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10. 2019-present | 國際耳內視鏡工作群組(IWGEES) 會員 Member of International Working Group on Endoscopic Ear Surgery (IWGEES)
11. 2020-present | 台灣耳鳴學會理事 Director of Taiwan Tinnitus Association
12. 2023-present | 台灣精準醫學學會會員 Member of Taiwan Precision Medicine Society
13. 2023-present | 台灣耳科醫學會秘書長 General Secretary of Taiwan Otology Society

近五年 SCI 論文(第一及共同作者) SCI publications in recent five years

1. Ming-Yu Yang, Ching-Nung Wu, Yu-Tsai Lin, Ming-Hsien Tsai, Chung-Feng Hwang, **Chao-Hui Yang***. Dissecting the Circadian Clock and Toll-like Receptor Gene Alterations in Meniere's Disease and Vestibular Migraine. Otolaryngology-Head and Neck Surgery 2025. DOI: 10.1002/ohn.1085.
2. **Chao-Hui Yang***, Ming-Hsien Tsai, Chung-Feng Hwang, Ming-Yu Yang*. Sleep disturbance in vestibular migraine and Meniere's disease: A comparative analysis. Otolaryngology-Head and Neck Surgery 2025 Jan;172(1):346-352.

3. **Chao-Hui Yang**, Wei-Che Lin, MD, Wei-Chih Chen, Sheng-Dean Luo, Ming-Yu Yang, Chung-Feng Hwang, Shu-Fang Chen*. Association of Autonomic Symptom Burden with Sudden Sensorineural Hearing Loss. Otolaryngology-Head and Neck Surgery 2024 Mar;170(3):862-869.
4. Yung-Hsuan Chen, Wei-Che Lin, Chung-Feng Hwang, Meng-Han Tsai, **Chao-Hui Yang***. Variability in Inner Ear Morphology Among a Family With Pendred Syndrome Due to a SLC26A4 Gene Variant. Ann Otol Rhinol Laryngol. 2024 Sep;133(9):828-833
5. **Chao-Hui Yang***, Ming-Yu Yang, Chung-Feng Hwang, Kuang-Hsu Lien*. Functional and Molecular Markers for Hearing Loss and Vertigo Attacks in Meniere's Disease. International Journal of Molecular Sciences 2023, 24(3):2504.
6. **Chao-Hui Yang**, Chung-Feng Hwang*, Nai-Wen Tsai, Ming-Yu Yang*. Expression of circadian clock genes in leukocytes of patients with Meniere's disease. Laryngoscope Investigative Otolaryngology. 2022;7:584-591.
7. **Chao-Hui Yang**, Chung-Feng Hwang, Jiin-Haur Chuang, Wei-Shiung Lian, Feng-Sheng Wang, Ming-Yu Yang*. Systemic toll-like receptor 9 agonist CpG oligodeoxynucleotides exacerbates aminoglycoside ototoxicity. Hearing Research 2021, 411:108368.
8. Kuang-Hsu Lien, **Chao-Hui Yang***. Sex Differences in the Triad of Acquired Sensorineural Hearing Loss. International Journal of Molecular Sciences 2021, 22(15):8111.
9. **Chao-Hui Yang**, Chung-Feng Hwang*, Jiin-Haur Chuang, Wei-Shiung Lian, Feng-Sheng Wang, Ethan-I. Huang, Ming-Yu Yang*. Constant Light Dysregulates Cochlear Circadian Clock and Exacerbates Noise-Induced Hearing Loss. International Journal of Molecular Sciences 2020, 21(20), 7535.
10. Chun-Hsien Ho, Teng-Yeow Tan, Chung-Feng Hwang, Wei-Che Lin, Ching-Nung Wu, **Chao-Hui Yang***. Association of carotid intima-media thickness with the risk of sudden sensorineural hearing loss. PeerJ 2020; 8 :e9276.
11. **Chao-Hui Yang**, Jui-Pin Lai, An-Chi Lee, Lu-Hui Cheng, Chung-Feng Hwang*. Prognostic Factors for Hearing Outcomes in Children with Cleft Lip and Palate. Plastic and Reconstructive Surgery 2019 Feb;143(2):368e-374e

Sleep Disturbance and Gene Alterations: Potential Insights for Differentiating Meniere's Disease from Vestibular Migraine

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Meniere's Disease

- Proposed by French doctor, Prosper Meniere
- Triad:
  - Vestibular symptoms (recurrent vertigo attack)
  - Auditory symptoms (tinnitus and fluctuate hearing loss)
  - Aural fullness
- Pathogenesis: endolymphatic hydrops in the cochlea and vestibule

Box 3 | **2015 proposed criteria of Meniere's disease**

Definite Meniere's disease

- At least two spontaneous episodes of vertigo, each lasting from 20 minutes to 12 hours
- Audiometrically documented low-frequency to medium-frequency sensorineural hearing loss in one ear, defining the affected ear on at least one occasion before, during or after one of the episodes of vertigo
- Fluctuating aural symptoms (hearing, tinnitus or fullness) in the affected ear
- Not better accounted for by another vestibular diagnosis

Probable Meniere's disease

- At least two episodes of vertigo or dizziness, each lasting from 20 minutes to 24 hours
- Fluctuating aural symptoms (hearing, tinnitus or fullness) in the affected ear
- Not better accounted for by another vestibular diagnosis

Criteria proposed by the Classification Committee of the Barany Society, the Japan Society for Equilibrium Research, the European Academy of Otology and Neurotology, the Equilibrium Committee of the American Academy of Otolaryngology–Head and Neck Surgery and the Korean Balance Society[21].

