

Mechanistic Research on Ménière's Disease from 2006 to 2026: A Bibliometric and Immune-Inflammatory Frontier Analysis

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Abstract

Mechanistic research on Ménière's disease is expanding, but its intellectual structure and emerging molecular directions remain incompletely characterized. We conducted a bibliometric and science-mapping study of PubMed-indexed literature published from June 1, 2006, to June 1, 2026. A reproducible MeSH- and synonym-based query retrieved 1895 records, which were manually screened for Ménière-specific or directly relevant mechanistic content; 309 publications were included in the main analysis. A secondary analysis evaluated 91 immune-inflammatory studies. Publication trends, contributors, sources, collaboration and citation networks, keyword evolution, and immune-inflammatory themes were examined. Annual output increased markedly in recent years, with China, Spain, and the United States contributing prominently. Otolaryngology & Neurotology was the most productive and locally influential journal, while endolymphatic hydrops, genetics, exome sequencing, magnetic resonance imaging, aldosterone, and inflammation were the leading filtered keywords. The focused analysis indicated a shift from broad autoimmune hypotheses toward cytokine-defined endotypes, innate immune signaling, and barrier dysfunction. Mechanistic research on Ménière's disease is moving toward biologically stratified investigation; prospective studies integrating longitudinal phenotyping, inner-ear imaging, genetics, and single-cell or spatial multiomics may help translate candidate mechanisms into biomarkers and targeted interventions.

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Keywords

Ménière's Disease, Bibliometric Analysis, Pathogenesis, Endolymphatic Hydrops, Inflammation, Science Mapping

1. Introduction

Ménière's disease is a chronic inner-ear disorder characterized by recurrent spontaneous vertigo, fluctuating sensorineural hearing loss, tinnitus, and aural fullness [1] [2]. Endolymphatic hydrops is its best-established pathological correlate, yet temporal-bone and imaging studies indicate that hydrops alone neither determines symptom onset nor explains the marked variability in disease course [3]-[5]. Consequently, contemporary models increasingly view Ménière's disease as a multifactorial syndrome in which susceptibility and local inner-ear injury converge through several biological routes [6].

Clinical subgroups, including familial, migraine-associated, autoimmune-associated, delayed, and sporadic phenotypes, further suggest biological heterogeneity [7]. Familial studies have implicated genes involved in extracellular structures and hair-cell function, including *OTOG*, *MYO7A*, and *TECTA* [8]. In parallel, NF- κ B-related signaling, cytokine profiling, transcriptomics, and single-cell multi-omics have identified inflammatory sub-groups involving IL-1 β , TNF-related pathways, and distinct monocyte programs [9]-[12]. Altered aquaporin and ion-transport regulation [13] [14], increased blood-labyrinth barrier permeability [15]-[17], and endolymphatic-sac metabolomic and proteomic changes [18] [19] provide additional links between systemic susceptibility, epithelial dysfunction, hydrops, and audiovestibular injury.

This expanding molecular, genetic, immunological, and imaging literature has produced a complex but fragmented evidence base. Narrative reviews can synthesize selected mechanisms, but they cannot objectively quantify the contributors, collaboration patterns, citation structure, or temporal evolution of research themes. Bibliometric analysis and science mapping offer complementary approaches for reconstructing a field's knowledge base, identifying influential contributors and documents, and detecting emerging topics across large bibliographic datasets [20] [21].

Previous bibliometric studies have mapped the overall Ménière's disease literature, global research hotspots, diagnosis and treatment, or the use of magnetic resonance imaging [22]-[25]. These analyses provided valuable descriptions of publication growth and collaboration but primarily reflected broad clinical, diagnostic, therapeutic, or imaging-oriented research. None applied mechanism-specific manual eligibility screening or separately reconstructed the immune-inflammatory knowledge base. The present study was therefore designed to isolate research directly addressing molecular and pathophysiological mechanisms and to distinguish emerging biological directions from the larger clinically oriented lit-

erature.

Accordingly, this study mapped the development of mechanistic research on Ménière's disease from 2006 to 2026. We evaluated publication growth, productive countries, institutions, authors and journals, collaboration and citation networks, and the evolution of filtered mechanistic keywords. Because inflammation emerged as a prominent and rapidly developing topic, we additionally performed a focused citation and thematic analysis of mechanism-oriented immune-inflammatory studies to characterize the transition from broad autoimmune hypotheses toward molecularly defined inflammatory endotypes and to identify priorities for future research.

2. Materials and Methods

2.1. Data Collection and Eligibility

PubMed was searched on July 1, 2026 for records published from June 1, 2006 through June 1, 2026. A single reproducible strategy combined the MeSH term and title/abstract synonyms for Ménière's disease with general mechanistic terms and named domains covering endolymphatic hydrops, genetics, inflammation and immunity, ion and water transport, blood-labyrinth barrier dysfunction, and oxidative stress. The complete search was:

("Meniere Disease" [Mesh] OR meniere*[Title/Abstract] OR ménière*[Title/Abstract]) AND (mechanis*[Title/Abstract] OR pathogenes*[Title/Abstract] OR molecular [Title/Abstract] OR "Endolymphatic Hydrops" [Mesh:noexp] OR "endolymphatic hydrops" [Title/Abstract] OR "Genetic Predisposition to Disease" [Mesh:noexp] OR genetic*[Title/Abstract] OR gene*[Title/Abstract] OR variant*[Title/Abstract] OR familial [Title/Abstract] OR "Inflammation" [Mesh:noexp] OR inflamm*[Title/Abstract] OR immun*[Title/Abstract] OR cytokine*[Title/Abstract] OR allerg*[Title/Abstract] OR "Ion Transport"[Mesh:noexp] OR "ion transport"[Title/Abstract] OR ion channel*[Title/Abstract] OR aquaporin*[Title/Abstract] OR vasopressin [Title/Abstract] OR "blood-labyrinth barrier" [Title/Abstract] OR "blood labyrinth barrier" [Title/Abstract] OR "Oxidative Stress" [Mesh:noexp] OR "oxidative stress" [Title/Abstract]) AND 2006/06/01:2026/06/01[dp]

The search retrieved 1895 unique PubMed records.

Mechanistic research was operationally defined as research that investigated, synthesized, or generated disease-relevant evidence about factors potentially involved in the initiation, modulation, progression, or biological heterogeneity of Ménière's disease. Eligible evidence therefore included etiologic or pathophysiologic hypotheses; environmental or physiological factors associated with attack onset or disease progression, including atmospheric pressure; disease-related genetic variants or gene-expression findings; molecular, cellular, immune, vascular or barrier, ion or water transport, oxidative-stress, and hydrops-related findings; and imaging or biomarker observations when the authors explicitly linked them to disease biology. Human studies were eligible when they included a defined Ménière's disease cohort or a separately evaluable Ménière group and reported dis-

ease-relevant findings. Animal, cell, and tissue studies were eligible when the experimental model explicitly investigated Ménière's disease, experimentally induced endolymphatic hydrops, or a pathological process directly linked to Ménière's disease. Reviews were retained when Ménière's disease was a principal topic. Purely epidemiological, diagnostic, imaging, or treatment reports were excluded only when they provided no etiologic or pathophysiologic interpretation. Studies focused on sudden sensorineural hearing loss, non-Ménière vertigo, tinnitus, or other inner-ear disorders were excluded when they lacked a separately evaluable Ménière cohort, a Ménière-related model, or an explicit mechanistic synthesis applicable to Ménière's disease. Incidental mentions, examples, and differential diagnoses were insufficient for inclusion.

