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Immune-Related Disorders Associated With Ménière's Disease: A Systematic Review and Meta-analysis

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Abstract

Objective. To analyze evidence supporting an association between immune-related diseases and Ménière's disease (MD) since it has long been thought to be related to autoimmune disorders and allergies.

Data Sources. We retrieved records from Pubmed, Web of Science, Scopus, and Cochrane Library to identify studies published between January 2002 and October 2022.

Review Methods. Articles were independently assessed by 2 reviewers and verified by a third reviewer. Published cross-sectional studies, cohort/longitudinal studies, case series, and noncomparative cohort studies were considered eligible for inclusion. We conducted a systematic review and meta-analysis according to a registered protocol on the International Prospective Register of Systematic Reviews and Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines. Selected studies were classified into 2 groups: epidemiological and genetic association studies. Relative frequencies and odds ratios (ORs) for each autoinflammatory/autoimmune disease or genetic marker reported to be associated with MD.

Results. Fifteen studies from 6 countries met our inclusion criteria. Nine are epidemiological studies and 6 are genetic association studies. The epidemiological studies were used to perform 3 different meta-analyses. Airway allergic disease and autoimmune thyroid disease showed a significant association with MD (OR = 2.27 [2.08-2.48] and OR = 1.35 [1.25-1.46]); while rheumatoid arthritis did not (OR = 0.63 [0.28-1.41]). Other comorbidities also showed a significant association with MD like chronic obstructive pulmonary disease, vitiligo, fibromyalgia, arthritis, and psoriasis.

Conclusion. Epidemiological evidence supports an association between MD and immune-related disorders in European and Asian populations, with population-specific effects. The evaluation of thyroid diseases, airway allergic diseases, and other inflammatory diseases should be implemented in the clinical management of MD patients.

Keywords

allergy, autoimmune disorders, immune-related disorders, Ménière's disease, proinflammatory cytokines

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Ménière's Disease (MD) is a rare chronic disorder of the inner ear characterized by sensorineural hearing loss, episodic vertigo, tinnitus, and aural fullness.[1] Its origin is considered to be multifactorial, and epidemiological evidence suggests a genetic contribution and an association with autoimmune diseases.[2]

Data are supporting an altered immune response in MD. The finding of elevated levels of autoantibodies or circulating immune complexes against inner ear antigens in the serum of some patients with MD[3] and the association of allelic variants in the *TLR10, NFKB1*, and *MICA* genes with the progression of hearing loss in patients with MD[4-6] support this hypothesis. A subset of MD patients has basal elevated levels of proinflammatory cytokines and allergic extracts from *Aspergillus* and *Penicillium* may induce a higher proinflammatory response supporting a chronic inflammatory disorder involving tumor necrosis factor (TNF)-α and interleukin (IL)-1β.[7] Moreover, bilateral MD was reported to be

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associated with a common regulatory variant (rs4947296) in a large case-control study involving multiple genes and nuclear factor (NF)-κB-mediated inflammation.[8]

Epidemiological studies show that MD displays an elevated prevalence of systemic and tissue-specific immune-related diseases such as rheumatoid arthritis,[9] allergic rhinitis,[10] systemic lupus erythematosus,[11] allergic dermatitis,[12] ankylosing spondylitis,[11] asthma,[13] and several thyroid diseases.[14] Taken together, these findings suggest an autoimmune background in a subset of patients with MD; however, the population-specific effect involving genetic and shared environmental factors has not been considered and they may explain differences in the pathophysiology of MD across different continents. For these reasons, we conducted a systematic review and meta-analysis to evaluate the available evidence to support an association between MD and immune-related diseases.

