRS as a scalable tool for both diagnostic presence and severity stratification (Shoushtarian et al., 2025). Building on this, Shoushtarian et al. (2026) demonstrated that fNIRS-derived connectivity measures could predict subjective tinnitus severity on a continuous scale, with predictive performance improving significantly when restricted to clinically homogeneous subtypes, such as severe tinnitus sufferers and cochlear implant users. While limited cortical penetration and modest sample sizes remain challenges, these findings highlight fNIRS as a scalable complement to fMRI. Beyond cortical imaging, highly accessible peripheral ocular imaging has also emerged; Sung et al. (2026) utilised enhanced depth imaging optical coherence tomography (EDI-OCT) to show significant macular choroidal thinning in individuals with chronic subjective tinnitus compared to healthy controls, suggesting that disturbances in choroidal perfusion and systemic microvascular changes might serve as viable indicators of clinical burden.

Cognitive and Behavioural Biomarkers

Cognitive-behavioural biomarkers reflect the influence of attentional control, salience processing, and cognitive load on tinnitus perception and burden. In selective auditory attention paradigms, tinnitus participants have demonstrated exaggerated attention-related modulation of cortical responses relative to controls, including markedly enhanced N1 and P2 amplitudes to task-relevant tones. These effects have been interpreted as reflecting heightened salience of tinnitus-related frequencies or increased vigilance, and attention-modulated cortical responses achieved good discrimination between tinnitus and control participants (AUC = 0.81; sensitivity and specificity >75%) (Richardson et al., 2024).

Electrophysiological studies using auditory oddball paradigms have further reported prolonged P300 latencies and reduced P300 amplitudes in tinnitus patients with sensorineural hearing loss, with these alterations scaling with subjective tinnitus severity (Majhi et al., 2019). Although confounded by hearing loss and task demands, these findings provide objective evidence that higher-order cognitive ERP components are more sensitive to tinnitus burden than to tinnitus presence. In a normal-hearing subjective tinnitus cohort, Yodthong et al. (2025) further evaluated P300 latency and amplitude across younger (18–40 years) and older (41–60 years) age subgroups. Tinnitus patients in both subgroups exhibited a significantly delayed P300 latency compared to

age-matched healthy controls ($p=0.03$ and $p<0.01$, respectively), although P300 amplitudes did not show a statistically significant difference. Consistent with some previous observations, they noted no direct correlation between these P300 characteristics and self-reported tinnitus severity or duration.

Behavioural and autonomic indices have been explored as objective correlates of tinnitus-related functional interference. Early reaction-time studies demonstrated faster responses to tinnitus-matched frequencies compared to acoustically similar non-tinnitus frequencies despite comparable audiometric thresholds, indicating frequency-specific attentional prioritisation rather than peripheral hearing loss effects (Goodwin & Johnson, 1980). More recent work has shown that listening effort and psychophysiological stress markers co-vary with tinnitus severity, further suggesting that measures indexing cognitive load and autonomic arousal may capture tinnitus burden more effectively than tinnitus presence alone (Giliberto et al., 2025).

Consistent with this interpretation, pupillometric studies examining competition between tinnitus and external sounds during auditory short-term memory tasks have reported increased baseline pupil diameter and enhanced task-evoked pupillary responses in individuals with chronic tinnitus (Zekveld et al., 2010). Task-evoked pupillary response amplitude was significantly associated with Tinnitus Handicap Inventory scores, supporting pupillometry as a marker of tinnitus intrusiveness and functional burden rather than tinnitus presence per se (Barrett et al., 2022).

Behavioural assessments of cognitive performance further supported this association. In a cross-sectional study, objectively measured cognitive processing speed was independently associated with tinnitus severity and predicted handicap after controlling for psychiatric distress, with effects observed in individuals with clinically bothersome tinnitus (THI $\geq$ 30) (Das et al., 2012). Psychobiological correlates of tinnitus-related distress have also been reported, with a blunted cortisol awakening response observed in individuals with higher tinnitus distress, while total cortisol output was unrelated to severity (Jackson, 2019).