Variable symptoms and course

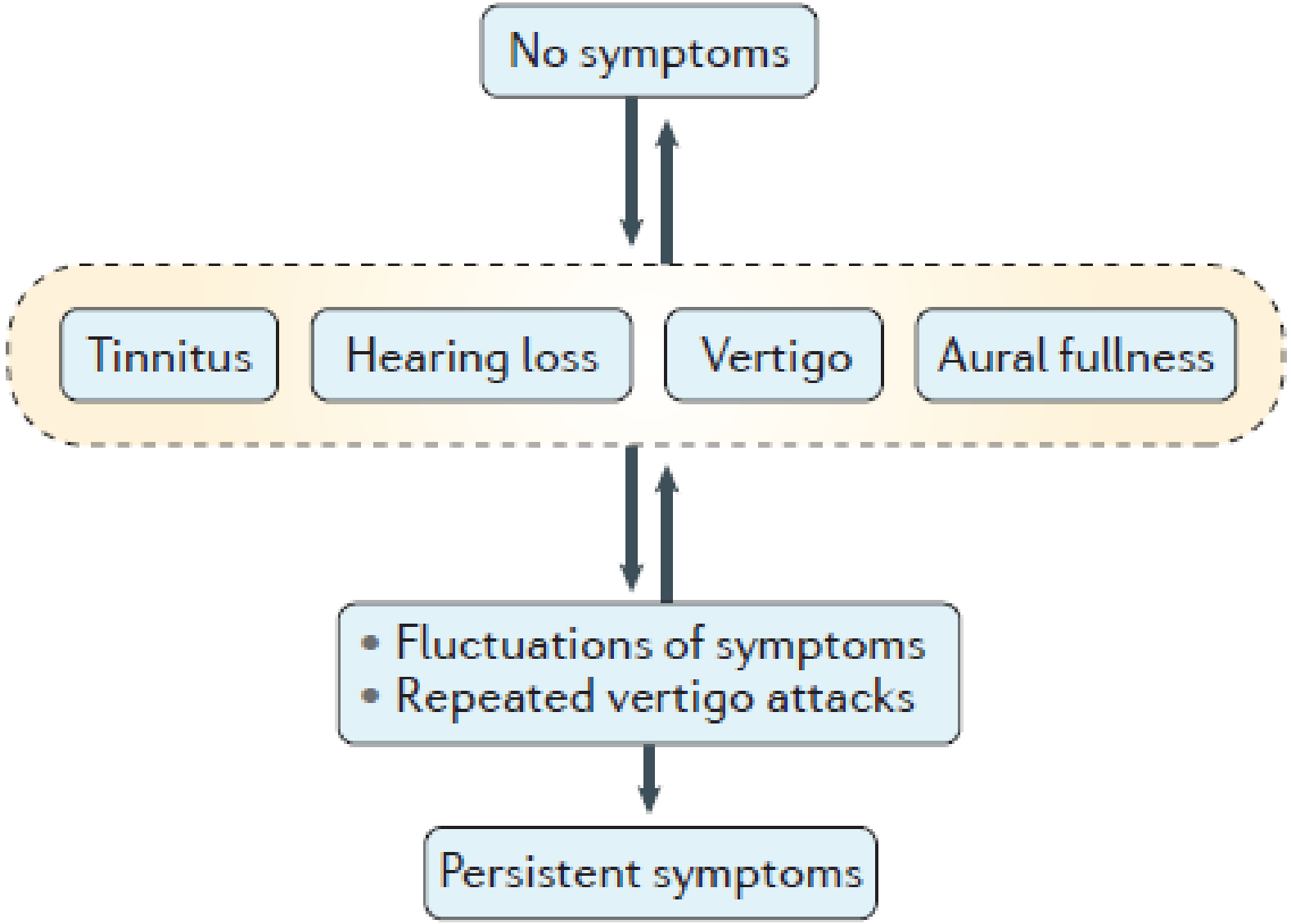


Figure 1 | **Clinical symptoms associated with Meniere's**

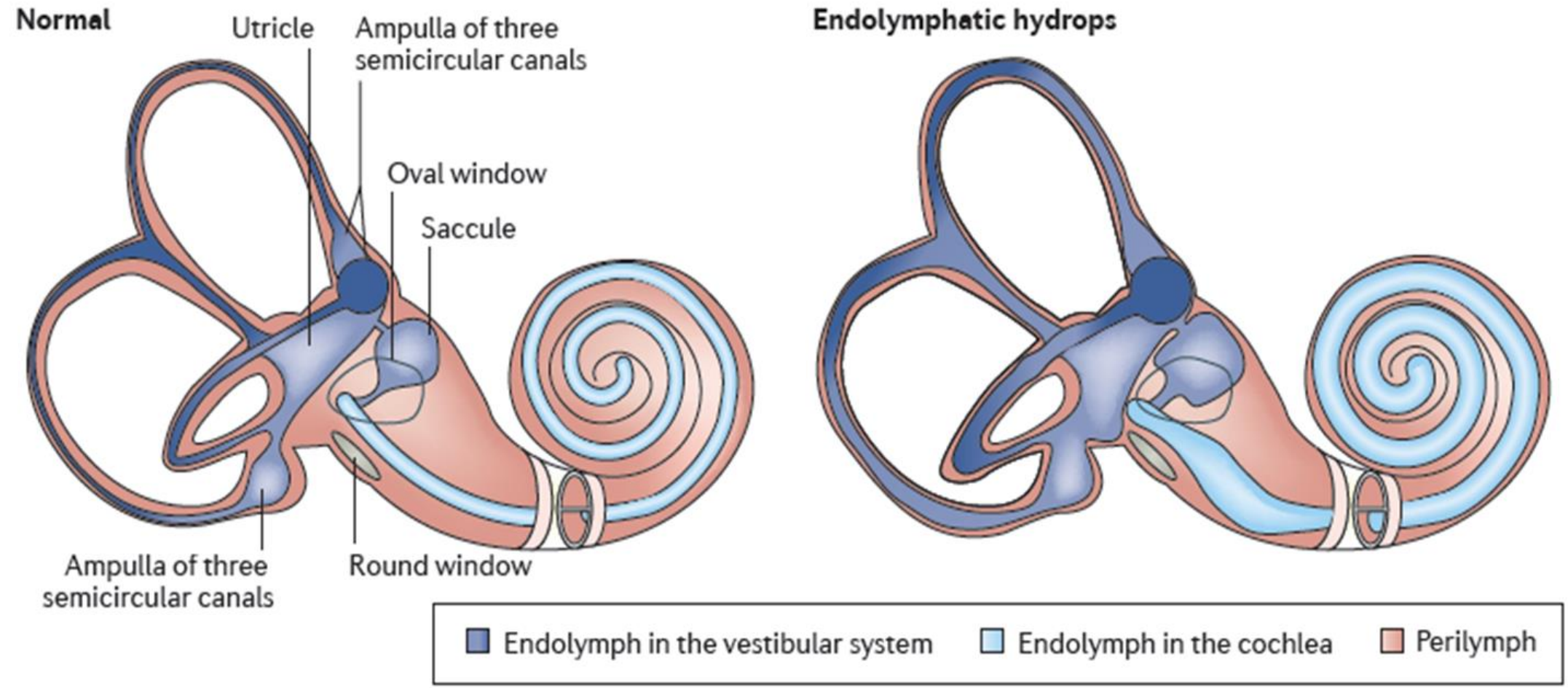


Figure 4 | **Endolymphatic hydrops.** Endolymphatic hydrops (EH) is characterized by an accumulation of fluid

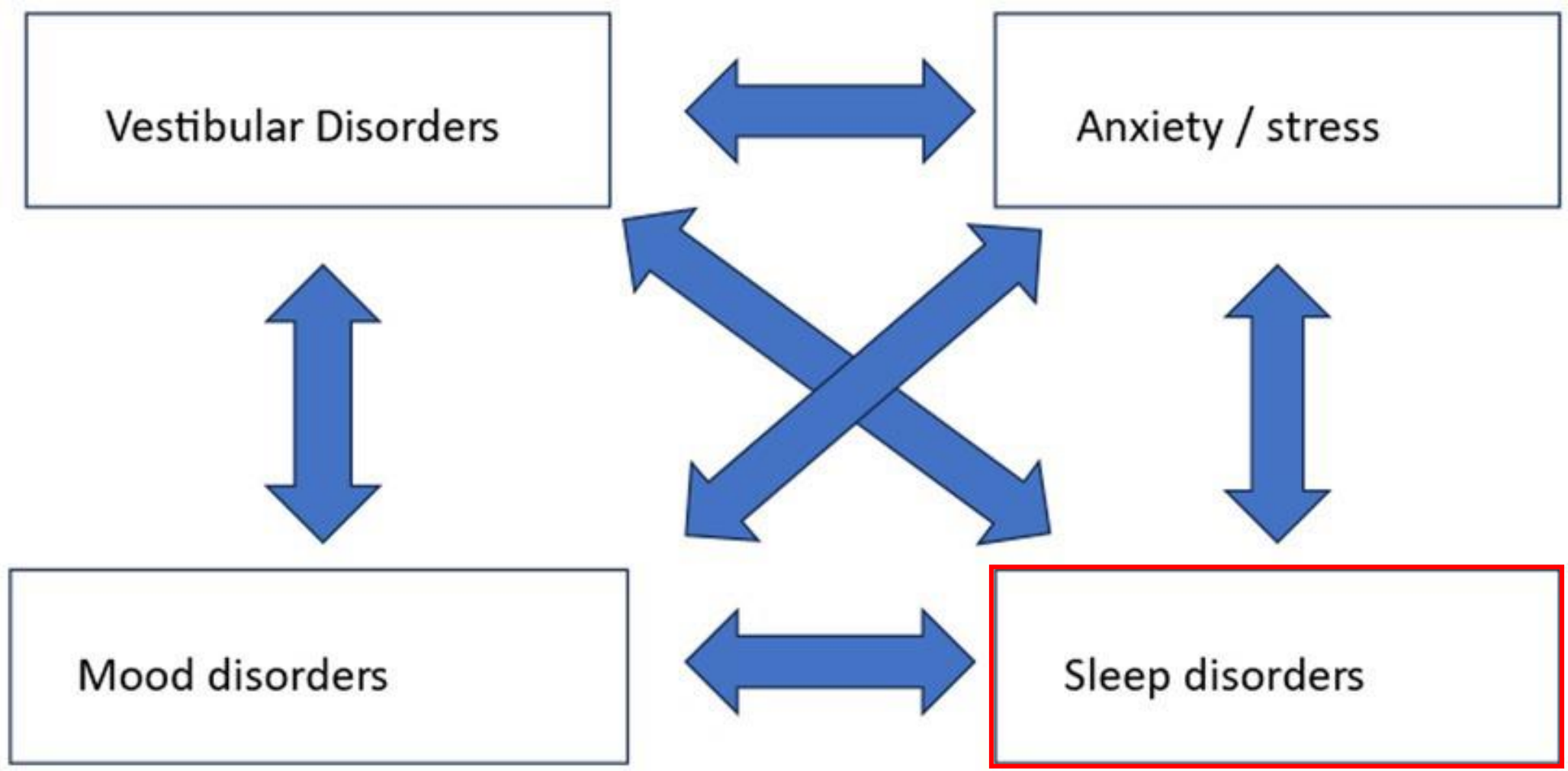
Similarity between MD and VM

- Migraine occurs more often in patients with MD related to the general population
- VM patients may also experience tinnitus, auditory fullness and changeable sensorineural hearing loss
- Sex: both female predominant
- Age: middle age (40-50s)