Methods

Search Strategy

We performed a systematic search of the literature published between January 2002 and October 2022, using 4 electronic data sources: Pubmed, Web of Science, Scopus, and Cochrane. The search was conducted on October 21, 2022. The search strategy used the string: ("autoimmune" OR "autoinflammatory" OR "asthma" OR "allergic rhinitis" OR "allergic dermatitis" OR "rheumatoid arthritis" OR "lupus" OR "ankylosing spondylitis" OR psoriasis OR "Crohn disease" OR "ulcerative colitis" OR "autoimmune thyroid disease") AND ("meniere disease" OR "meniere's disease" OR "meniere syndrome" OR "meniere's syndrome").

Eligibility Criteria

Published cross-sectional, case-control, and cohort studies were considered eligible for inclusion. The list of references for these studies was inspected and eligible studies were also included. Studies were excluded if they did not mention the word "Meniere" in the title, abstract, or keywords or if they were review articles, single case reports, books, or editorials or if they did not include a comparison or control group; studies not published in English were also excluded (**Figure 1**).

Selection Process

Literature search results were imported to the Zotero reference manager (www.zotero.org), and duplicate references were removed. We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines[15] to document the number of studies identified during the searching process, for both the included and excluded studies (Supplemental Table S1, available online).

Two investigators (L.F. and J.V.) independently collected the data and discrepancies were resolved through discussion with the review team. Outcome data was then independently verified by a third reviewer (J.A.L.-E.). The protocol was registered and can be accessed in the International Prospective Register of Systematic Reviews with the number CRD42022364759.

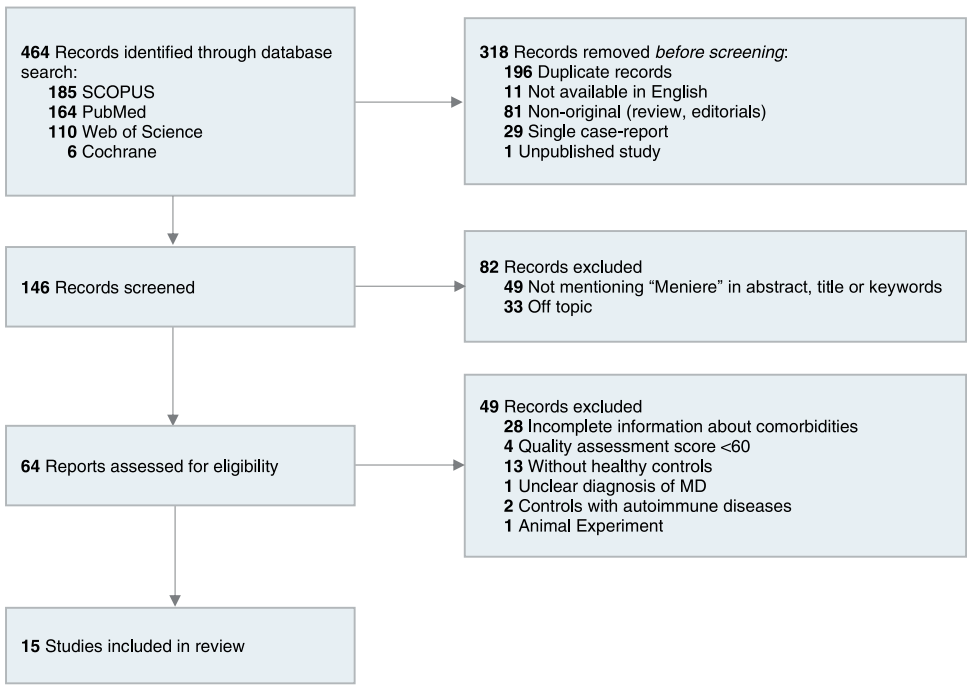

Figure 1. Systematic review flowchart showing the process to include the studies. MD, Ménière's disease.

Data Extraction

One investigator extracted all relevant study characteristics, methods, and results from each included study. Another different investigator verified all extracted data and discrepancies were resolved through discussion with a third reviewer. Studies were divided into 2 groups: Epidemiological studies and genetic association studies, according to their main outcome.