Collectively, these findings indicate that cognitive, behavioural, and autonomic measures primarily index tinnitus severity and functional impact rather than tinnitus presence, supporting their role as complementary, severity-sensitive components within multimodal biomarker frameworks rather than standalone diagnostic markers.

Molecular and Biochemical Biomarkers

Molecular and biochemical investigations of tinnitus have produced largely mixed and inconsistent findings. Large-scale studies of systemic inflammatory markers have predominantly reported null results. For instance, in a well-powered case–control analysis, several circulating inflammatory proteins were initially associated with tinnitus, but none remained significant after correction for multiple testing (Cederroth et al., 2023). Similarly, cross-sectional screening studies in individuals with near-normal hearing reported largely null associations (Mennink et al., 2024). Although age-stratified analyses identified elevated inflammatory markers in older adults with tinnitus, these findings are difficult to disentangle from age-related comorbidities and systemic inflammation (Tanaka et al., 2024). Exploratory population-based studies in older cohorts reported associations between inflammatory indices and tinnitus characteristics, including reduced circulating interleukin-10 and correlations with tinnitus duration or loudness, but these findings were derived from modest, age-restricted samples and remain sensitive to sampling conditions (Haider et al., 2020).

Consistent with these observations, a large-scale analysis of routine haematological and biochemical parameters reported minimal associations with tinnitus presence after adjustment for demographic and clinical covariates (Bulla et al., 2023). Smaller studies examining platelet- and leukocyte-derived indices reported subgroup-specific alterations, including elevated mean platelet volume and platelet distribution width in some tinnitus cohorts (Ulusoy et al., 2018; Sarıkaya et al., 2016). However, inflammatory ratios such as neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios were inconsistently altered, and a retrospective analysis indicated that elevations were primarily observed in individuals with concomitant high-frequency hearing loss, highlighting potential confounding by peripheral auditory pathology (Demir, 2021). Conversely, in a prospective, age- and sex-matched controlled clinical study of 107 patients experiencing severe subjective tinnitus (THI grades 3–5), Ozbay et al. (2015) reported a significantly elevated mean neutrophil-to-lymphocyte ratio in tinnitus patients compared to healthy controls (2.067 ± 1.43 vs. 2.136 ± 1.31, $p=0.002$). While other routine haematological parameters (such as lipid profiles and WBC counts) remained statistically similar, these findings suggest that NLR may serve as a potential clinical indicator of systemic stress or subclinical inflammatory activity in severe chronic tinnitus cohorts.

Micronutrient and standard haematological markers have also been explored due to their clinical accessibility. Associations between serum zinc levels and tinnitus were reported inconsistently (Berkiten et al., 2015), and preliminary group differences in platelet-related and haematological indices were observed in smaller studies (Yüksel et al., 2016). In contrast, a large case–control study involving over 700 participants reported no significant group-level differences in standard haematological parameters between tinnitus and control cohorts (Maihoub et al., 2025). Severity-focused analyses within this cohort indicated that lower haemoglobin and platelet levels were associated with higher tinnitus handicap scores and bilateral tinnitus, suggesting greater relevance to symptom burden than to tinnitus presence.

Genetic studies provide evidence for heritable contributions to tinnitus susceptibility. Large-scale analyses from the UK Biobank identified loci associated with tinnitus risk (Urbanek et al., 2021). Earlier candidate-gene studies reported genotype-dependent differences in tinnitus prevalence for GRM7, with limited evidence for NAT2, underscoring the modest and age-restricted nature of early genetic findings (Haider et al., 2017).

Exploratory analyses have also identified psychobiological signatures associated with tinnitus-related distress. Distinct physiological profiles were reported in individuals with high tinnitus distress, once again supporting differentiation between distress-related markers and biomarkers of mere tinnitus presence (Szczepek et al., 2014). Neurotrophic and stress-related biomarkers yielded variable results: plasma brain-derived neurotrophic factor levels were elevated in some tinnitus cohorts and decreased following tinnitus retraining therapy, with earlier studies reporting non-linear relationships with tinnitus severity and distress (Goto et al., 2012; Xiong et al., 2016). Subsequent studies reported altered serum BDNF in association with hearing loss or treatment response, although findings varied across cohorts (Basso et al., 2022; Ranjbar et al., 2023). Stress reactivity measures showed similarly mixed findings, with a blunted cortisol awakening response reported in individuals with high tinnitus distress, while hair-cortisol measures showed no consistent post-treatment changes (Basso et al., 2022; Jackson, 2019).