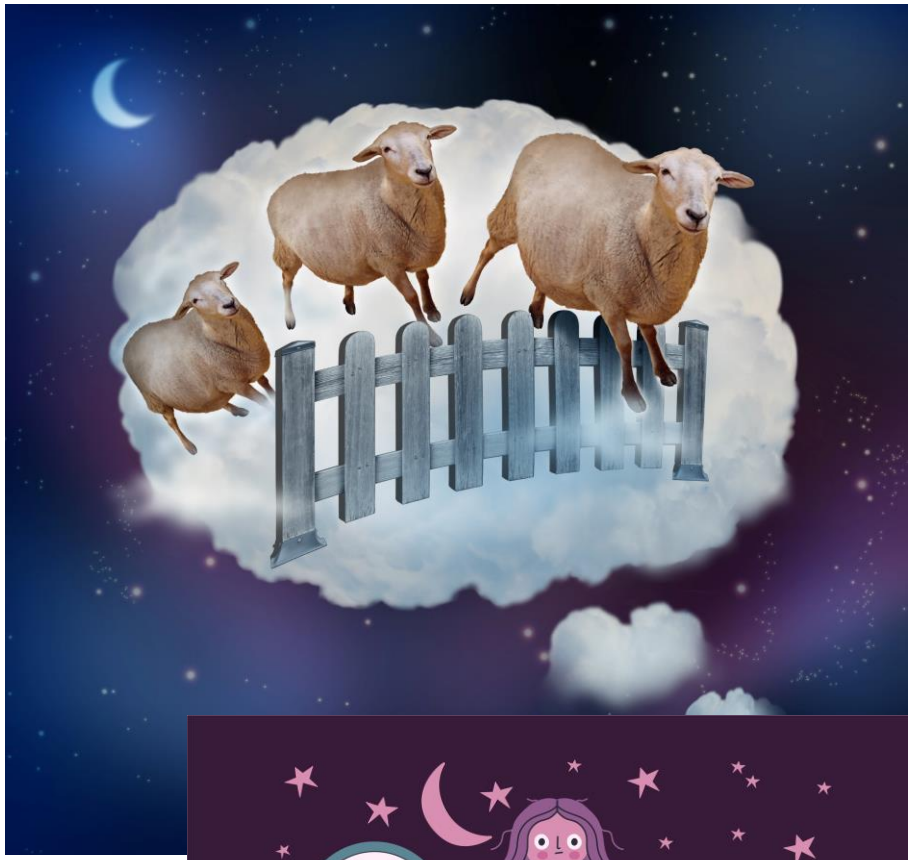
Variable	Disease			
	VM (n = 71)	MDVM (n = 21)	MD (n = 55)	VM versus MD
Auditory symptoms				
Fluctuating HL	9 (14%)	13 (62%)	43 (78%)	**<0.0001**
Progressive HL	14 (22%)	18 (86%)	51 (93%)	**<0.0001**
Tinnitus	37 (55%)	18 (86%)	53 (96%)	**<0.0001**
Aural fullness	33 (51%)	14 (67%)	43 (78%)	**0.0026**
Otalgia	17 (27%)	4 (24%)	9 (17%)	0.09
Hearing loss related to vertigo	8 (44%)	4 (22%)	21 (43%)	0.91
Tinnitus related to vertigo	13 (50%)	7 (39%)	27 (59%)	0.47
Aural fullness related to vertigo	16 (70%)	7 (50%)	24 (65%)	0.71

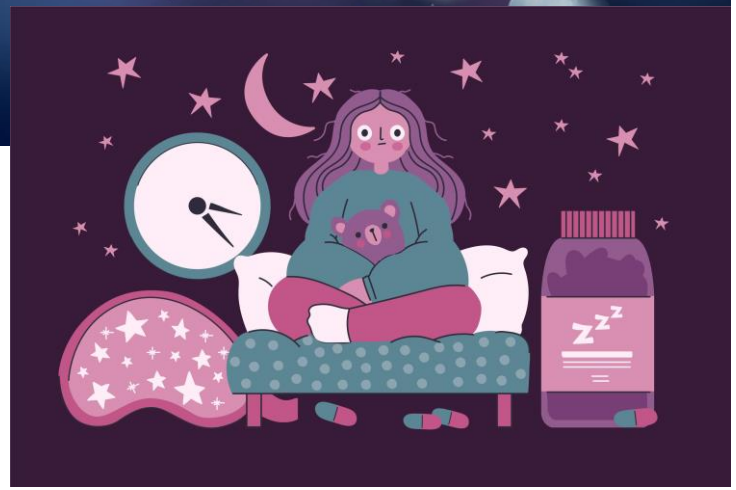
Neff et al., Otol Neurotol . 2012

history, history, history….



Leeuwen et al. Front Neurol. 2024

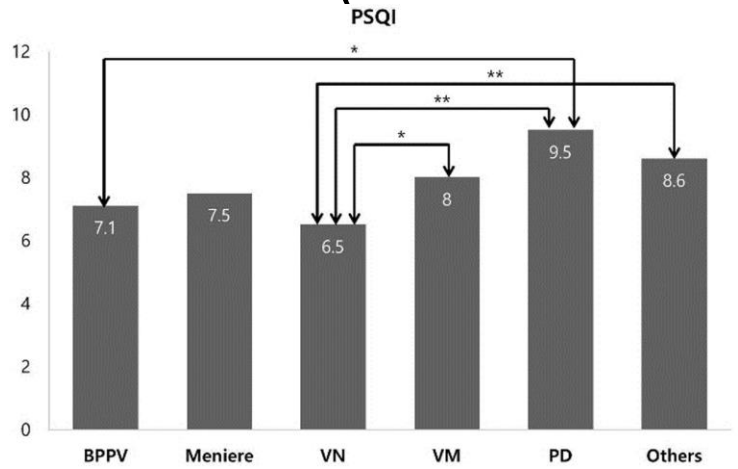




Sleep disturbance

Sleep disturbance in dizziness patients

- National Health Interview Survey for the US adult (*Albathi et al., J Vestib Res. 2017*):
  - Individuals with vestibular vertigo had a higher relative risk ratio for abnormally short or long sleep duration
- Japan : the prevalence of sleep disturbance (i.e., Pittsburgh Sleep Quality Index (PSQI) -J global score > 6) was 65.1% (*Sugaya et al, Acta Otolaryngol 2017*)
- South Korea: sleep disturbance was associated with psychogenic dizziness, BPPV, MD and VM (*Kim et al. PLOS one 2018*)



		BPPV		MD		VN		VM		PD		Other	
		PSQI	ISI	PSQI	ISI	PSQI	ISI	PSQI	ISI	PSQI	ISI	PSQI	ISI
DHI	PCC	0.269	0.306	0.293	0.143	0.330	0.235	0.491	0.415	0.176	0.113	0.142	0.165
	p	0.021*	0.008†	0.104	0.180	0.049*	0.168	0.000†	0.002†	0.458	0.636	0.409	0.336

*$p < 0.05$.
†$p < 0.01$.

https://doi.org/10.1371/journal.pone.0192705.t003

Sleep disturbance in MD

- UK-based Clinical Practice Research Datalink (*Bruderer et al. Audiol Neurootol. 2017*)
  - Depression, other affective disorders, sleeping disorders, anxiety, and migraine were more prevalent among MD cases than among controls
- Impaired Quality of Sleep in Ménière‘s Disease Patients (*Nakayama et al, J Clin Sleep Med. 2010*)
  - Total sleeping time in MD was significantly higher than in controls.
  - Stage 2 sleep was significantly longer and stage 3+4 shorter in MD than control
  - Arousal index was significantly higher in MD than in controls

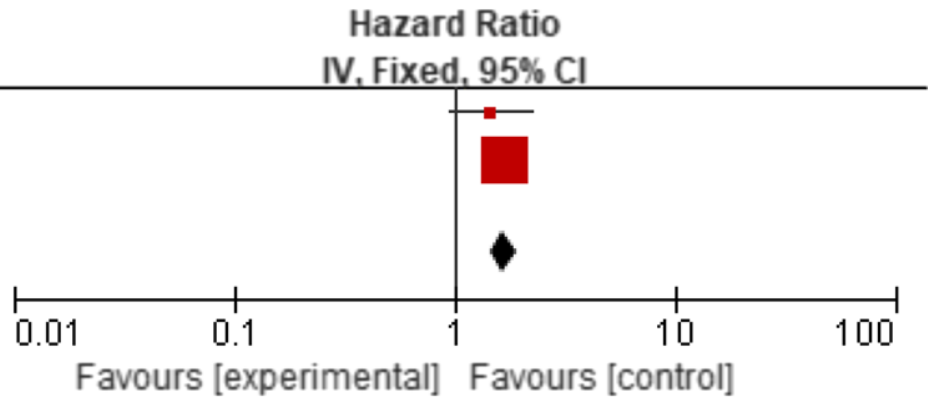
Sleep disturbance in MD

- Risk factors for Meniere disease: a systematic review and meta-analysis

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Kim JY 2019	0.3853	0.2174	10.3%	1.47 [0.96, 2.25]
Tsai MS 2018	0.5365	0.0737	89.7%	1.71 [1.48, 1.98]
Total (95% CI)			**100.0%**	**1.68 [1.47, 1.93]**