Risk of Bias Assessment

Two of us independently assessed the quality of reporting for each population-based study using the Strengthening the Reporting of Observational Studies in Epidemiology instrument.[16] Both reviewers agreed to include 8 of the population-based studies selected. Analysis of the concordance, according to Cohen κ coefficient, was 88.89% ($\kappa = 0.61$).

To assess the quality of the genetic association studies selected, we use the criteria proposed by Amanat et al.[2] We formulated 7 of the 8 questions initially proposed, leaving out question number 6 ("extreme phenotype") was not considered because it does not apply to our studies. With this method, we discarded 4 genetic studies from our review. We resolved all discrepancies during the risk of bias assessment by discussion or adjudication by a third investigator.

Statistical Analysis

We used the odds ratio (OR) to estimate the effect size of the association between MD and concomitant disease. Heterogeneity was examined using the Q test, and $p \leq 0.10$ was considered statistically significant. To quantify the dispersion of effect sizes in our meta-analysis, we used the I^2 index, and the following score was applied: less than 25% indicated very low; 25% to less than 50%, low; 50% to less than 75%, moderate; and 75% or greater, large.[17] For epidemiological studies, we classified the diseases into 2 subgroups. Asthma, allergic asthma, and allergic rhinitis were gathered into the umbrella term "Airway allergic diseases" and Graves' disease, hypothyroidism, thyroiditis, and goiter into "Autoimmune Thyroid Disease" to perform the meta-analysis. All statistical analyses and figures were performed by using "metafor" and "meta" R packages.[18]

Results

Study Screening

The first search found 464 records in the 4 repositories. Duplicates (n = 196), not published in English (n = 11), reviews and editorials (n = 81), single case-report (n = 29), and being unpublished (n = 1) were excluded. After the first screening, 49 papers were excluded because they did not contain the word "meniere" in their abstract or title and 33 were excluded for being considered off-topic. The remaining 64 articles were subjected to a second screening whereby 49 were excluded because they were not considered relevant to the aim of the review. Among the final 15 selected records, 9 were epidemiological and 6 were genetic association studies.

Study Characteristics

The studies were performed in Iran, Italy, South Korea, Spain, Taiwan, and the United Kingdom, comprising 12 case-control studies, 2 population-based cohort studies, and 1 case study. Data sources varied across studies: health care system or nationwide studies (n = 9), recruited participants in the community (n = 6).

The data from 6 studies[9,10,12-14,19] were extracted from the Korean National Health Insurance Service-Health Screening Cohort 2002 to 2015, which is a nationwide cohort sample of data representing approximately 1 million patients.[20] Another Asian Nationwide study included[21] used the Longitudinal Health Insurance Database 2000, which contains the medical reimbursement claims data of 1 million people randomly sampled from the entire population of Taiwan registered in 2000. On the other hand, the European population study was performed using the UKBiobank data,[22] which recruited 502,682 volunteers between 37 and 73 years of age between 2006 and 2010 in the United Kingdom.

All genetic association studies were case-control studies. The allelic variants included genes involved in inflammation and immune response, such as *HLA-DBR1*,[23] *MIF*,[24] *CCL5*,[25] *NFKB1*,[5] *TLR10*,[4] and several genes in the TWEAK/Fn14/CD163 pathway.[8]

MD-Associated Diseases in Epidemiological Studies

Autoimmune thyroid disease was found to be significantly associated with MD in both Asian and European descendent populations (**Figure 2** and **Table 1**). A strong significant association between MD and airway allergic diseases was observed in the East Asian population; however, this association has not been reported in the European population.

Other conditions such as chronic obstructive pulmonary disorder (COPD), vitiligo, and fibromyalgia were also found to be associated with MD in East Asian populations; in contrast, arthritis and psoriasis were reported to be associated with MD in European populations (**Figure 3**).

Meta-analysis of Epidemiological Studies

Airway Allergic Disease

The meta-analysis (Supplemental Table S2, available online) included 2 studies in East Asian populations showing a significant association between airway allergic disease and MD (OR = 2.27 [2.08-2.48]; $z = 18.75$; $p < 0.001$).