In contrast to broadly inflammatory and haematological markers, metabolomic profiling demonstrated more consistent associations. A large case-control study identified metabolic signatures associated with persistent tinnitus, including dysregulated lipid metabolism and metabolites such as homocitrulline (Zeleznik et al., 2023). Population-based analyses further reported associations between tinnitus prevalence and a higher Atherogenic Index of Plasma, with evidence of partial mediation by hypertension (Miao et al., 2025). Emerging multi-omics studies integrating metabolomics with gut microbiota profiling reported coordinated alterations in microbial composition and circulating metabolites, although these findings remain exploratory due to cross-sectional designs and modest sample sizes (J Wang et al., 2025).

Finally, novel biochemical markers continue to emerge. Altered

plasma proteasome activity has been reported in individuals with mild tinnitus compared to controls, representing an early-stage and exploratory direction in tinnitus biomarker research (Yun et al., 2020). Further expanding the panel of circulating peripheral markers, Prakash et al. (2026) quantified outer hair cell (OHC) proteins and found that serum levels of the 97 kDa isoform of prestin were significantly elevated in patients with chronic subjective tinnitus compared to healthy controls, even after controlling for age, hearing thresholds, and noise exposure, highlighting circulating prestin as a promising biomarker of cochlear dysfunction.

Emerging and Novel Biomarker Approaches

Emerging research continues to expand the tinnitus biomarker landscape beyond established neurophysiological and molecular domains. At the molecular level, exploratory epigenetic approaches have examined whether DNA methylation patterns are associated with tinnitus-related vulnerability. A pilot epigenome-wide association study in young adults identified differential DNA methylation signatures in individuals with tinnitus, implicating genes involved in neural plasticity, stress regulation, and sensory processing (Bhatt et al., 2024). Although constrained by small sample size, cross-sectional design, and the absence of diagnostic performance metrics, these findings provide preliminary evidence that epigenetic variation may be associated with tinnitus-related biological vulnerability.

Beyond molecular approaches, novel neurophysiological paradigms and technologies are being explored as potential objective assessment tools. Asymmetric intensity-deviant responses in auditory oddball paradigms have been proposed as sensitive indicators of aberrant predictive coding in tinnitus, providing a mechanistically grounded electrophysiological signal consistent with disrupted prediction-error processing (Yukhnovich et al., 2023). In parallel, pilot studies using IoT-enabled EEG systems demonstrated the feasibility of continuous, home-based electrophysiological monitoring in individuals with chronic tinnitus, highlighting the potential for scalable and ecologically valid data acquisition outside traditional laboratory settings (Lam et al., 2024). Although preliminary, these approaches represent emerging directions in portable and real-world tinnitus biomarker research.

DISCUSSION

This systematic review synthesised evidence on diagnostic biomarkers for tinnitus across neurophysiological/audiological, neuroimaging, cognitive-behavioural, and molecular domains. Across modalities, many studies report statistically significant differences between tinnitus and control groups; however, findings are frequently inconsistent and often fail to replicate. Methodological heterogeneity (including variation in tinnitus phenotyping, hearing status, comorbidity profiles, experimental paradigms, and analytic pipelines) combined with small sample sizes, particularly in electrophysiology and neuroimaging, substantially limits comparability and reproducibility (Altıntaş et al., 2023; Cardon et al., 2022; Melcher et al., 2000; Richardson et al.,