Two reviewers independently screened titles and abstracts and consulted the full text when eligibility remained unclear. Disagreements were resolved by discussion and consensus, with senior-author adjudication when required. After screening, 1586 records were excluded and the investigator-defined set of 309 publications was used for the main bibliometric analysis; author and affiliation variants were standardized only after eligibility had been finalized. The identification, single-search retrieval, manual screening, and final inclusion process is summarized in **Figure S1**.

2.2. Data Analysis

PubMed supplied titles, abstracts, indexing terms, publication dates, authors, and affiliations. Bibliographic records were analyzed with the bibliometrix package in R [20], with CiteSpace supporting bibliographic-format conversion and citation-network processing [26]. Publication-level global citation counts and cited-reference lists were retrieved from OpenAlex in July 2026 and matched by PMID or DOI [27]. Local citation counts, direct-citation links, historiography, and document co-citations were calculated within the 309-record corpus from the matched reference lists; records without a reliable reference match were retained for descriptive productivity analyses but omitted from network calculations requiring unavailable reference data. Author productivity used full publication counting after name disambiguation. Country and institution productivity used full counting of author-affiliation occurrences; accordingly, cumulative country or institution totals could exceed 309 and were labeled as occurrences rather than publications. Descriptive and science-mapping analyses included annual output, source productivity, country and institutional contributions, author productivity, collaboration networks, citation impact, historiography, document co-citation, and keyword co-occurrence and temporal evolution. Predefined nonspecific Ménière-related terms were removed before the keyword analysis, and the six most frequent retained keywords were visualized.

For the focused immune-inflammatory analysis, a secondary PubMed search combined Ménière's disease with terms related to inflammation, immunity, autoimmunity, cytokines, inflammasomes, immunogenetics, the blood-labyrinth bar-

rier, and the endolymphatic sac. This search retrieved 338 records; after mechanistic screening using the same disease-specific principles, 91 studies were retained. Their annual output, influential publications, mechanistic themes, and direct citation backbone were evaluated. Relative Citation Ratio values were retrieved from the NIH iCite database in July 2026 and matched by PMID as a field- and time-normalized indicator of article influence; records without an available RCR were retained in the other analyses but omitted from RCR-based ranking [28].

3. Results

3.1. Publication Output Accelerated with Expanding Global Collaboration

The PubMed search retrieved 1895 records, of which 309 met the manually applied eligibility criteria and were included in the main bibliometric analysis. Annual publication output showed an overall upward trajectory from 2006 to 2026 despite pronounced year-to-year fluctuations, reaching 28 publications in 2025; the 21 records assigned to 2026 reflected partial-year coverage at the retrieval date (**Figure 1(A)**). Mean annual citations varied across publication years, peaking at 6.65 for articles published in 2016, and declined among the newest records because of the shorter citation window (**Figure 1(B)**). Bradford's law identified 11 core journals, compared with 38 journals in Zone 2 and 103 in Zone 3, showing that a small subset of sources accounted for a substantial proportion of the 309-document corpus (**Figure 1(C)**).

The country collaboration network retained three major interconnected clusters, with Spain and Australia acting as prominent hubs in the blue cluster, China and the United States occupying central positions in the orange cluster, and a predominantly European green cluster (**Figure 1(D)**). Geographic mapping showed that China, Spain, and the United States accounted for the largest country-attributed contributions (**Figure 1(E)**). Under full counting of author-affiliation occurrences, cumulative totals reached 577 for China, 317 for Spain, 183 for the United States, and 105 each for Italy and Japan (**Figure 1(F)**). Citation impact was uneven across countries: Luxembourg ranked first in total citations (203), followed by China (122) and the United States (112) (**Figure 1(G)**).

An exploratory logistic model estimated a maximum annual output of approximately 54 publications around 2053 (**Figure 1(H)**). Because model fit was moderate ($R^2 = 0.553$) and the projection extended far beyond the observed period, it should be interpreted only as a descriptive scenario rather than a precise forecast.

3.2. Institutional and Author Contributions Were Highly Concentrated

Cumulative author-affiliation occurrences increased markedly in the later study years (**Figure 2(A)**). After affiliation disambiguation, Shandong University had the highest count (105), followed by Universidad de Granada (63), Central South University (47), and the University of Sydney (43); Huazhong University of Sci-

ence and Technology and Harvard Medical School were tied at 27 occurrences (**Figure 2(B)**). These results indicate strong contributions from Chinese, Spanish, and Australian research centers.