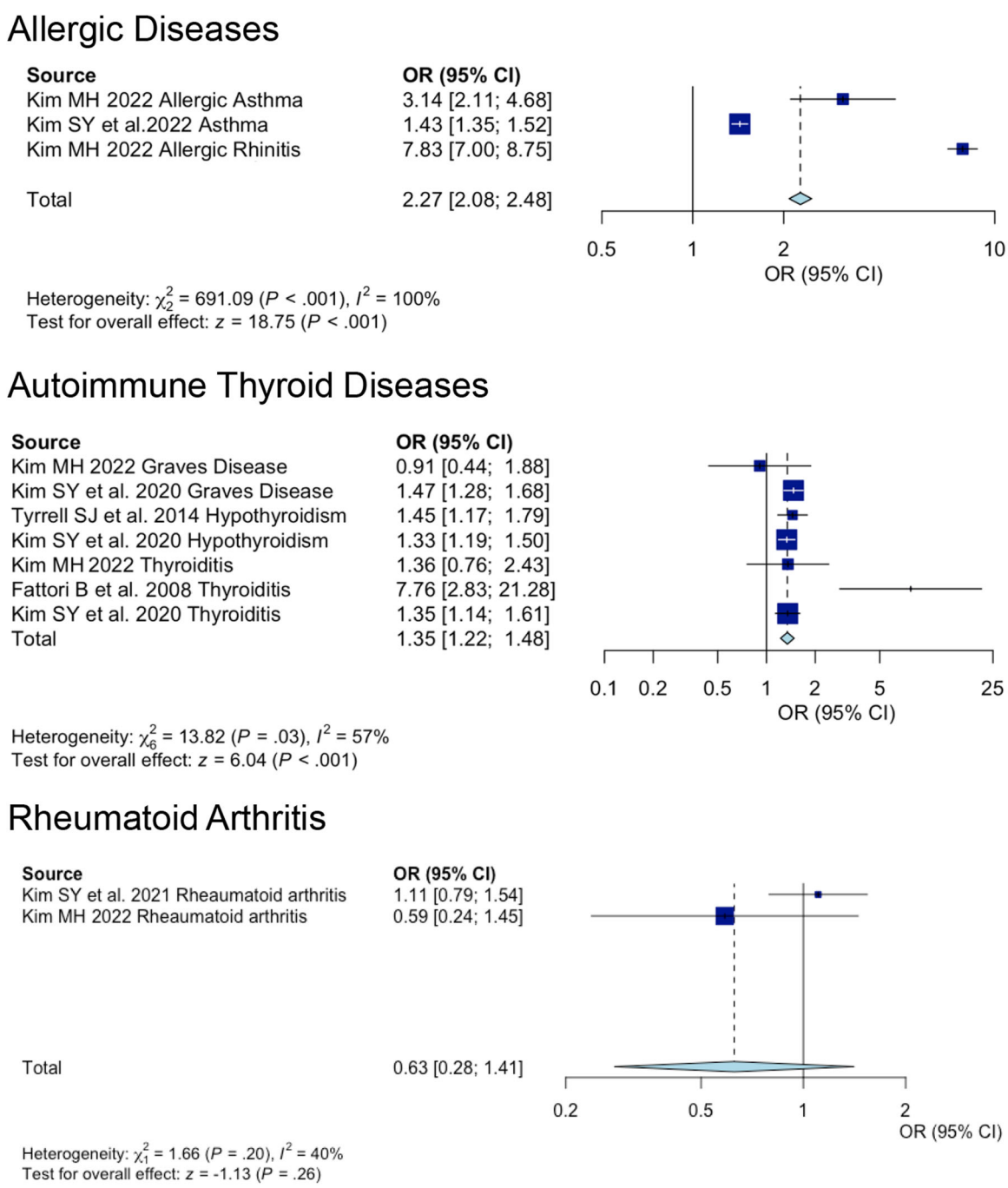

Figure 2. Meta-analyses of case-control studies showing an association between Ménière's disease and allergic diseases, autoimmune thyroid disease, and rheumatoid arthritis. CI, confidence interval; OR, odds ratio.