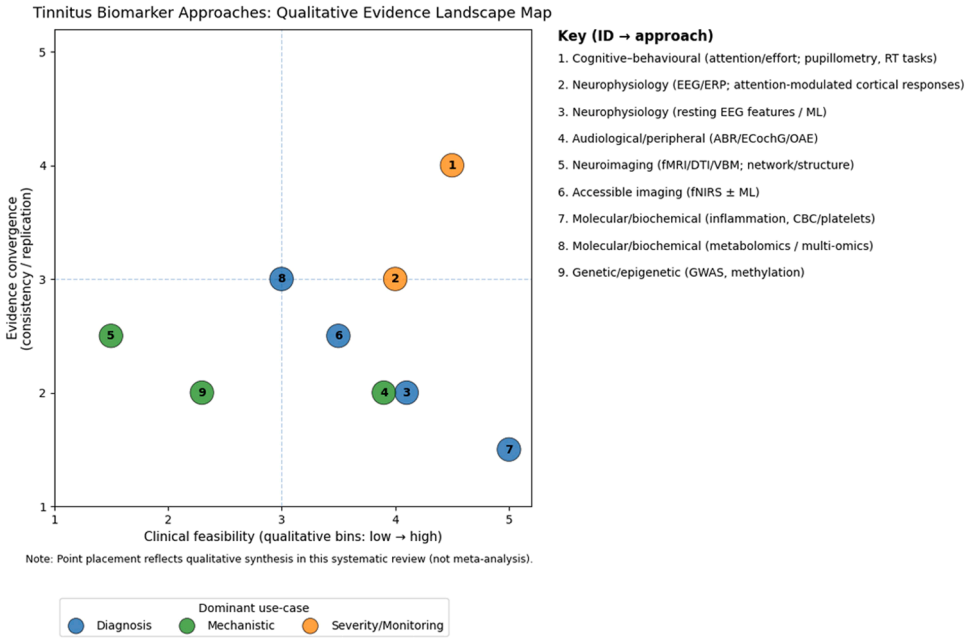

Figure 3. Qualitative evidence landscape map of objective tinnitus biomarker approaches. Biomarker domains reviewed in this systematic review are positioned according to (a) clinical feasibility (x-axis; qualitative bins from low to high, reflecting cost, accessibility, and workflow burden) and (b) evidence convergence (y-axis; qualitative bins reflecting cross-study consistency and replication). Each numbered marker corresponds to a specific approach listed in the key; marker colours indicate the dominant use-case emphasised in the literature (diagnosis, mechanistic insight, or severity/monitoring). Dashed reference lines denote midpoints of the qualitative scales, and approaches occupying the upper-right quadrant indicate relatively greater feasibility and convergence. To improve readability, approaches falling within the same qualitative bin are slightly offset. Notably, point placement reflects a narrative synthesis of the included evidence rather than meta-analytic effect estimates.

Each biomarker domain was positioned according to the following scoring rubric (on a scale of 1–5):

Clinical Feasibility (X-axis):

- Score 1–2 (Low): High cost, highly specialised/invasive equipment, limited clinical accessibility, and lengthy workflow (e.g., fMRI, sMRI).
- Score 3 (Medium): Moderate cost, moderately accessible in specialised centres, with some workflow/processing burden (e.g., fNIRS, custom EEG paradigms).
- Score 4–5 (High): Low cost, widely accessible in standard clinical/audiological environments, with rapid acquisition (e.g., standard blood labs, audiological tests).

Evidence Convergence (Y-axis):

- Score 1–2 (Low): Mostly null, conflicting, or un-replicated findings across very few studies.
- Score 3 (Medium): Mixed or heterogeneous evidence across a modest number of studies; emerging trends without systematic validation.
- Score 4–5 (High): Highly consistent replication and cross-study consistency across multiple well-powered cohorts.

2024). This cross-domain pattern of variable feasibility and evidential convergence is summarised in Figure 3.

A central finding emerging from this literature is that tinnitus may be poorly captured as a binary diagnostic entity. Across multiple modalities, neural and behavioural alterations appear to scale with symptom burden rather than tinnitus presence. Greater tinnitus severity is associated with broader recruitment of non-auditory systems, including attentional, limbic, and default-mode networks, whereas milder tinnitus is characterised by more spatially restricted alterations (Xie et al., 2025). This pattern likely contributes to the inconsistent performance of "tinnitus versus control" contrasts and supports dimensional and stratified frameworks as more realistic routes to clinically meaningful biomarker development (Figs. 4-6).