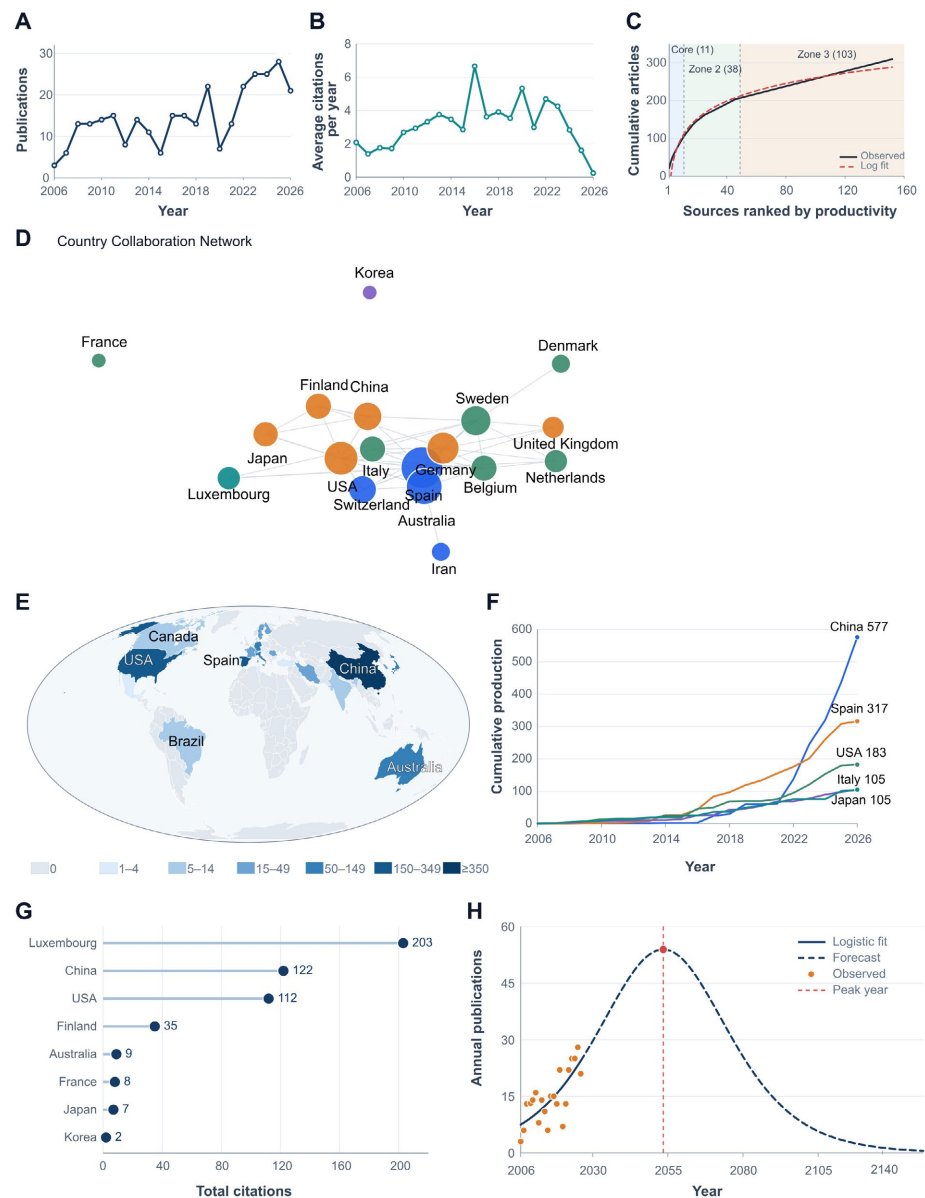


Figure 1. Temporal evolution, source concentration, geographic distribution, and international collaboration in mechanistic research on Ménière's disease, 2006 - 2026. (A) Annual publication output. (B) Mean annual citation rate; the recent decline should be interpreted in the context of citation lag. (C) Bradford source zones. (D) Country collaboration network; node size represents weighted collaboration strength, edge width represents collaboration frequency, and color represents cluster membership. (E) Geographic distribution of country-attributed author-affiliation occurrences. (F) Cumulative author-affiliation occurrences for the five leading countries under full counting. (G) Total citations assigned to the most highly cited countries. (H) Exploratory logistic growth model; points indicate observed output, the solid curve the fitted trajectory, the dashed curve the projection, and the vertical line the estimated peak year (approximately 54 publications around 2053; $R^2 = 0.553$).



Figure 2. Leading affiliations, productive authors, and collaboration structure in mechanistic research on Ménière's disease, 2006 - 2026. (A) Cumulative author-affiliation occurrence counts of five highlighted affiliations. (B) Affiliations ranked by author-affiliation occurrence count after name consolidation. (C) Annual production of the leading authors; bubble size indicates publication count and color indicates citations per year. (D) Authors ranked by publication count after author-name disambiguation. (E) Co-authorship network; node size indicates PageRank, edge width collaboration strength, and color collaboration cluster.

Author productivity was similarly concentrated (**Figure 2(C)**). José Antonio López-Escámez was the most productive author, with 48 publications, followed by Álvaro Gallego-Martínez (18); Lidia Frejo contributed 16 publications, while Andrés Soto-Varela and Ismael Aran each contributed 15 publications (**Figure 2(D)**). López-Escámez maintained the longest publication trajectory, whereas several Chinese investigators became increasingly active in recent years.

The co-authorship network contained several interconnected research communities (**Figure 2(E)**). A major Spanish-led cluster centered on López-Escámez and included Aran, Soto-Varela, Frejo, Requena, and Pérez-Carpene, whereas a dis-

tinct Chinese cluster included Wang, Zhang, Song, and Li. López-Escámez established an otology and neurotology research group in 2002 and helped develop the international Ménière’s Disease Consortium; his work integrates clinical phenotyping, genomics, immunogenetics, and inflammatory endotyping. His position in the network therefore reflects both sustained productivity and a central role in multicenter collaboration.

Among the Chinese contributors, Yongdong Song and Haibo Wang were central members of the Shandong University-Shandong Provincial ENT Hospital network. Their earlier work encompassed vestibular phenotyping and surgical management of intractable Ménière’s disease, while recent studies extended this program toward translational immunology. In 2026, Song was a co-first author and Wang the senior author of a study linking oxidative stress-induced DNA release and macrophage STING activation to endolymphatic hydrops and audio-vestibular dysfunction. They also contributed to research associating sympathetic stress signaling, CD11b-positive myeloid inflammation, and G-CSF with disease progression.

3.3. Otology Journals and Landmark Reviews Shaped the Field

Following the contributor analysis, we examined publication venues and the intellectual structure of the field. Otology & Neurotology published the largest number of included articles (n = 21), followed by Acta Oto-Laryngologica (n = 15) and Scientific Reports (n = 12) (Figure 3(A)). Otology & Neurotology also showed the strongest sustained growth (Figure 3(B)) and the highest local h-index (h = 11), followed by Acta Oto-Laryngologica (h = 10) (Figure 3(C)). The participation of otology, neurology, genetics, and multidisciplinary journals underscores the cross-disciplinary nature of this literature.

Nakashima *et al.* (2016) was the most globally cited document (313 citations), followed by Gürkov *et al.* (2016; 233 citations) (Figure 3(D)). The historiographic map connected earlier foundational studies with later genetic, immune-inflammatory, and molecular investigations (Figure 3(E)). The co-citation network separated the knowledge base into interconnected clusters, with López-Escámez *et al.* (2015) and Merchant *et al.* (2005) acting as central references (Figure 3(F)).

To clarify the basis of their influence, we reviewed the leading cited documents in greater detail (Table 1). The two most cited records were broad reviews that synthesized widely relevant conceptual frameworks, whereas the leading original studies defined clinical subgroups, supported autoimmune involvement, or demonstrated familial clustering and genetic heterogeneity in Ménière’s disease.

Table 1. Characteristics of the Leading Globally Cited Documents.

Type	Article	Principal contribution	Global citations
Review	Nakashima <i>et al.</i> (2016)	Integrated pathophysiology, diagnosis, imaging, treatment, and quality-of-life evidence for Ménière’s disease.	313
Review	Gürkov <i>et al.</i> (2016)	Re-evaluated endolymphatic hydrops and proposed a pathology- and imaging-based classification of hydropic ear disease.	233

Continued

Original	Frejo <i>et al.</i> (2017)	Cluster analysis of 988 unilateral cases identified five clinically distinct Ménière's disease subgroups.	169
Original	Gazquez <i>et al.</i> (2011)	Analysis of 690 cases found increased prevalence of several systemic autoimmune diseases.	164
Original	Requena <i>et al.</i> (2013)	Demonstrated familial clustering and genetic heterogeneity in Ménière's disease.	142