Heterogeneity: $Chi^2 = 0.43$, $df = 1$ ($P = 0.51$); $I^2 = 0\%$

Test for overall effect: $Z = 7.46$ ($P < 0.00001$)



Hu et al. Eur Arch Otorhinolaryngol. 2022

Sleep disturbance in VM

- VM group
  - reduced sleep efficiency, lower REM and slow-wave sleep, and prolonged sleep latency (Wu et al. Sleep Breath. 2020)
  - lower sleep efficiency, higher wake time after sleep onset, and a higher incidence of severe OSA and periodic leg movements (Xue et al. Front Psychiatry, 2021)
  - poor sleep quality, thalamic-cortical hyperfunction and active arousal system (Zhou et al. Sleep Med 2023)
- Patients tended to experienced more severe VM attacks in early hours of a day, especially for those sufferers with longer duration of illness or poor sleep quality (Liu et al., Front Neurol. 2020)

Does sleep disturbance in MD differ from VM?

Our study

- Enrolled patients from the Kaohsiung CGMH otolaryngology department
- VM: probable or definite VM
- MD: definite MD
- Only VM and MD patients who had experienced recent vertigo attacks within the past month were enrolled
- Mini Sleep Questionnaire (MSQ), a validated tool for assessing sleep quality by Zomer
- 1 to 7 (1 = never; 4=sometimes; 7=always)

Yang et al. Otolaryngology-Head and Neck Surgery 2025 Jan;172(1):346-352.

Table 1. Mini Sleep Questionnaire (MSQ)

MSQ items	No	Yes
MSQ insomnia		
Difficulty falling asleep	1	2
Waking up too early	1	2
Mid-sleep awakening	1	2
Hypnotic medication use	1	2
MSQ hypersomnia		
Falling asleep during the day	1	2
Feeling tired upon waking up in the morning	1	2
Snoring	1	2
Headaches on awakening	1	2
Excessive daytime sleepiness	1	2
Excessive movements during sleep	1	2

MSQ insomnia score = the sum of the above 4 items, MSQ hypersomnia score = the sum of the above 6 items, MSQ total score = MSQ insomnia score + MSQ hypersomnia score.

- A scale of 1 (never) as no (score = 1)
- A scale of 4 (sometimes) and 7 (always) as yes (score = 2)

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Table 2. Clinical characteristics in VM, MD and control groups

Parameters	VM group (n=35)	MD group (n=39)	Control group (n =13)	*P* value
Age (year, mean ± SD)	45.3 ± 12.6	50.3 ± 12	43.6 ± 5.8	0.086
Sex (n, %)				0.062
Male	4 (11.4)	11 (28.2)	5 (38.5)	
Female	31 (88.6)	28 (71.8)	8 (61.5)	
MSQ items checked "yes" (n, %)				
Difficulty falling asleep	26 (74.3)	18 (46.2)	1 (7.7)	**<0.001**
Waking up too early	20 (57.1)	23 (59)	3 (23.1)	0.081
Hypnotic medication use	9 (25.7)	8 (20.5)	0 (0)	0.139
Falling asleep during the day	2 (5.7)	4 (10.3)	0 (0)	0.617
Feeling tired upon waking up in the morning	23 (65.7)	24 (61.5)	3 (23.1)	**0.026**
Snoring	14 (40)	23 (59)	5 (38.5)	0.206
Mid-sleep awakening	27 (77.1)	29 (74.4)	3 (23.1)	**0.001**
Headaches on awakening	21 (60)	12 (30.8)	2 (15.4)	**0.005**
Excessive daytime sleepiness	9 (25.7)	15 (38.5)	2 (15.4)	0.256
Excessive movements during sleep	12 (34.3)	12 (30.8)	1 (7.7)	0.180
MSQ total scores (median (IQR))	15 (13-16)	14 (13-16)	11 (10-12.5)	**<0.001**
MSQ insomnia scores (median (IQR))	6 (5-7)	6 (5-7)	4 (4-5)	**<0.001**
MSQ hyposomnia scores (median (IQR))	8 (7-9)	8 (7-10)	7 (6-8)	**0.017**

Yang et al. Otolaryngology-Head and Neck Surgery 2025 Jan;172(1):346-352.

Groups / MSQ items	VM	MD
MSQ Insomnia		
Difficulty falling asleep	v.s. Control ($P < 0.001$) v.s. MD ($P = 0.015$)	v.s. Control ($P = 0.014$) v.s.VM ($P = 0.015$)
Waking up too early	—	—
Mid-sleep awakening	v.s. Control ($P = 0.001$)	vs. Control ($P = 0.001$)
Hypnotic medication use	—	—

Groups / MSQ items	VM	MD
MSQ Hypersomnia		
Falling asleep during the day	—	—
Feeling tired upon waking up in the morning	v.s. Control ($P = 0.009$)	—
Snoring	—	—
Headaches on awakening	v.s. Control ($P = 0.007$) v.s. MD ($P = 0.012$)	v.s.VM ($P = 0.012$)
Excessive daytime sleepiness	—	—
Excessive movements during sleep	—	—

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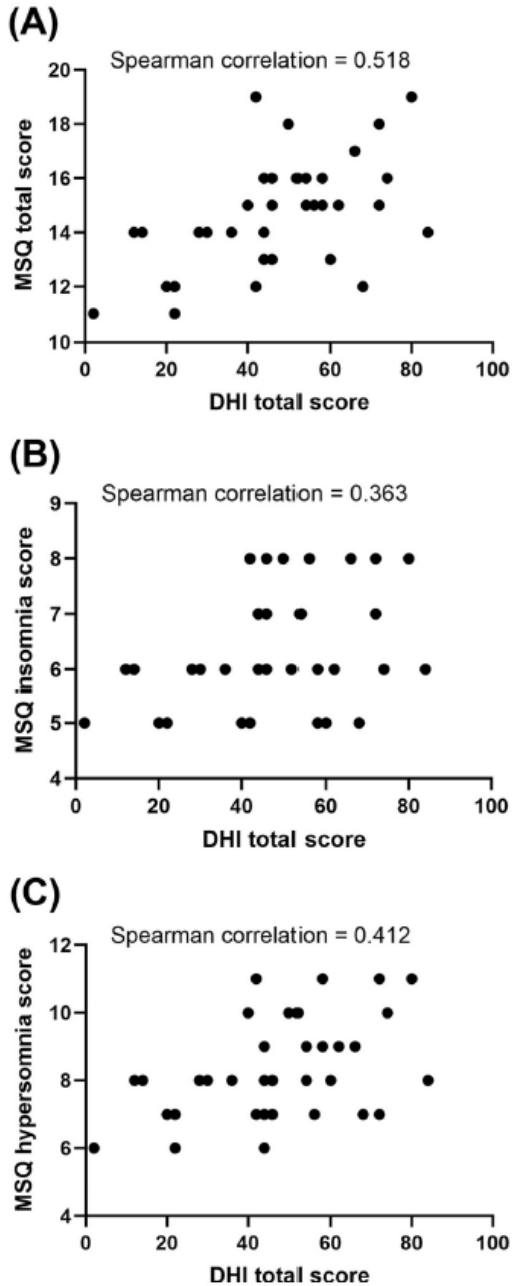