Autoimmune Thyroid Disease

Four studies were used to perform the meta-analysis (2 Asian, 2 European) finding a significant association between autoimmune thyroid disease and MD (OR = 1.35 [1.25-1.46]; $z = 7.38$; $p < 0.001$).

Rheumatoid Arthritis

The meta-analysis performed with 2 studies in the East Asian population was not significant (OR = 0.63 [0.28-1.41]; $z = -1.13$; $p = 0.26$).

Genetic Association Studies

The genetic association studies selected were performed on common variants (minor allelic frequency > 0.05) in candidate genes and they were carried out in Spain, Italy,[4,5,23] and Iran[24,25] (**Table 2**). Two of them included a replication study,[4,23] both in the Southern European population. These studies were performed in several Toll-like receptors (TLRs) and human leukocyte antigen (HLA) class II genes, but replication studies were conducted with small sample sizes and were not able to confirm the associations.[4,23]

Table 1. Epidemiological Studies Organized According to the Diseases Studied

Associated disease	Source	Year	Country	Study design	Nparticipants	Age,mean (SD)	Female, %	Frequency in cases, %	Frequency in controls, %	OR (95% CI)	STROBE score
Chronic obstructive pulmonary disease	Kim SY et al	2021	Korea	Nested case-control	38,670	NA	64.4	8.53	6.44	1.43 (1.30- 1.57)	21
Allergic asthma	Kim MH	2022	Korea	Nested case-control	22,143	49 (16.5)	67.2	1.59	0.51	3.15 (2.08-4.64)	17
Asthma	Kim SY et al	2022	Korea	Nested case-control	38,670	NA	64.4	23.78	17.89	1.45 (1.36- 1.54)	21
Allergic Rhinitis	Kim MH	2022	Korea	Nested case-control	22,143	49 (16.5)	67.2	79.43	33.05	7.82 (7.00-8.76)	17
Hay fever, rhinitis, and eczema	Tyrrell JS et al	2014	United Kingdom	Cross-sectional	504,058	59.4 (7)	58.4	21.41	19.87	1.10 (0.96-1.25)	19
Allergy or Hypersensitivity	Tyrrell JS et al	2014	United Kingdom	Cross-sectional	504,058	59.4 (7)	58.4	1.02	0.70	1.48 (0.83-2.41)	19
Atopic Dermatitis	Hahn HJ et al	2019	Korea	Population-based cohort	1,113,656	NA	49.9	0.52	0.73	0.72 (0.53-0.95)	17
Psoriasis	Tyrrell JS et al	2014	United Kingdom	Case-control	504,058	59.4 (7)	58.4	1.96	1.10	1.80 (1.20-2.58)	19
Vitiligo	Hahn HJ	2019	Korea	Population-based cohort	1,113,656	NA	49.9	0.24	0.11	2.16 (1.36-3.24)	17
Type 1 Diabetes Mellitus	Kim MH	2022	Korea	Nested case-control	22,143	49 (16.5)	67.2	0.15	0.39	0.40 (0.09-1.08)	17
Goiter	Kim SY et al	2020	Korea	Nested case-control	40,915	40-85+	64.7	5.65	4.21	1.37 (1.23-1.53)	20
Graves' Disease	Kim MH	2022	Korea	Nested case-control	22,143	49 (16.5)	67.2	0.40	0.44	0.93 (0.41-1.79)	17
	Kim SY et al	2020	Korea	Nested case-control	40,915	40-85+	64.7	3.57	2.46	1.47 (1.28-1.69)	20
Hypothyroidism	Kim SY et al	2020	Korea	Nested case-control	40915	40-85+	64.7	4.70	3.57	1.34 (1.19-1.51)	20
	Tyrrell JS et al	2014	United Kingdom	Case-control	504,058	59.4 (7)	58.4	6.82	4.81	1.4 (1.2-1.8)	19
Thyroiditis	Kim MH	2022	Korea	Nested case-control	22,143	49 (16.5)	67.2	0.65	0.48	1.37 (0.73-2.36)	17
	Kim SY et al	2020	Korea	Nested case-control	40,915	40-85+	64.7	2.13	1.58	1.35 (1.14-1.61)	20
	Fattori B et al	2007	Italy	Case-control	132	48.4 (14.4)	56.1	38.00	7.32	7.41 (2.82-22.38)	19
Rheumatoid arthritis	Kim MH	2022	Korea	Nested case-control	22,143	49 (16.5)	67.2	0.25	0.42	0.61 (0.21-1.35)	17
	Kim SY et al	2021	Korea	Nested case-control	15,190	NA	73.2	21.63	19.98	1.13 (0.81- 1.57)	22
Arthritis	Tyrrell JS et al	2014	United Kingdom	Case-control	504,058	59.4 (7)	58.4	20.97	10.41	2.28 (2.00-2.59)	19