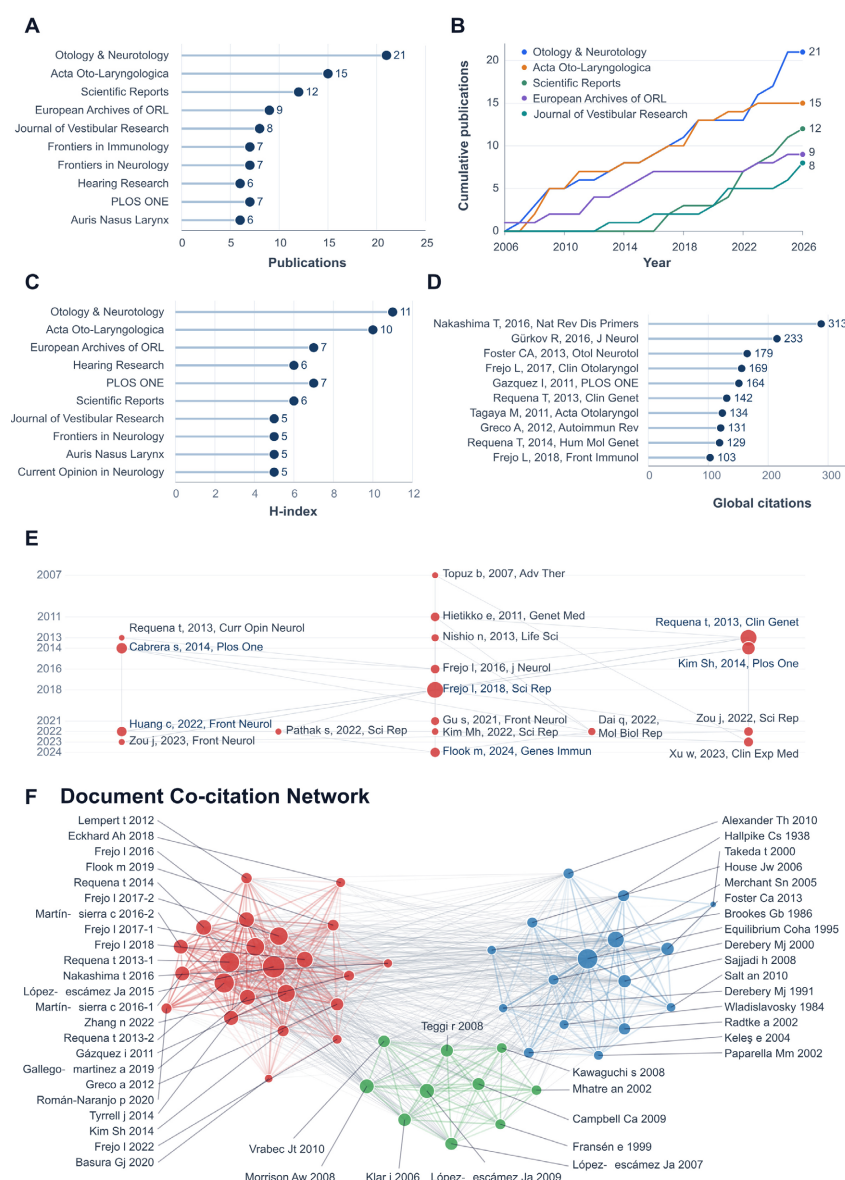


Figure 3. Publication sources, highly cited documents, and intellectual structure of mechanistic research on Ménière's disease, 2006 - 2026. (A) Sources ranked by publication count. (B) Cumulative output of leading sources. (C) Local source impact measured by h-index within the dataset. (D) Documents ranked by global citations. (E) Historiographic network of direct citation relationships. (F) Document co-citation network; node size indicates PageRank centrality, edge width indicates co-citation strength, and color indicates cluster membership.

3.4. Genetics and Inflammation Emerged as Major Themes

Building on the journal and citation analyses, we evaluated the thematic composition of the filtered keyword dataset. Endolymphatic hydrops was the most frequent term (31 occurrences), followed by exome sequencing and genetics (eight each), magnetic resonance imaging (six), and aldosterone and inflammation (five each) (**Figure 4(A)**). Its cumulative frequency increased most strongly, particularly in 2025, whereas the remaining topics showed more gradual growth (**Figure 4(B)**).

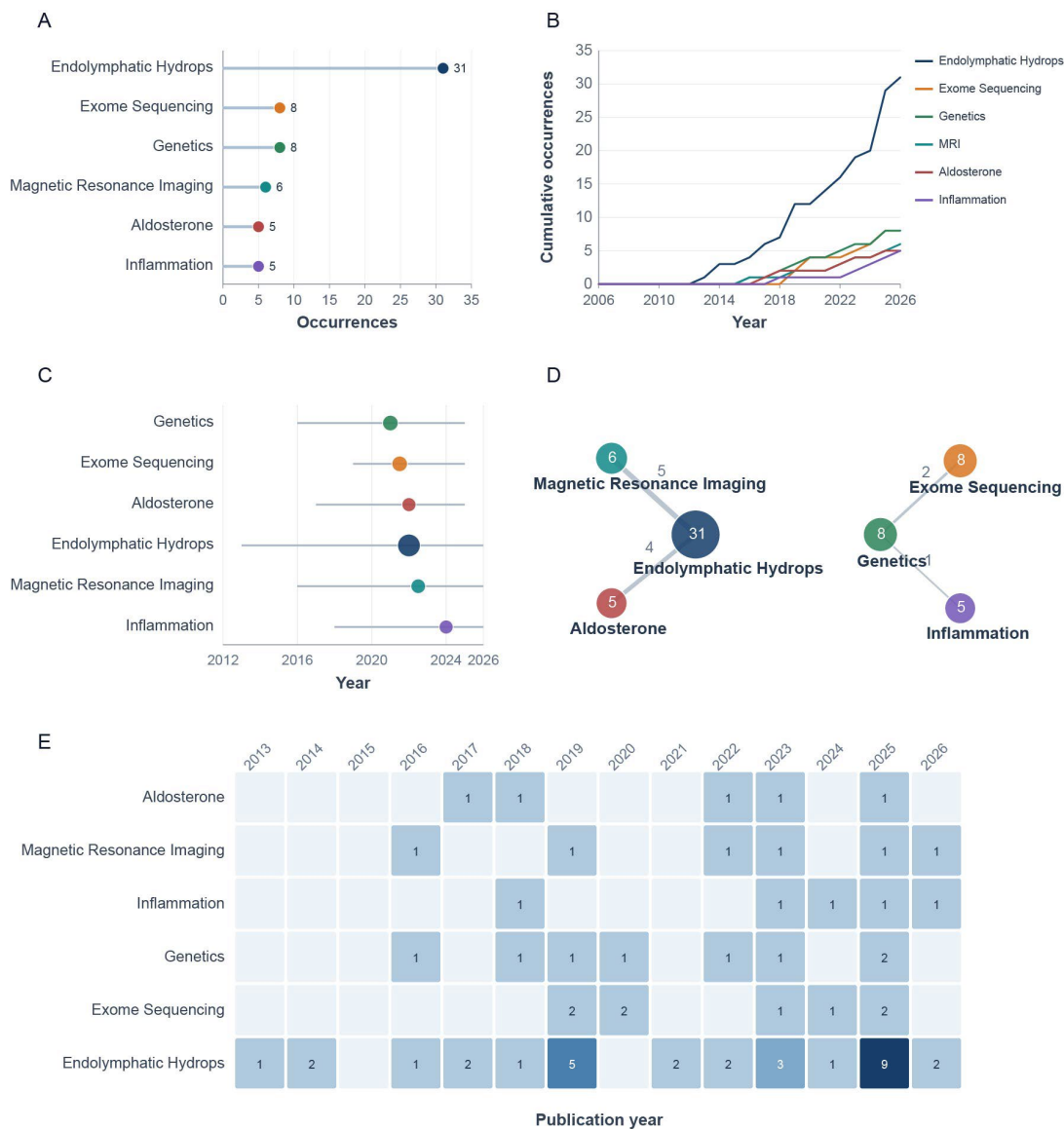


Figure 4. Keyword landscape and temporal evolution after removal of predefined nonspecific terms. (A) Frequencies of the six most frequent retained keywords. (B) Cumulative keyword occurrences, 2006 - 2026. (C) Temporal span of each keyword; lines indicate first and last publication years, while bubble position and size indicate median year and frequency. (D) Keyword co-occurrence network; node size indicates frequency and edge width the number of shared documents. (E) Annual keyword heatmap; darker cells indicate higher frequencies.