At the physiological level, several candidates show translational promise but vary widely in clinical specificity. Electrophysiological and audiological markers, such as altered auditory brainstem responses (e.g., Wave V latency), ERP components (e.g., P300), and otoacoustic emissions, often reflect state-dependent or treatment-sensitive changes rather than stable diagnostic-trait markers, and are frequently confounded by attentional demands or peripheral auditory dysfunction (Altıntaş et al., 2023; Cardon et al., 2022; Edvall et al., 2022; Haider et al., 2022; Yang et al., 2013). Similarly, while fMRI has successfully mapped distributed network-level alterations across limbic, attentional, and auditory regions, its clinical utility is constrained by high cost and analytic variability (Gopal et al., 2017; Melcher et al., 2000). Indeed, recent fNIRS work demonstrating that connectivity measures can predict subjective severity on a continuous scale, with predictive performance improving significantly within clinically homogeneous subtypes (Shoushtarian et al., 2026), directly supports this dimensional approach over binary contrasts. Simultaneously, the application of end-to-end deep learning frameworks directly to resting-state EEG (e.g., Allgaier et al., 2021) shows the viability of convolutional neural networks for automated feature extraction, though such classifiers remain heavily constrained by a reliance on internal validation rather than independent, multi-site cohorts. Conversely, biochemical markers are highly accessible but historically weak; large-scale analyses of routine haematological and inflammatory panels report mostly null associations (Bulla et al., 2023; Cederroth et al., 2023), whereas targeted metabolomic profiles (e.g., lipid metabolic signatures) offer a more promising, scalable avenue for objective monitoring, pending replication (Zeleznik et al., 2023). Rather than relying on general systemic inflammatory screenings, future molecular research should prioritise targeted peripheral indices of cochlear damage. For instance, the quantification of elevated circulating outer hair cell proteins, such as the 97 kDa isoform of prestin (Prakash et al., 2026), provides a promising biochemical marker of subclinical cochlear dysfunction that bypasses normal audiometric thresholds. This peripheral vulnerability may interact with localised microvascular alterations, as evidenced by ocular neuroimaging showing significant macular choroidal thinning in chronic tinnitus cohorts (Sung et al., 2026), suggesting a possible link between systemic microvascular health and auditory phantom perception. Overall, the emerging evidence aligns with predictive-coding frameworks, including the Sensory Precision Model, which conceptualise tinnitus as a disorder of maladaptive precision weighting and persistent auditory inference (Chen et al., 2024; Yasoda-Mohan et al., 2024; Yukhnovich et al., 2023). Within this framework, tinnitus arises when internally generated auditory predictions are assigned abnormally high precision relative to sensory input, causing spontaneous neural activity or noise to be persistently inferred as a meaningful sound despite the absence of an external stimulus (Sedley et al., 2016). Empirical support for this view includes evidence of enhanced prediction-error signalling, altered pre-stimulus activity, and distributed network-level connectivity changes in tinnitus, particularly in individuals with minimal hearing loss, consistent with a domain-general predisposition to maladaptive predictive coding (Mohan et al., 2022; Sedley et al., 2019). These predictive-coding accounts highlight the role of the thalamus as a crucial gatekeeper for sensory prediction errors. Empirically, this is supported by recent sleep electrophysiology demonstrating altered sleep spindle density and amplitude in individuals with tinnitus (Park et al., 2026). These alterations point to disrupted thalamocortical loop integrity and auditory thalamic reticular nucleus (TRN) dysfunction, which may permit internally generated auditory predictions to be assigned abnormally high precision and escape top-down sensory gating. Convergent electrophysiological findings, such as altered neural variability and attention-modulated cortical responses, are also compatible with disruptions in precision weighting and attentional gain (Cardon et al., 2022; Richardson et al., 2024). Neuroimaging evidence of severity-linked recruitment of cognitive and limbic systems further supports models emphasising aberrant salience assignment and top–down modulation rather than peripheral damage alone (Gopal et al., 2017; Xie et al., 2025).