(*continued*)

Table 1. (continued)

Associated disease	Source	Year	Country	Study design	Nparticipants	Age,mean (SD)	Female, %	Frequency in cases, %	Frequency in controls, %	OR (95% CI)	STROBE score
Ankylosing spondylitis	Kim MH	2022	Korea	Nested case-control	22,143	49 (16.5)	67.2	0.15	0.11	1.36 (0.31-3.95)	17
Fibromyalgia	Le TP et al	2020	Taiwan	A population-based retrospective cohort study	165,507	45.9 (16.9)	59.4	51.50	32.40	2.22 (2.12-2.32)	20

Abbreviations: CI, confidence interval; OR, odds ratio; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.

For allelic variants in the genes *MIF*, *NFKB1*, and *RANTES* (CCL5), no replication studies were performed, and they cannot be considered associated with MD.

The best evidence in genetic association studies with a replication cohort arises from the Immunochip, a genotyping array that included loci previously associated with 12 autoimmune disorders. A sex and age-matched case-control study including 420 Spanish patients with bilateral MD and 1630 controls identified a locus at 6p21.33, supporting an association (meta-analysis for the leading signal rs4947296, OR = 2.09 [1.66-2.63]; $p = 1.39 \times 10^{-9}$).[8] Gene expression profiles of homozygous genotype-selected peripheral blood mononuclear cells (PBMCs) for the variant rs4947296 demonstrated that this signal is a transexpression quantitative trait locus in PBMCs that regulates several TNF-related pathways, being the TWEAK/Fn14 pathway the top candidate. This pathway is involved in the modulation of inflammation in several human autoimmune diseases, including multiple sclerosis, systemic lupus erythematosus, or rheumatoid arthritis.

Discussion

This systematic review and meta-analysis summarize evidence from 9 epidemiological studies and 6 genetic studies to assess an association between MD and immune-related disorders. Taken together, these studies support an association of MD with autoimmune thyroid disease in European and Asian populations, suggesting a common immunogenetic contribution probably mediated by common variants with pleiotropic effects in several immune pathways.[26] One of these pathways is the TWEAK/Fn14 pathway which seems to be regulated by an eQTL (rs4947296) that is associated with bilateral MD[8] and early-onset hyperthyroidism.[27] However, more common variants associated with MD and autoimmune thyroid disease should contribute to this association and remain to be discovered.