Genetics first appeared in 2016, followed by aldosterone in 2017, inflammation in 2018, and exome sequencing in 2019; inflammation and magnetic resonance imaging remained active through 2026 (**Figure 4(C)**). In the co-occurrence network, endolymphatic hydrops was linked mainly to magnetic resonance imaging and aldosterone, while genetics clustered with exome sequencing and, less strongly, inflammation (**Figure 4(D)**). The annual heatmap confirmed persistent interest in endolymphatic hydrops, increasing activity in genetics and exome sequencing, and more continuous representation of inflammation and magnetic resonance imaging during 2023 - 2026 (**Figure 4(E)**).

3.5. Inflammatory Research Shifted toward Molecularly Defined Endotypes

The increasing prominence of inflammation in **Figure 4** motivated a focused analysis of immune-inflammatory mechanisms. A PubMed search combining Ménière's disease with terms related to inflammation, immunity, autoimmunity, cytokines, inflammasomes, immunogenetics, the blood-labyrinth barrier, and the endolymphatic sac retrieved 338 records published from June 1, 2006, to June 1, 2026. After title and abstract screening, 91 studies with direct mechanistic relevance were retained; records limited to incidental inflammatory mentions, non-Ménière conditions, epidemiology, diagnosis, imaging, or non-mechanistic treatment were excluded.

Annual output remained low during the early period but increased after 2020: 52 of the 91 studies were published during 2021 - 2026, with a peak of 11 studies in 2024 (**Figure 5(A)**). Greco *et al.* (2012) was the most cited article (95 citations), followed by Frejo *et al.* (2018) and Calabrese *et al.* (2010), each with 86 citations (**Figure 5(B)**). Several recent studies showed high Relative Citation Ratios despite lower cumulative citation counts, indicating strong impact relative to articles of similar age and field.

Theme evolution showed a shift from broad autoimmune hypotheses toward more specific inflammatory mechanisms (**Figure 5(C)**). Autoimmunity and allergy dominated 2007 - 2012 (13 studies), whereas cytokines and immune endotypes increased to 14 studies in 2023 - 2026. Immunogenetics and multi-omics remained active across successive periods, and studies of the blood-labyrinth barrier and endolymphatic sac increased in the latest interval. Innate signaling and inflammasome research also emerged, although the number of studies remained limited.

The temporal citation network connected early studies of autoimmunity, allergy, and oxidative injury with later work on cytokine-defined endotypes, immunogenetics, multi-omics, innate signaling, inflammasome activation, and barrier dysfunction (**Figure 5(D)**). Node position indicates publication year and dominant theme, node size represents citation count, and edges denote direct citations within the 91-study dataset. Together, the network supports a transition toward biologically defined subgroups and more specific molecular and barrier-related mechanisms.

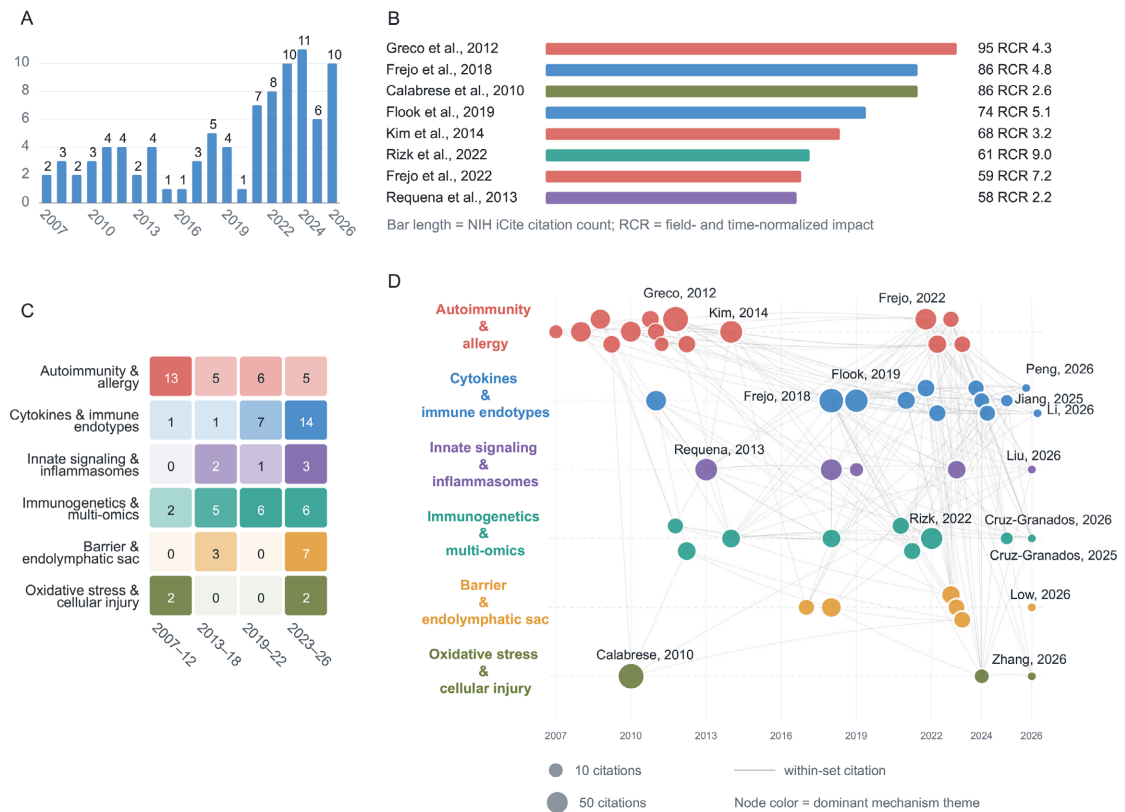


Figure 5. Evolution and citation structure of immune-inflammatory research in Ménière’s disease. (A) Annual output of 91 mechanism-focused studies, 2007 - 2026. (B) Eight influential articles ranked by NIH iCite citation count; the Relative Citation Ratio provides field- and time-normalized impact. (C) Evolution of six mechanistic themes. (D) Direct citation backbone of 50 influential or emerging studies; node size indicates citation count, color the dominant theme, and edges direct citation relationships within the dataset.