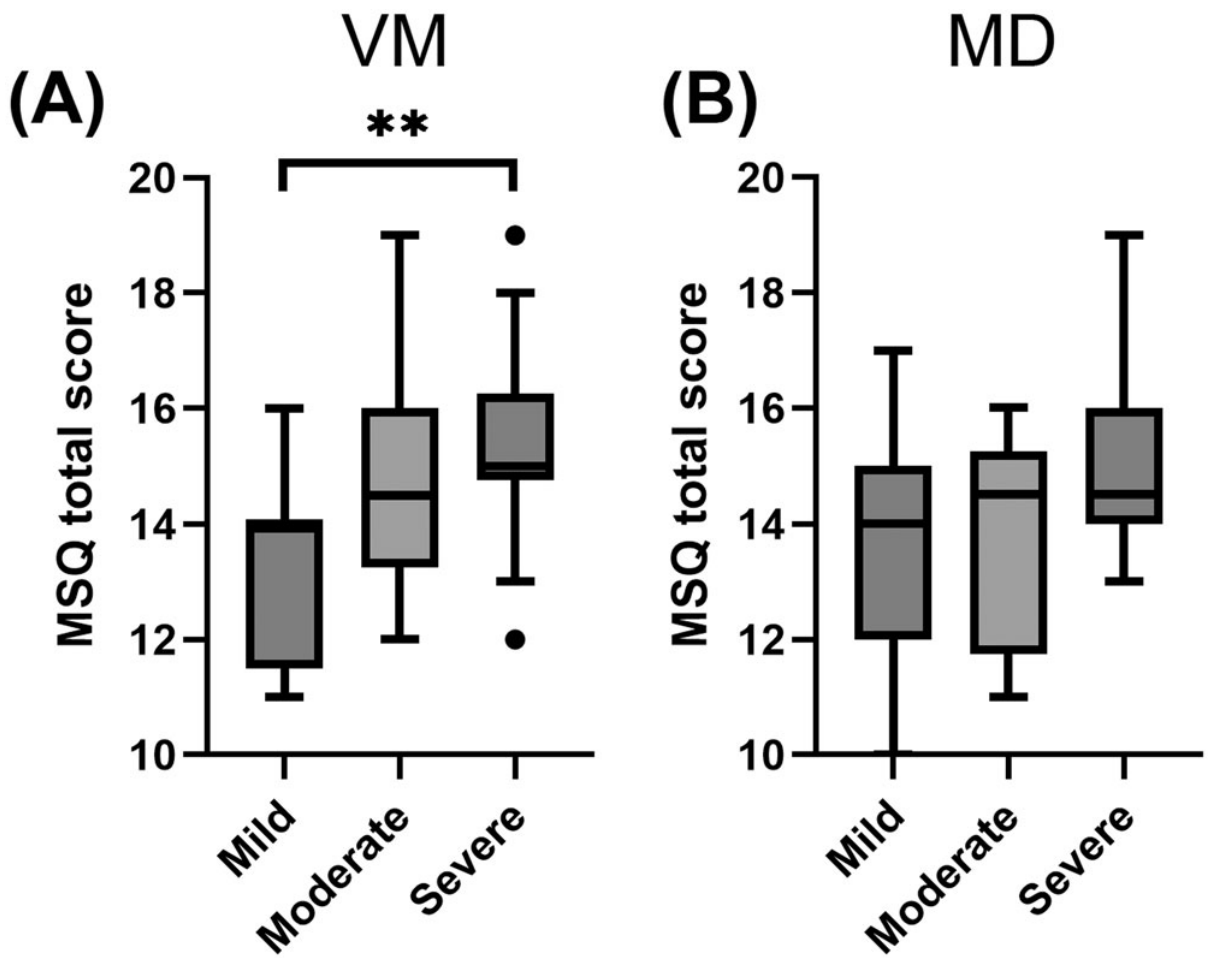

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Discussion

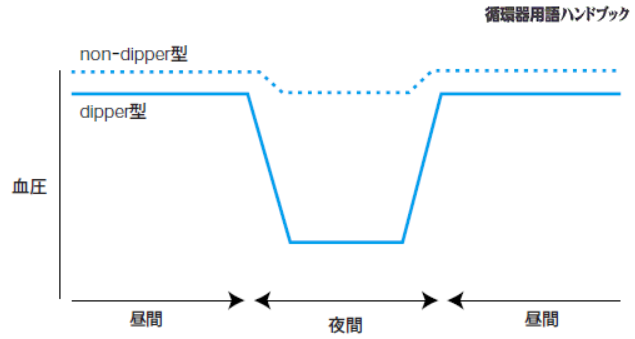

図. dipper/non-dipper

- Association between lower sleep efficiency and MD
  - Decreased deep sleep and an elevated arousal index in MD patients may related to abnormal nocturnal blood pressure regulation (nondippers), which can lead to hypoxia (*Huart et al., Hypertension. 2023*)
  - Disturbances in circulation may affect inner ear function, leading to abnormal endolymph homeostasis in MD (*Byun et al. J Vestib Res. 2022*)

Yang et al. Otolaryngology-Head and Neck Surgery 2025 Jan;172(1):346-352.

Discussion

- Association between lower sleep efficiency and VM
  - Patients with migraine have consistently reported poor sleep both precipitating and during attacks (*Vgontzas et al. Headache, 2019*)
  - During the onset of migraine, the synthesis of orexin-A and orexin-B in the hypothalamus promotes arousal and consequently affects sleep efficiency (*Schulte et al. Neurology. 2017*)
  - Sleep disturbance, which is a strong precipitating factor for migraine, also affects the vestibular nuclei and nociceptive system, contributing to trigeminovascular reflex activation in VM (*Espinosa-Sanchez et al Front Neurol. 2015*)

Yang et al. Otolaryngology-Head and Neck Surgery 2025 Jan;172(1):346-352.

Effects of Lifestyle Modification on Vestibular Migraine

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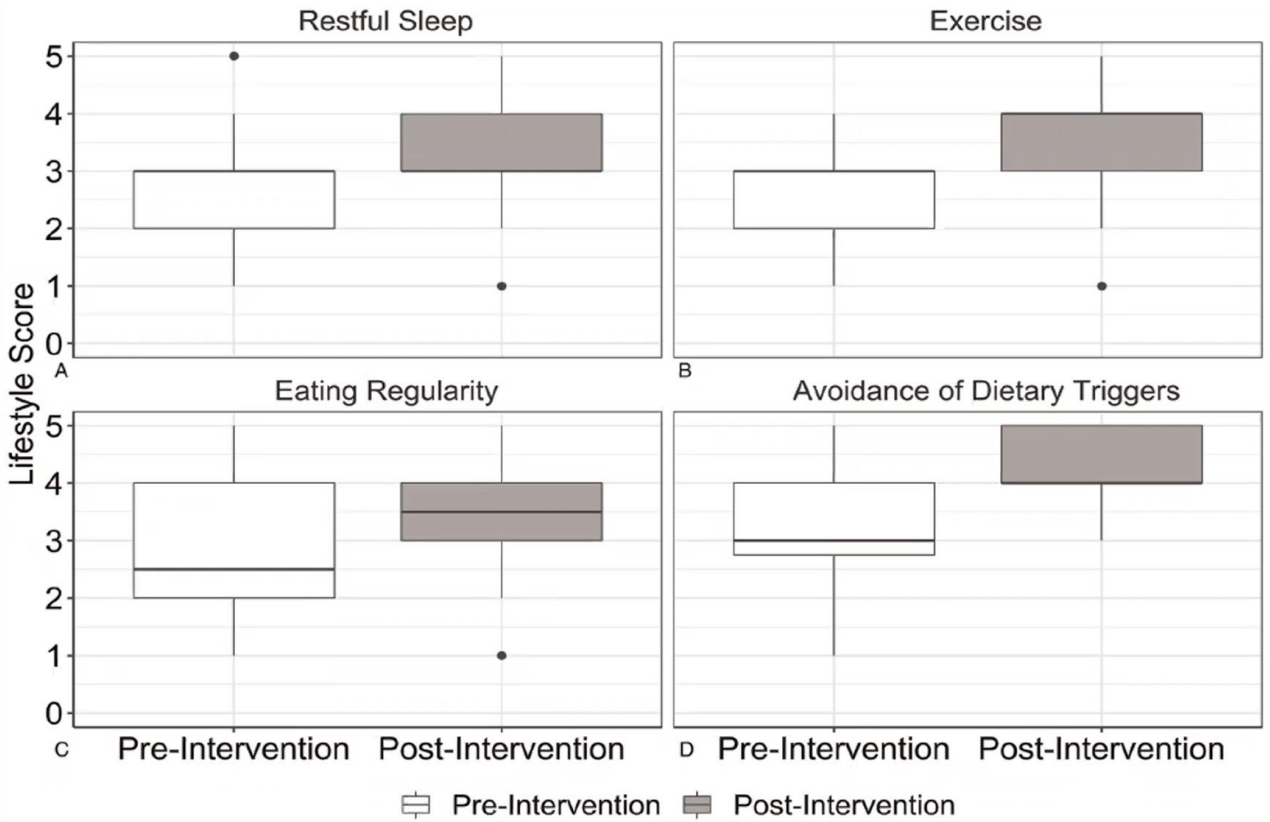
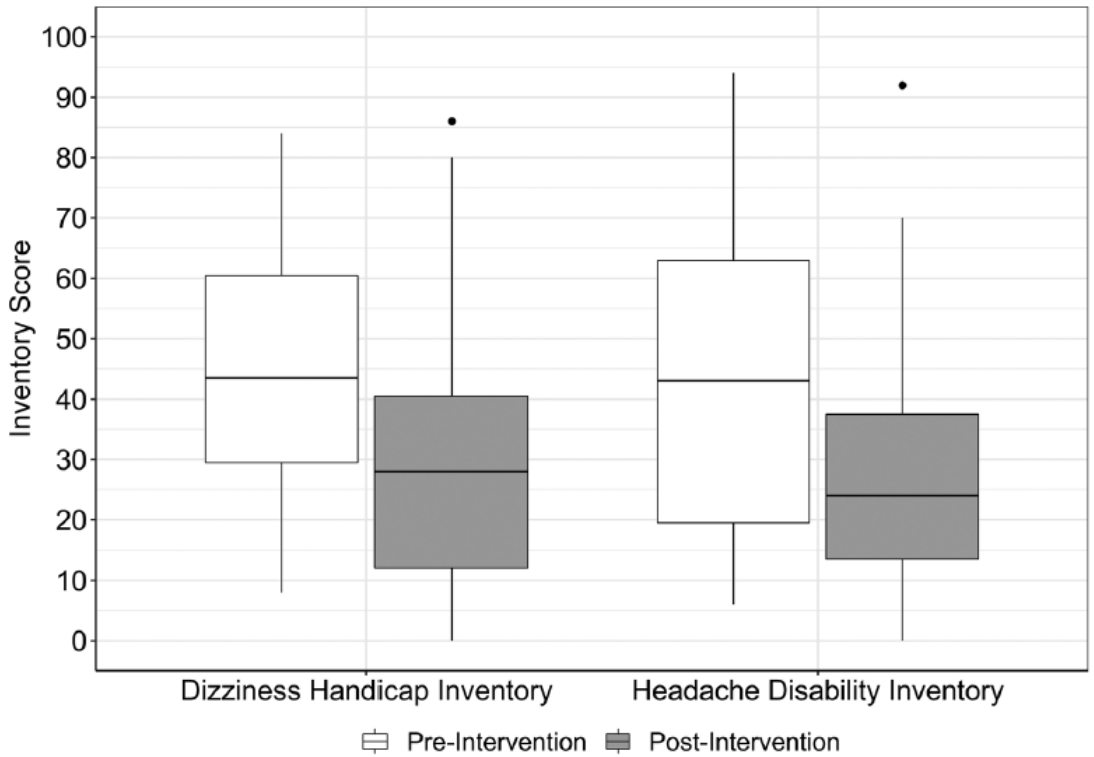