Population-based studies allow us to know the relationship between MD and different diseases, considering the combined effect of common and rare genetic variation and the shared environment.[28] Interestingly, we have found population-specific effects in several population-based studies, including airway allergic disease, COPD, fibromyalgia and vitiligo in East Asian populations and rheumatoid arthritis and psoriasis in European population from the UK. Of note, the association with allergic disorders was confirmed in 3 studies in the East Asian population, but this association has not been reported in the European population. In contrast, rheumatoid arthritis and psoriasis were not associated with MD in the East Asian population.[9,10] This population-specific association in MD suggest different environmental factors that may contribute to maintaining an allergic inflammation in East Asian populations and an increased susceptibility to autoimmune disorders in

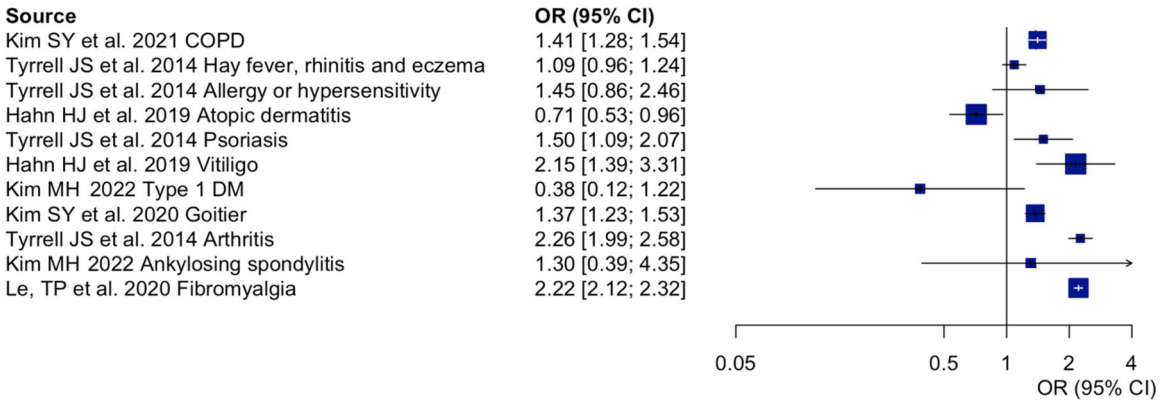

Figure 3. Epidemiological studies investigating the association of Ménière's disease with allergy, autoimmune or inflammatory diseases. CI, confidence interval; COPD, chronic obstructive pulmonary disorder; DM, diabetes mellitus; OR, odds ratio.

European populations with the different immune response across different populations.

Most of the population-based studies have been performed in Asia, while the only large European population study was carried out by retrieving data from the UK Biobank. This may have consequences when analyzing associations between diseases and MD because the phenotype and the associated comorbidities differ between populations and the immune response may vary in MD according to the host-environment interaction.

The prevalence of autoimmune and allergic diseases is different in both East Asian and European populations, and we have observed significant differences in allergic diseases.[29,30] However, further population-based studies are needed to assess the role of allergy in MD in European population across different countries since the climate and the allergic environment is different in the Mediterranean, central Europe, and Scandinavian countries.

The reported genetic associations of MD with allelic variants in HLA or TLR genes are probably population-specific, and they represent the adaptation of the immune system to environmental constraints.[31] The major weakness of gene association studies related to the immune system that have been previously associated with autoimmune diseases is that do not include ancestry markers[32]; for this reason, their findings cannot be replicated in an independent cohort, and we cannot rule out a population stratification or population-specific association.

An autoimmune background has also been reported in certain families with MD,[33,34] but the main genes involved in familial MD are *OTOG*, *MYO7A,* and *TECTA* and they are not related to the immune system.[35-37]

Several studies have found an increased prevalence of migraine in patients with MD and patients with migraine had a higher risk of MD; however, pathophysiological links between MD, autoimmune disorders, and migraine have not been established.[38]

Accordingly, the role of autoimmunity and autoinflammation in MD deserves further research, since epidemiological evidence is limited to self-reported data in the European population. The TWEAK/Fn14/CD163 pathway is involved in the modulation of inflammation in several human autoimmune diseases (multiple sclerosis, systemic lupus erythematosus, or rheumatoid arthritis) and metabolic disease.[39] The allelic variant rs4947296 is a regulatory element associated with bilateral MD in European, but its role in Asian populations has not been established. Although some potential therapeutic options have been previously suggested for autoimmune/autoinflammatory MD, including IL-1β or IL-6 blockers, clinical trials are needed in MD patients with high levels of cytokines to assess its effectiveness.[40]