4. Discussion

Mechanistic research on Ménière’s disease has accelerated since 2020, with China and Spain forming major collaborative centers and the field shifting from a predominantly hydrops-centered description toward genetic susceptibility, immune-inflammatory endotypes, innate immune signaling, and blood-labyrinth barrier dysfunction. In contrast to earlier bibliometric maps dominated by broad clinical, diagnostic, therapeutic, or imaging themes [22]-[25], mechanism-focused screening revealed a more specific transition toward genetic susceptibility, molecular endotypes, epithelial stress, and innate immune activation.

The author analysis identified José Antonio López-Escámez as the most influential contributor, while Yongdong Song and Haibo Wang represented an increasingly prominent Chinese research network. López-Escámez’s work has progressed from international diagnostic criteria and multicenter clinical phenotyping to familial genes and cytokine- and multiomic-defined endotypes [1] [7]-[12]. Wang established a large clinical and translational platform for vertigo and hearing disorders, within which Song has moved from vestibular phenotyping and surgical studies toward experimental mechanisms. Their recent investigations of

sympathetic stress signaling and macrophage STING activation exemplify this transition from symptom control to therapeutically tractable upstream pathways [29] [30].

Citation impact should be interpreted in relation to article scope. Nakashima *et al.* and Gürkov *et al.* became foundational by integrating pathology, diagnostic criteria, imaging, and treatment while in vivo hydrops imaging was reshaping clinical concepts [2] [4]. Among original studies, Frejo *et al.*'s five-subtype analysis of 988 unilateral cases offered a reproducible framework for genetic, biomarker, and trial research [7], Gazquez *et al.* supported an association with systemic autoimmunity [31], and Requena *et al.* demonstrated familial clustering and genetic heterogeneity [32]. These studies were influential because they transformed heterogeneous clinical observations into testable immunologic and genetic subgroups. The subsequent genome-wide study of 8969 cases broadened the genetic architecture by implicating inner-ear developmental loci, although the modest effects support susceptibility rather than genetic determinism [33].

Figure 5 shows that inflammatory research is moving from a nonspecific autoimmune hypothesis toward testable cellular endotypes. Clinical cohort and peripheral-blood profiling studies identified an IL-1 β -high subgroup with increased IL6 and INHBA expression [10], separated monocyte-driven disease from an immunologically inactive subgroup using single-cell multiomics [11], and distinguished autoimmune, allergic, autoinflammatory, and low-cytokine longitudinal patterns [12]. These clinical associations and peripheral biomarker findings define candidate endotypes but do not by themselves establish causality. They are consistent with broader syntheses of NF- κ B-mediated inflammation and cytokine-defined endophenotypes [34], while Mendelian-randomization findings provide preliminary genetic-instrument evidence for selected circulating mediators [35]. Experimental studies in disease-relevant models have extended this framework upstream and closer to attacks: stress-related β -adrenergic signaling activated pro-inflammatory myeloid cells [29], DNA released after oxidative hair-cell injury activated STING in vestibular macrophages [30], and macrophage-derived CXCL8 was proposed to recruit inflammatory cells during attacks [36]. Together with clinical imaging and tissue evidence of blood-labyrinth barrier permeability [15]-[17], these findings support interaction among systemic inflammation, local epithelial stress, and resident macrophages. However, IL-1 β /NLRP3, cGAS-STING, CXCL8, and adrenergic signaling should be regarded as candidate mechanisms requiring independent human confirmation, not as validated therapeutic targets.

Future studies should therefore recruit patients by validated clinical and molecular endotype and pair samples obtained during attacks and remission with delayed-contrast inner-ear MRI, audiovestibular measures, genetics, and single-cell or spatial multiomics. Causal models should test the sequence linking epithelial stress, ion and water transport, barrier leakage, macrophage activation, cytokine recruitment, and hydrops; endolymphatic-sac receptor and transport biology offers an additional mechanistic bridge [13] [14] [37]. Candidate mechanisms re-

quiring further confirmation include IL-1 β /NLRP3, TNF-related endotypes, CXCL8, cGAS-STING, sympathetic β -adrenergic signaling, and blood-labyrinth barrier regulation. Biomarker-enriched early-phase trials with objective hearing, vestibular, imaging, and molecular endpoints will be required before these pathways can be generalized to clinical care.

This study has several limitations. Restriction to PubMed may have omitted relevant records indexed only in other databases, whose coverage and retrieval functions differ [38]. Although two reviewers screened records independently and resolved disagreements by consensus, screening agreement was not formally quantified; manual eligibility decisions, keyword exclusion, and author or affiliation consolidation therefore still involved judgment. Citation-based indicators also favor older publications despite the complementary use of the Relative Citation Ratio [28], while keywords depend on reporting practices and may not capture mechanisms described only in full text. Finally, the long-term publication projection and the focused inflammatory analysis should be regarded as exploratory rather than predictive.

5. Conclusion

This study depicts a field in transition from descriptive hydrops research to biologically stratified investigation. Internationally connected research networks, clinically useful subtyping, and rapidly advancing genetic and inflammatory evidence support an integrated model in which susceptibility, barrier disturbance, epithelial stress, and immune activation converge. Determining which mechanism predominates in each patient and disease stage is the essential next step toward reproducible biomarkers and individualized therapy.

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Author Contributions

Shengxi Jin: Writing—original draft. Yuxi Guo: Formal analysis and visualization. Hui Dang, Guoqiao Chen, and Shoude Zhang: Data curation and investigation. Yinzhe Gai and Hong Pan: Writing—review and editing. Xiuwen Jiang: Conceptualization, supervision, and funding acquisition. All authors reviewed and approved the final manuscript.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

- [1] Lopez-Escamez, J.A., Carey, J., Chung, W., Goebel, J.A., Magnusson, M., Mandalà,