Interpretation of this literature is constrained by pervasive

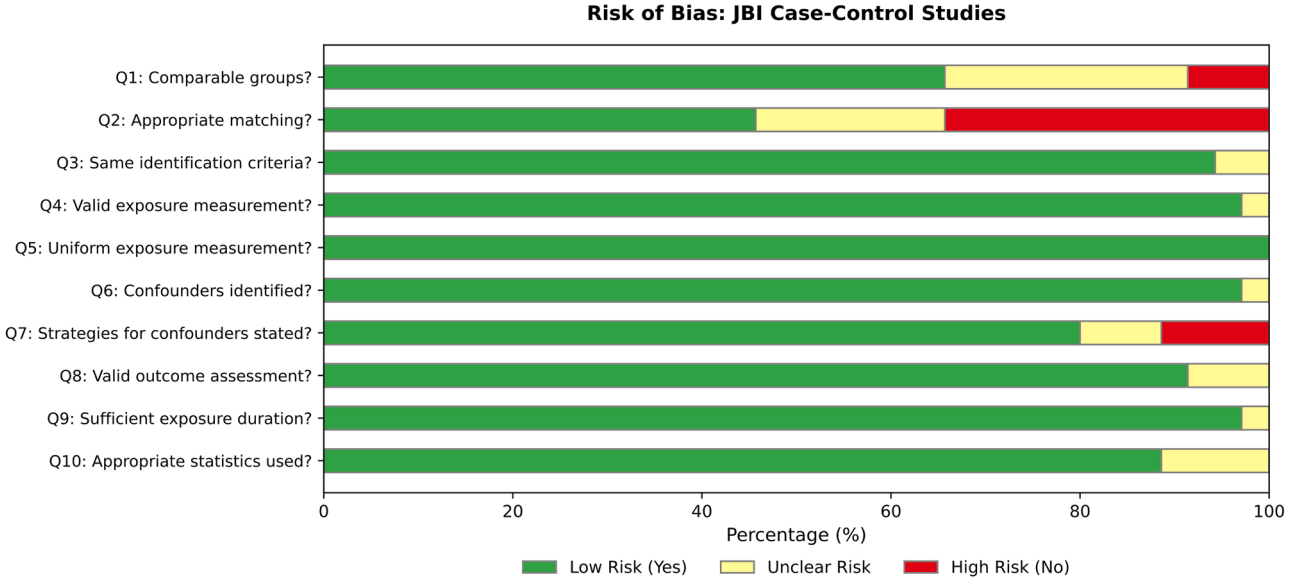

Figure 4. Aggregated Risk of Bias for Case-Control Studies. Bar chart representing the cumulative percentage of low risk (green), unclear risk (yellow), and high risk (red) evaluations across each of the ten appraisal domains of the JBI Critical Appraisal Tool for the 35 included case-control studies.