Study Limitations

There are several limitations in this systematic review that we need to address: (1) Language and limited sample size: we only included 9 population-based and 6 genetic studies published in English; (2) all the high-quality population-based studies have been performed in the East Asian population, (3) *demographics*: some studies did not detail enough patients' features like sex, age, age of onset, ear involvement, laterality, ethnicity, and so forth, to allow a better comparison between them, and (4) *self-reports*: UKBiobank data are self-reported and many of the clinical diagnosis in the database have not been confirmed with the clinical records. Because of all mentioned above, we found great heterogeneity in the meta-analysis. Additionally, the associations of rheumatoid arthritis and psoriasis with MD will need independent confirmation in a large European cohort.

Conclusions

1. Epidemiological evidence supports an association between MD and immune-related disorders in both European and Asian populations, with population-specific effects.
2. The evaluation of thyroid diseases, airway allergic diseases, and other inflammatory diseases should be implemented in the clinical management of MD patients.

Table 2. Outcome Summary of the Genetic Studies Included in the Systematic Review

Gene	Pathways	Source	Year	Country	N	Age, mean (SD)	Female, %	SNP	Locus	Allele/ genotype	Frequency in cases, %	Frequency in controls, %	Outcome	OR(95% CI)	Replication study
HLA-DBR1	Adaptive immune system	Lopez-Escamez, JA et al	2007	Spain	330	56.1 (9.4)	52.4	HLA-DB-R1*1101	6p21.32	HLA-DBR1*1101	18.7	6.2	HLADR-B1*1101 associated with bilateral MD.	3.65 (1.5-9.1)	Yes
Locus in 6p21.33	TWEAK/ Fn14 pathway	Frejo L et al	2017	Spain	2050	NA	59.3	rs4947296	6p21.33	CC	NA	NA	Association with bilateral MD.	2.09 (1.66-2.63)	Yes
MIF	Innate immunity response	Yazdani N et al	2013	Iran	172	37.7 (11.3)	65.28	MIF-173	22q11.23	GG	75	59	*MIF* gene polymorphism associated to MD.	2.08 (1.02-4.3)	No
NFKB1	Proinflammat-ory cytokine production	Cabrera S et al	2014	Spain	1344	46.6 (12.5)	60.4	rs3774937, rs4648011	4q24	rs3774937-C rs4648011-G	30.45 36.31	32.3 36.3	Poor hearing outcome in patients with unilateral MD.	0.92 (0.76-1.11) 1 (0.84-1.2)	No
RANTES (CCL5)	Cytokine signaling	Yazdani N et al	2015	Iran	172	39.7 (11.5)	64.79	RANTES −403G>A	17q12	GG	60	56	AA/GA genotypes in MD protective effect in males.	1.2 (0.6-2.3)	No
TLR10	Inflammasome activation	Requena T et al	2013	Spain and Italy	2021	NA	48	rs11096955	4p14	CC	17.6	23.9	Associated with bilateral SNHL in MD.	0.56 (0.26-1.21)	Yes

Abbreviations: CI, confidence interval; MD, Ménière's disease; NA, Not available; OR, odds ratio; SNHL, ensorineural hearing loss; SNP, single-nucleotide polymorphism.

Author Contributions

Jose A. Lopez-Escamez, review data, statistical analysis, write and review the manuscript; **Jesus Vela**, literature search and review, study selection and data extraction, manuscript writing and review; **Lidia Frejo**, idea and study design, literature search and review, selection and data extraction, writing and review.

Disclosures

Competing interests: None.

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Supplemental Material

Additional supporting information is available in the online version of the article.

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