Roberts et al. Effects of Lifestyle Modification on Vestibular Migraine. Otol Neurotol Jul 2021.

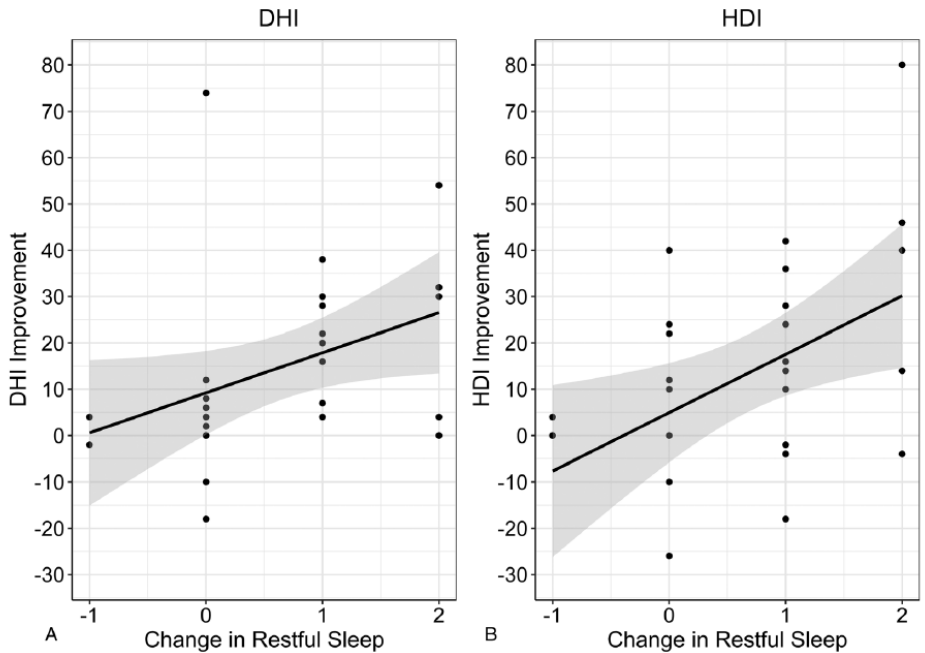
Roberts et al., Otol Neurotol. 2021

- Getting restful sleep is the most important way to improve dizziness and headache symptoms

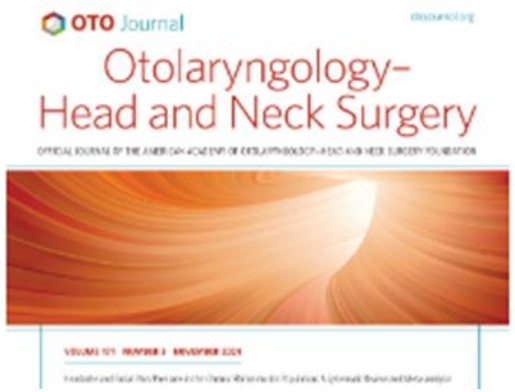
TABLE 3. *Results of linear mixed-effects model analysis of post-intervention Dizziness Handicap Inventory and Headache Disability Inventory scores*

	DHI			HDI		
Predictors	Estimates	95% CI	*p*	Estimates	95% CI	*p*
(Intercept)	−14.01	−44.16 to 16.15	0.345	−7.39	−43.60 to 28.82	0.676
Age	0.14	−0.32 to 0.60	0.525	−0.02	−0.57 to 0.53	0.942
Sex [M]	18.66	−2.14 to 39.46	0.076	4.09	−20.88 to 29.07	0.737
Restful sleep	**12.72**	**3.4521.99**	**0.01**	**14.49**	**3.36–25.62**	**0.013**
Exercise	1.09	−5.40 to 7.59	0.73	0.84	−6.96 to 8.64	0.824
Eating regularly	0.82	−6.82 to 8.47	0.825	7.34	−1.84 to 16.52	0.111
Avoidance of dietary triggers	6.55	−0.62 to 13.73	0.071	3.65	−4.97 to 12.26	0.388
Observations		28			28	
R^2/R^2 adjusted		0.322/0.128			0.352/0.166	

Significant predictors are indicated by bold typeface. DHI, Dizziness Handicap Inventory; HDI, Headache Disability Inventory.