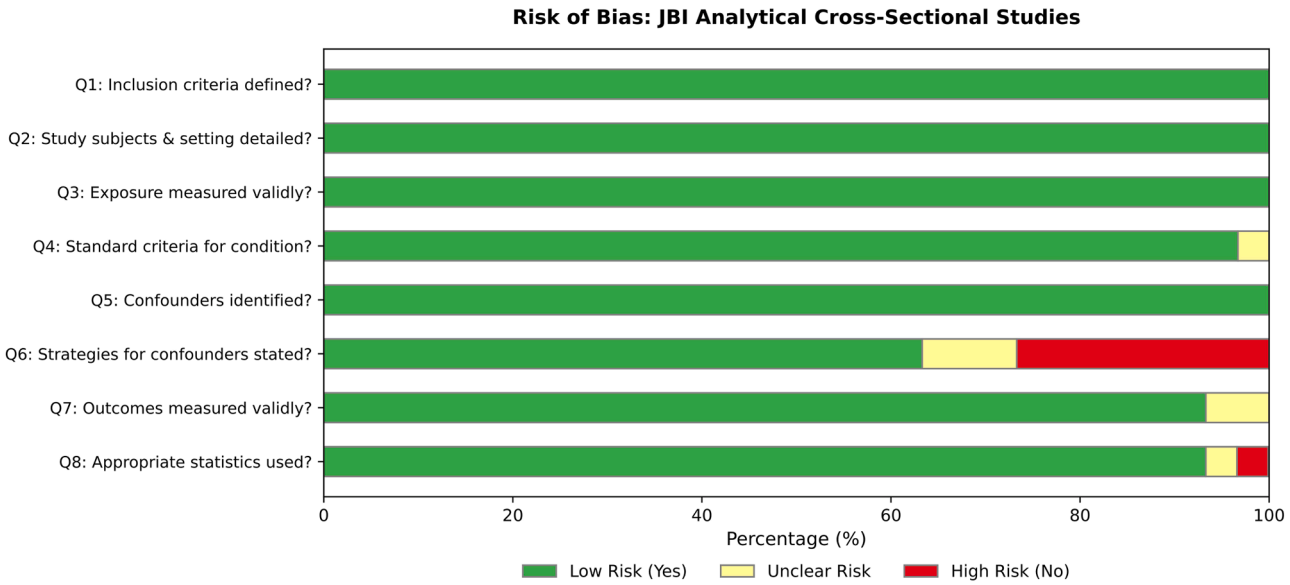

Figure 5. Aggregated Risk of Bias for Analytical Cross-Sectional Studies. Bar chart representing the cumulative percentage of low risk (green), unclear risk (yellow), and high risk (red) evaluations across each of the eight appraisal domains of the JBI Critical Appraisal Tool for the 30 included analytical cross-sectional studies.

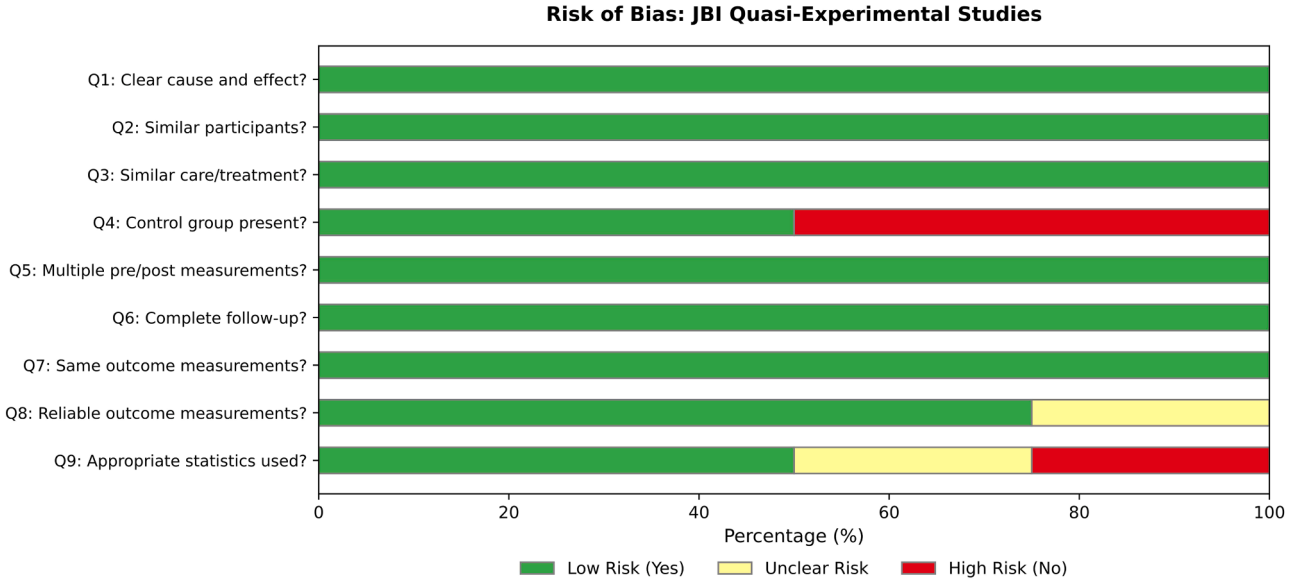

Figure 6. Aggregated Risk of Bias for Quasi-Experimental Studies. Bar chart representing the cumulative percentage of low risk (green), unclear risk (yellow), and high risk (red) evaluations across each of the nine appraisal domains of the JBI Critical Appraisal Tool for the 4 included quasi-experimental studies.

methodological limitations. Many studies are underpowered, control of key confounders (including psychiatric comorbidity, medication use, hyperacusis, and hearing loss) is inconsistent, and technical variability in recording and analysis pipelines remains substantial (Altıntaş et al., 2023; Richardson et al., 2024; Sobhany et al., 2025). Even large-scale studies employing stringent correction and cross-validation have failed to identify reliable signatures for some proposed biomarkers, underscoring the difficulty of deriving robust diagnostic markers (S. J. Kim et al., 2025). A further conceptual challenge lies in disentangling tinnitus-specific mechanisms from correlates of peripheral auditory damage and broader health exposures, including occupational noise and solvent exposure, which independently affect auditory and systemic physiology (Staudt et al., 2019).