- M., *et al.* (2015) Diagnostic Criteria for Menière's Disease. *Journal of Vestibular Research*, **25**, 1-7. <https://doi.org/10.3233/ves-150549>
- [2] Nakashima, T., Pykkö, I., Arroll, M.A., Casselbrant, M.L., Foster, C.A., Manzoor, N.F., *et al.* (2016) Meniere's Disease. *Nature Reviews Disease Primers*, **2**, Article No. 16028. <https://doi.org/10.1038/nrdp.2016.28>
- [3] Merchant, S.N., Adams, J.C. and Nadol Jr., J.B. (2005) Pathophysiology of Meniere's Syndrome: Are Symptoms Caused by Endolymphatic Hydrops? *Otology & Neurotology*, **26**, 74-81. <https://doi.org/10.1097/00129492-200501000-00013>
- [4] Gürkov, R., Pykkö, I., Zou, J. and Kentala, E. (2016) What Is Menière's Disease? A Contemporary Re-Evaluation of Endolymphatic Hydrops. *Journal of Neurology*, **263**, 71-81. <https://doi.org/10.1007/s00415-015-7930-1>
- [5] Foster, C.A. and Breeze, R.E. (2013) Endolymphatic Hydrops in Ménière's Disease: Cause, Consequence, or Epiphenomenon? *Otology & Neurotology*, **34**, 1210-1214. <https://doi.org/10.1097/mao.0b013e31829e83df>
- [6] Rizk, H.G., Mehta, N.K., Qureshi, U., Yuen, E., Zhang, K., Nkrumah, Y., *et al.* (2022) Pathogenesis and Etiology of Ménière Disease: A Scoping Review of a Century of Evidence. *JAMA Otolaryngology—Head & Neck Surgery*, **148**, 360-368. <https://doi.org/10.1001/jamaoto.2021.4282>
- [7] Frejo, L., Martin-Sanz, E., Teggi, R., Trinidad, G., Soto-Varela, A., Santos-Perez, S., *et al.* (2017) Extended Phenotype and Clinical Subgroups in Unilateral Meniere Disease: A Cross-Sectional Study with Cluster Analysis. *Clinical Otolaryngology*, **42**, 1172-1180. <https://doi.org/10.1111/coa.12844>
- [8] Parra-Perez, A.M. and Lopez-Escamez, J.A. (2023) Types of Inheritance and Genes Associated with Familial Meniere Disease. *Journal of the Association for Research in Otolaryngology*, **24**, 269-279. <https://doi.org/10.1007/s10162-023-00896-0>
- [9] Frejo, L., Requena, T., Okawa, S., Gallego-Martinez, A., Martinez-Bueno, M., Aran, I., *et al.* (2017) Regulation of Fn14 Receptor and NF- κ B Underlies Inflammation in Meniere's Disease. *Frontiers in Immunology*, **8**, Article ID: 1739. <https://doi.org/10.3389/fimmu.2017.01739>
- [10] Flook, M., Rojano, E., Gallego-Martinez, A., Escalera-Balsera, A., Perez-Carpena, P., Moleon, M.D.C., *et al.* (2024) Cytokine Profiling and Transcriptomics in Mononuclear Cells Define Immune Variants in Meniere Disease. *Genes & Immunity*, **25**, 124-131. <https://doi.org/10.1038/s41435-024-00260-z>
- [11] Cruz-Granados, P., Frejo, L., Perez-Carpena, P., Amor-Dorado, J.C., Dominguez-Duran, E., Fernandez-Nava, M.J., *et al.* (2024) Multiomic-Based Immune Response Profiling in Migraine, Vestibular Migraine and Meniere's Disease. *Immunology*, **173**, 768-779. <https://doi.org/10.1111/imm.13863>
- [12] Frejo, L., Cara, F.E., Flook, M., Robles-Bolivar, P., Escalera-Balsera, A., Montilla-Ibañez, M.A., *et al.* (2025) Allergy and Autoinflammation Drive Persistent Systemic Inflammatory Response in Meniere Disease: A Longitudinal Study. *Clinical Immunology*, **271**, Article 110413. <https://doi.org/10.1016/j.clim.2024.110413>
- [13] Maekawa, C., Kitahara, T., Kizawa, K., Okazaki, S., Kamakura, T., Horii, A., *et al.* (2010) Expression and Translocation of Aquaporin-2 in the Endolymphatic Sac in Patients with Meniere's Disease. *Journal of Neuroendocrinology*, **22**, 1157-1164. <https://doi.org/10.1111/j.1365-2826.2010.02060.x>
- [14] Matsubara, A., Miyashita, T., Nakashima, K., Mori, N., Song, S. and Hoshikawa, H. (2022) Low-Salt Diet Increases mRNA Expression of Aldosterone-Regulated Transporters in the Intermediate Portion of the Endolymphatic Sac. *Pflügers Archiv-European Journal of Physiology*, **474**, 505-515.

- <https://doi.org/10.1007/s00424-021-02661-9>
- [15] Pakdaman, M.N., Ishiyama, G., Ishiyama, A., Peng, K.A., Kim, H.J., Pope, W.B., *et al.* (2016) Blood-Labyrinth Barrier Permeability in Menière Disease and Idiopathic Sudden Sensorineural Hearing Loss: Findings on Delayed Postcontrast 3D-FLAIR MRI. *American Journal of Neuroradiology*, **37**, 1903-1908. <https://doi.org/10.3174/ajnr.a4822>
 - [16] Ishiyama, G., Lopez, I.A., Ishiyama, P., Vinters, H.V. and Ishiyama, A. (2017) The Blood Labyrinthine Barrier in the Human Normal and Meniere's Disease Macula Utricle. *Scientific Reports*, **7**, Article No. 253. <https://doi.org/10.1038/s41598-017-00330-5>
 - [17] Song, C.I., Pogson, J.M., Andresen, N.S. and Ward, B.K. (2021) MRI with Gadolinium as a Measure of Blood-Labyrinth Barrier Integrity in Patients with Inner Ear Symptoms: A Scoping Review. *Frontiers in Neurology*, **12**, Article ID: 662264. <https://doi.org/10.3389/fneur.2021.662264>
 - [18] Huang, L., Wang, Q., Huang, C., Zhou, Z., Peng, A. and Zhang, Z. (2023) Untargeted Metabolomic Analysis in Endolymphatic Sac Luminal Fluid from Patients with Meniere's Disease. *Journal of the Association for Research in Otolaryngology*, **24**, 239-251. <https://doi.org/10.1007/s10162-023-00887-1>
 - [19] Deng, W., Luo, Y., Wu, H., Lao, H., Zhu, Y., Wang, L., *et al.* (2025) Microscale Proteomic Analysis of the Endolymphatic Sac in Menière's Disease Patients. *Otology & Neurotology*, **46**, 587-592. <https://doi.org/10.1097/mao.0000000000004464>
 - [20] Aria, M. and Cuccurullo, C. (2017) Bibliometrix: An R-Tool for Comprehensive Science Mapping Analysis. *Journal of Informetrics*, **11**, 959-975. <https://doi.org/10.1016/j.joi.2017.08.007>
 - [21] Donthu, N., Kumar, S., Mukherjee, D., Pandey, N. and Lim, W.M. (2021) How to Conduct a Bibliometric Analysis: An Overview and Guidelines. *Journal of Business Research*, **133**, 285-296. <https://doi.org/10.1016/j.jbusres.2021.04.070>
 - [22] Zou, W., Li, Q., Peng, F. and Huang, D. (2022) Worldwide Meniere's Disease Research: A Bibliometric Analysis of the Published Literature between 2002 and 2021. *Frontiers in Neurology*, **13**, Article ID: 1030006. <https://doi.org/10.3389/fneur.2022.1030006>
 - [23] Wang, B., Li, Y., Zhang, Q., Sun, J., Tian, Y., Ma, D., *et al.* (2023) A Bibliometric and Visualization Study of Meniere's Disease: Current Status and Global Hotspots and Emerging Trends. *Medicine*, **102**, e33156. <https://doi.org/10.1097/md.00000000000033156>
 - [24] Wu, Y., Quan, X., Hu, Y., Song, J. and Tian, C. (2025) Current Status and Trends in Research Relating to the Diagnosis and Treatment of Meniere's Disease: A Bibliometric Analysis. *The Journal of International Advanced Otolaryngology*, **21**, 1-11. <https://doi.org/10.5152/iao.2025.251975>
 - [25] Wu, X. (2026) Global Research Trends in Magnetic Resonance Imaging and Meniere's Disease: A Bibliometric and Visualized Study. *European Archives of Otorhino-Laryngology*, **283**, 2279-2290. <https://doi.org/10.1007/s00405-025-09965-x>
 - [26] Chen, C. (2006) CiteSpace II: Detecting and Visualizing Emerging Trends and Transient Patterns in Scientific Literature. *Journal of the American Society for Information Science and Technology*, **57**, 359-377. <https://doi.org/10.1002/asi.20317>
 - [27] Priem, J., Piwowar, H. and Orr, R. (2022) OpenAlex: A Fully-Open Index of Scholarly Works, Authors, Venues, Institutions, and Concepts. *26th International Conference on Science and Technology Indicators*, Granada, 7-9 September 2022.
 - [28] Hutchins, B.I., Yuan, X., Anderson, J.M. and Santangelo, G.M. (2016) Relative Cita-