Roberts et al., Otol Neurotol. 2021



Otolaryngology-Head and Neck Surgery

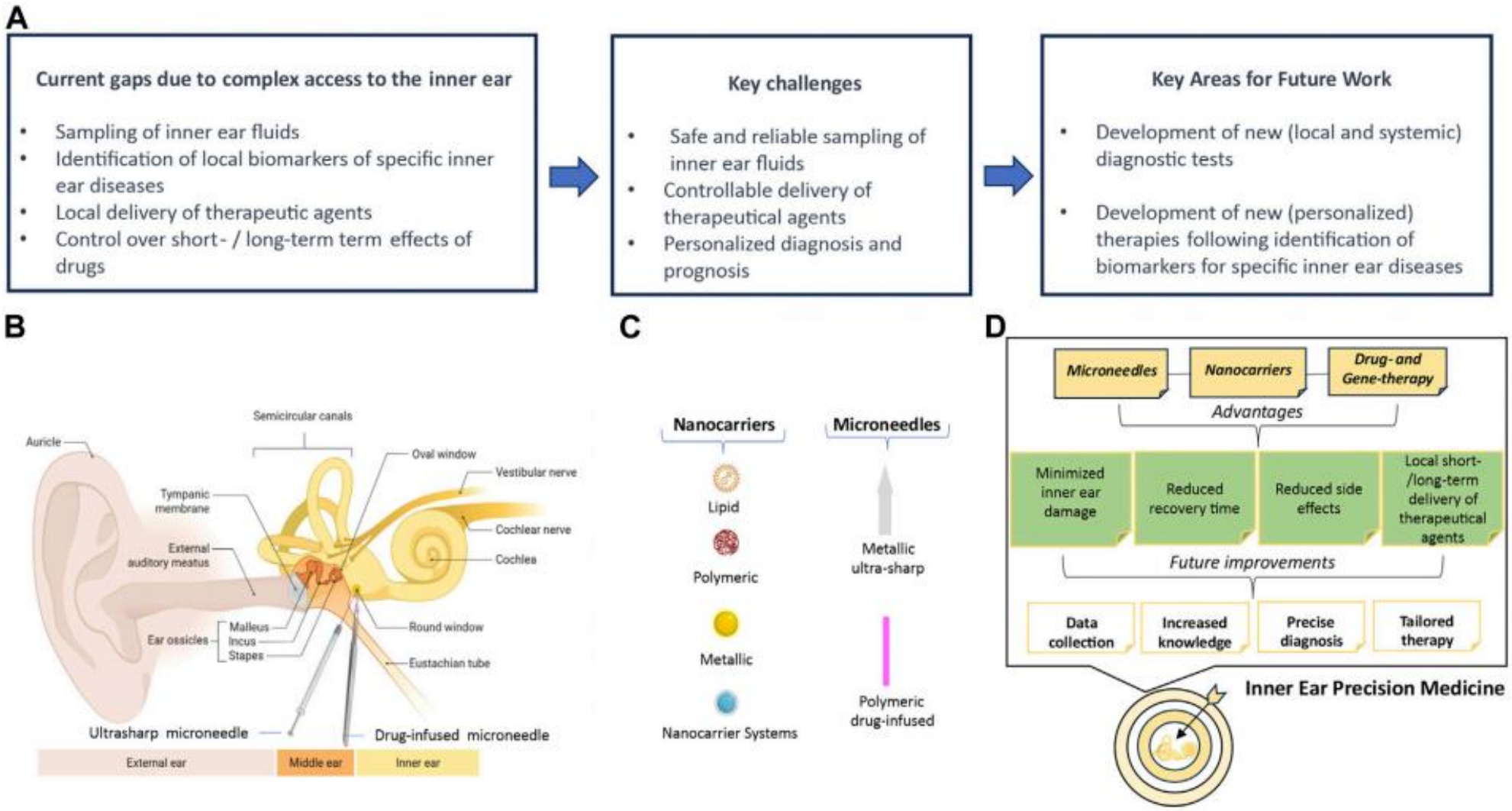
Sleep disturbance in vestibular migraine and Meniere's disease: A comparative analysis

DOI: 10.1002/ohn.1049

Academy's Choice

- Bulletin: *Stories from the Road: AIC-CURE Children's Hospital of Kenya*
- OTO Journal: *Sleep Disturbance in Vestibular Migraine and Meniere's Disease: A Comparative Analysis*
- OTO Open: *Clinical Efficacy and Outcomes of Electro-Pneumatic Intracorporeal Lithotripsy in the Management of Sialolithiasis*

Precision medicine: a new era for inner ear diseases



Tavazzani et a; Front Pharmacol. 2024

International Journal of
Molecular Sciences

MDPI

Review

Functional and Molecular Markers for Hearing Loss and Vertigo Attacks in Meniere's Disease

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Yang et al. Int J Mol Sci. 2023 Jan 28;24(3):2504.

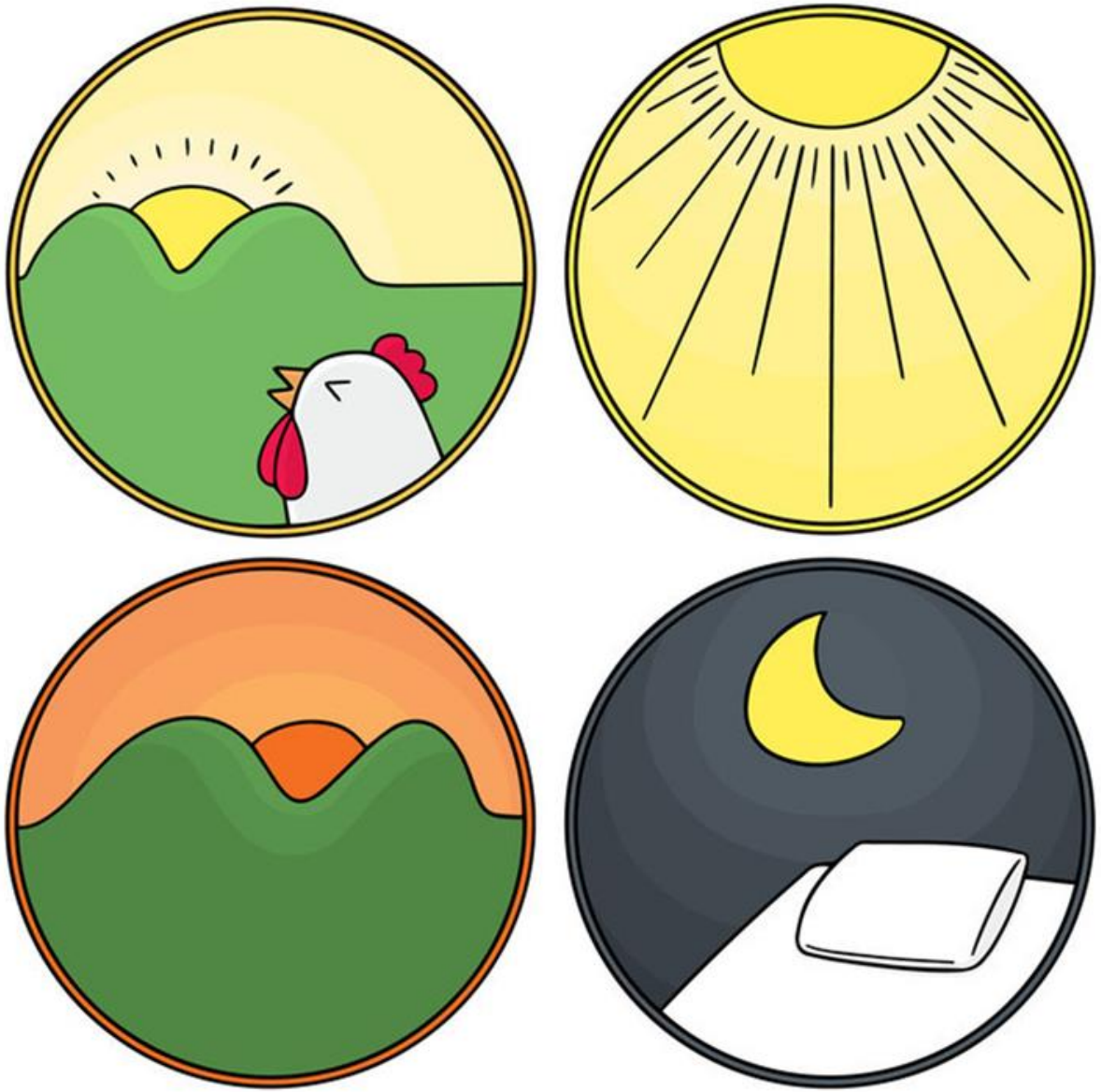
The inner ear research of our group

Innate immunity

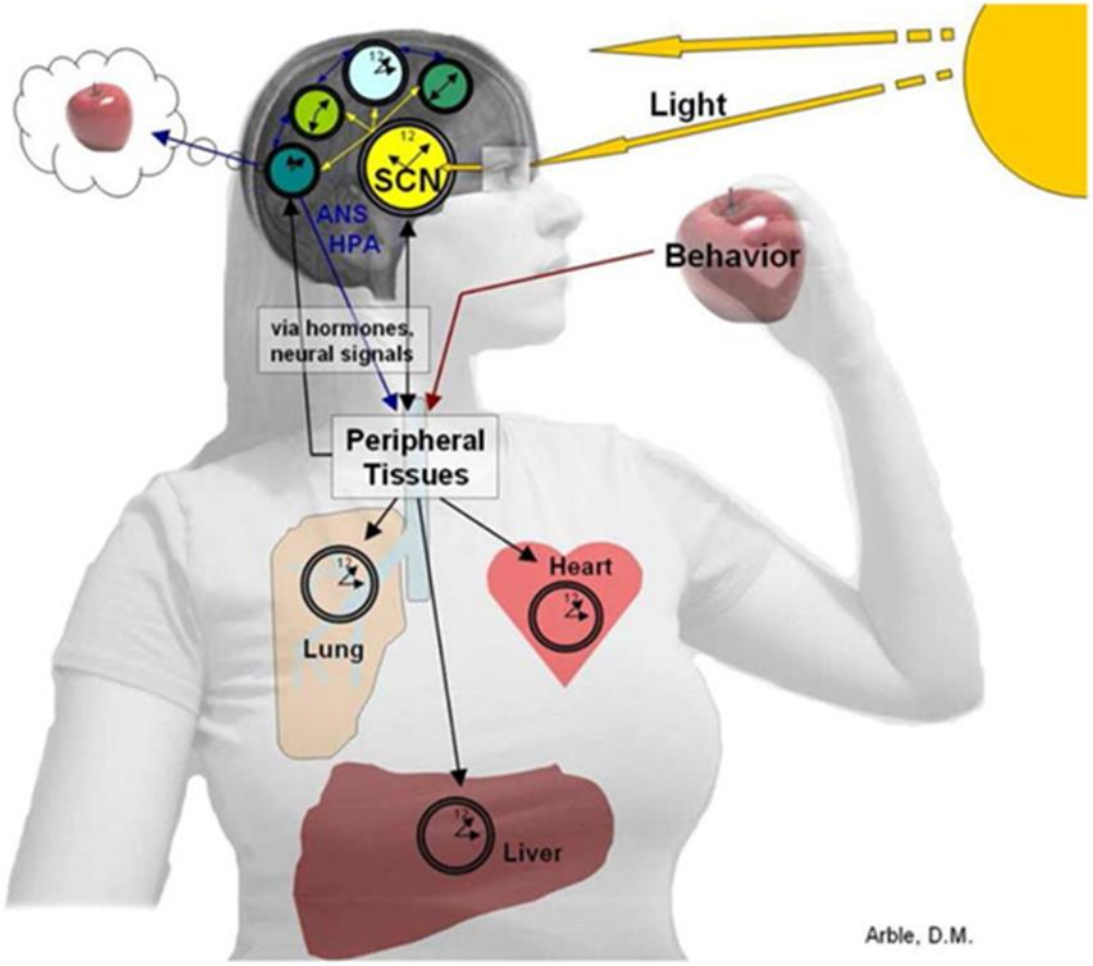
- Sudden hearing loss (Yang et al., Laryngoscope, 2015)
- Aminoglycoside ototoxicity (Yang et al., Hearing Research, 2021)
- Meniere's disease (Yang et al., Otolaryngology-Head and Neck Surgery 2025)