In addition to constraints within the primary literature, a methodological consideration of the review process is that the initial screening, data extraction, and quality appraisals were led by a single primary reviewer. To mitigate individual appraisal bias and maximise reproducibility, all study selection decisions, extracted data parameters, and JBI risk-of-bias ratings were subsequently cross-checked and independently validated by two co-authors. Any procedural uncertainties or eligibility queries were resolved through consensus with a senior author. While this primary-plus-consensus validation model differs from a dual-independent screening protocol initiated at the first stage, this multi-step verification process was designed to ensure rigorous quality control and safeguard the overall consistency of our synthesis.

Lastly, our search was restricted to English-language publications indexed across three primary databases with a single grey-literature pass. This search strategy represents a potential source of language and publication bias, which should be acknowledged, particularly within the molecular and biochemical literature where non-indexed,

localised, or non-English language registries may exist.

Future progress will require larger, better-phenotyped cohorts and greater methodological standardisation. Harmonised definitions of tinnitus and comprehensive phenotyping capturing severity, distress, duration, laterality, hearing status, hyperacusis, and relevant comorbidities are essential for improving reproducibility and enabling meaningful cross-study synthesis. Shifting away from binary diagnostic contrasts toward dimensional and subtype-specific analyses is likely to yield more stable and clinically informative biomarkers. Electrophysiological research should prioritise paradigms with improved specificity and test–retest reliability, alongside transparent, standardised preprocessing and preregistered analytic strategies. Molecular studies should move beyond broad inflammatory screening toward targeted, pathway-informed approaches, with metabolomic signals requiring replication in independent and longitudinal cohorts to establish clinical relevance.

Clinical translation will likely depend on multimodal biomarker panels rather than single markers. Integrating electrophysiological, cognitive–behavioural, molecular, and feasible imaging measures may better capture the heterogeneous components of tinnitus pathophysiology and improve diagnostic and prognostic performance. Machine-learning approaches can facilitate multimodal integration, but their utility will depend on interpretability, rigorous external validation, and replication across sites. Critically, future translation of these machine-learning models must address the methodological boundaries that commonly inflate pilot performance. Many current classifiers exhibit a high risk of overfitting due to high-dimensional feature spaces trained on small cohorts, alongside optimistic estimates generated solely through internal cross-validation. Furthermore, because cognitive electrophysiological features (such as P300 or N2 amplitudes) are highly sensitive to auditory deprivation, classifiers risk modelling subtle, unmatched hearing thresholds rather than the subjective phantom percept itself, underscoring why strict audiological matching and multi-site external validation remain critical bottlenecks. Scalable technologies such as portable EEG, fNIRS, and wearable physiological sensors offer opportunities for longitudinal and ecologically valid assessment, but require careful validation before clinical implementation.

In conclusion, while tinnitus biomarker research is expanding, evidence remains fragmented and no candidate has yet demonstrated sufficient reproducibility and diagnostic accuracy for routine clinical use. Biomarkers indexing cognitive–behavioural and attentional processes currently show the strongest potential for near-term translation, whereas metabolomic signatures represent a promising longer-term avenue. Progress will depend on standardised methods, dimensional models of tinnitus heterogeneity, and rigorous multimodal validation in large, well-characterised populations.

CRediT authorship contribution statement

Nathan Shields: Writing – original draft, Methodology. **Elva Arulchelvan:** Writing – original draft. **Fabian Broecker:** Writing – original draft, Visualization. **Sven Vanneste:** Writing – original draft, Supervision, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Sven Vanneste reports financial support was provided by Rainwater Charitable Foundation. Sven Vanneste reports financial support was provided by RNID. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.heares.2026.109770.

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