- tion Ratio (RCR): A New Metric That Uses Citation Rates to Measure Influence at the Article Level. *PLOS Biology*, **14**, e1002541. <https://doi.org/10.1371/journal.pbio.1002541>
- [29] Li, X., Zhang, N., Song, Y., Zhang, T., Lyu, Y., Jian, H., *et al.* (2026) A Stress-Neuroendocrine-Myeloid Inflammation Axis Is Associated with the Progression of Ménière's Disease. *Brain, Behavior, & Immunity-Health*, **52**, Article 101193. <https://doi.org/10.1016/j.bbih.2026.101193>
 - [30] Liu, J., Li, N., Mu, Y., Song, Y., Lu, Y., Xu, X., *et al.* (2026) Sting Signaling in Vestibular Macrophages Underlies Ménière's Disease Pathogenesis. *Journal of Neuroinflammation*, **23**, Article No. 161. <https://doi.org/10.1186/s12974-026-03812-4>
 - [31] Gazquez, I., Soto-Varela, A., Aran, I., Santos, S., Batuecas, A., Trinidad, G., *et al.* (2011) High Prevalence of Systemic Autoimmune Diseases in Patients with Menière's Disease. *PLOS ONE*, **6**, e26759. <https://doi.org/10.1371/journal.pone.0026759>
 - [32] Requena, T., Espinosa-Sanchez, J.M., Cabrera, S., Trinidad, G., Soto-Varela, A., Santos-Perez, S., *et al.* (2013) Familial Clustering and Genetic Heterogeneity in Meniere's Disease. *Clinical Genetics*, **85**, 245-252. <https://doi.org/10.1111/cge.12150>
 - [33] Shi, Z., Mandla, R., Li, J., Li, X., Zhang, Z., Chen, S., *et al.* (2026) Genome-Wide Analysis Implicates Inner Ear Development in Ménière Disease. *The American Journal of Human Genetics*, **113**, 1509-1520. <https://doi.org/10.1016/j.ajhg.2026.05.011>
 - [34] Frejo, L. and Lopez-Escamez, J.A. (2022) Cytokines and Inflammation in Meniere Disease. *Clinical and Experimental Otorhinolaryngology*, **15**, 49-59. <https://doi.org/10.21053/ceo.2021.00920>
 - [35] Xie, S., Zhang, R., Tang, Y. and Dai, Q. (2024) Exploring Causal Correlations between Inflammatory Cytokines and Ménière's Disease: A Mendelian Randomization. *Frontiers in Immunology*, **15**, Article ID: 1373723. <https://doi.org/10.3389/fimmu.2024.1373723>
 - [36] Peng, L., Zhu, B., Li, Y., Lan, Y., Zhan, X., Pan, X., *et al.* (2026) Macrophage-Derived CXCL8 as a Mediator of Inflammatory Attacks in Meniere's Disease. *Frontiers in Immunology*, **17**, Article ID: 1683879. <https://doi.org/10.3389/fimmu.2026.1683879>
 - [37] Møller, M.N., Kirkeby, S., Vikeså, J., Nielsen, F.C. and Caye-Thomasen, P. (2016) Expression of Histamine Receptors in the Human Endolymphatic Sac: The Molecular Rationale for Betahistine Use in Menieres Disease. *European Archives of Oto-Rhino-Laryngology*, **273**, 1705-1710. <https://doi.org/10.1007/s00405-015-3731-5>
 - [38] Gusenbauer, M. and Haddaway, N.R. (2020) Which Academic Search Systems Are Suitable for Systematic Reviews or Meta-Analyses? Evaluating Retrieval Qualities of Google Scholar, PubMed, and 26 Other Resources. *Research Synthesis Methods*, **11**, 181-217. <https://doi.org/10.1002/jrsm.1378>

Supplementary Material

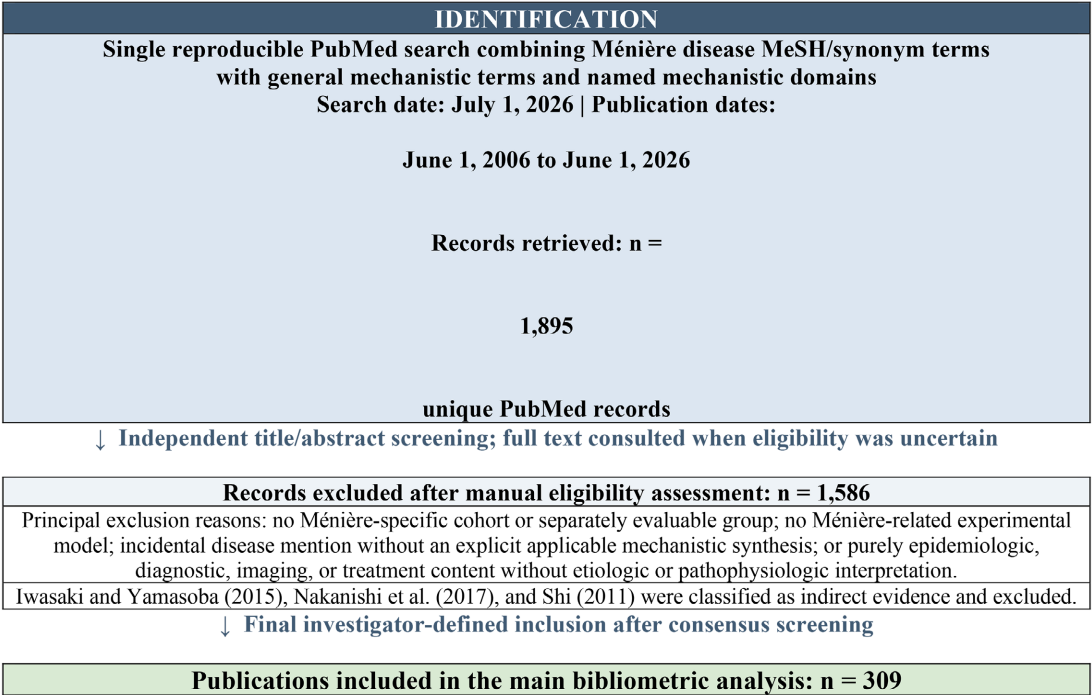


Figure S1. Mechanism-focused literature identification, screening, and inclusion flow.