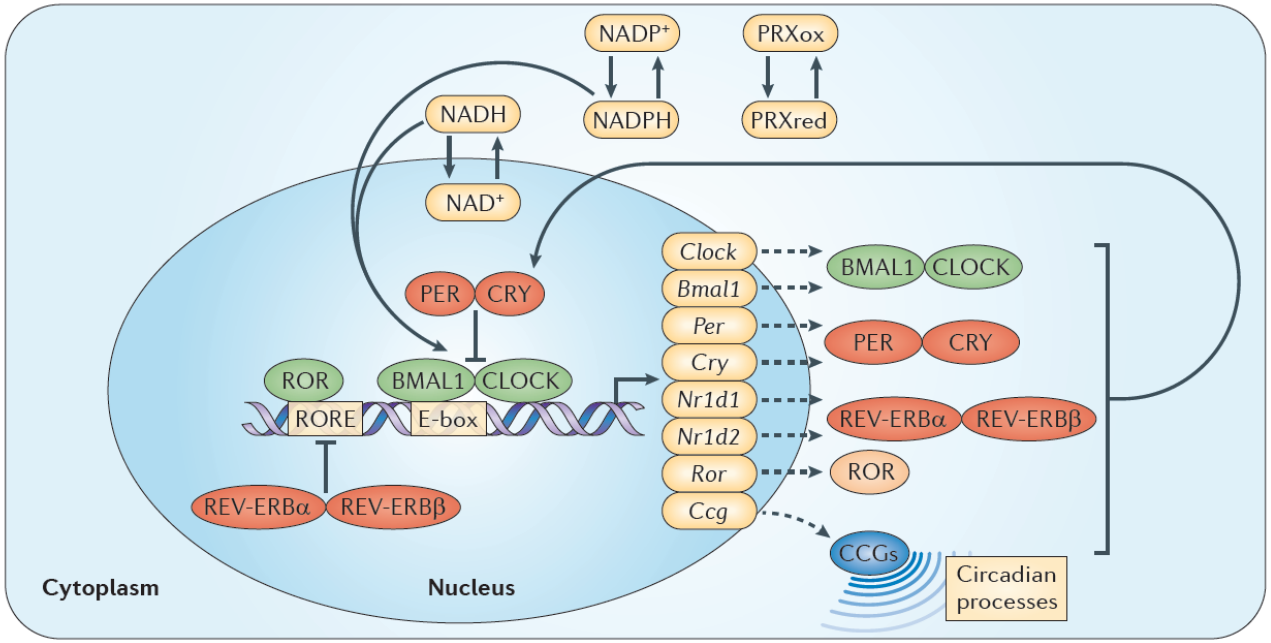
Circadian clock

- Sudden hearing loss (Yang et al., Medicine, 2015)
- Noise-induced hearing loss (Yang et al., International Journal of Molecular Sciences, 2020)
- Meniere’s disease (Yang et al., Laryngoscope Investigative Otolaryngology, 2022)
- Vestibular migraine (Yang et al., Otolaryngology-Head and Neck Surgery 2025)

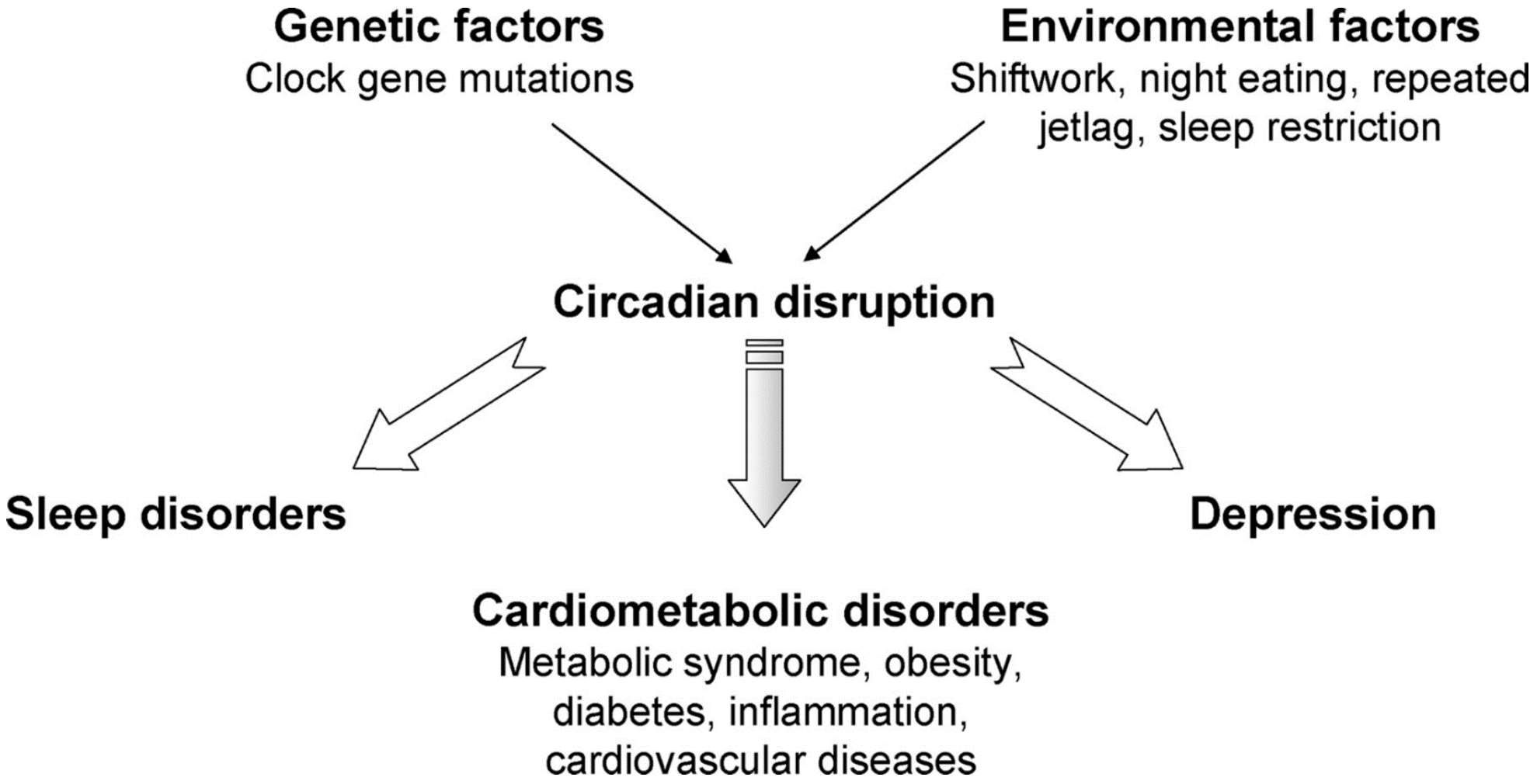


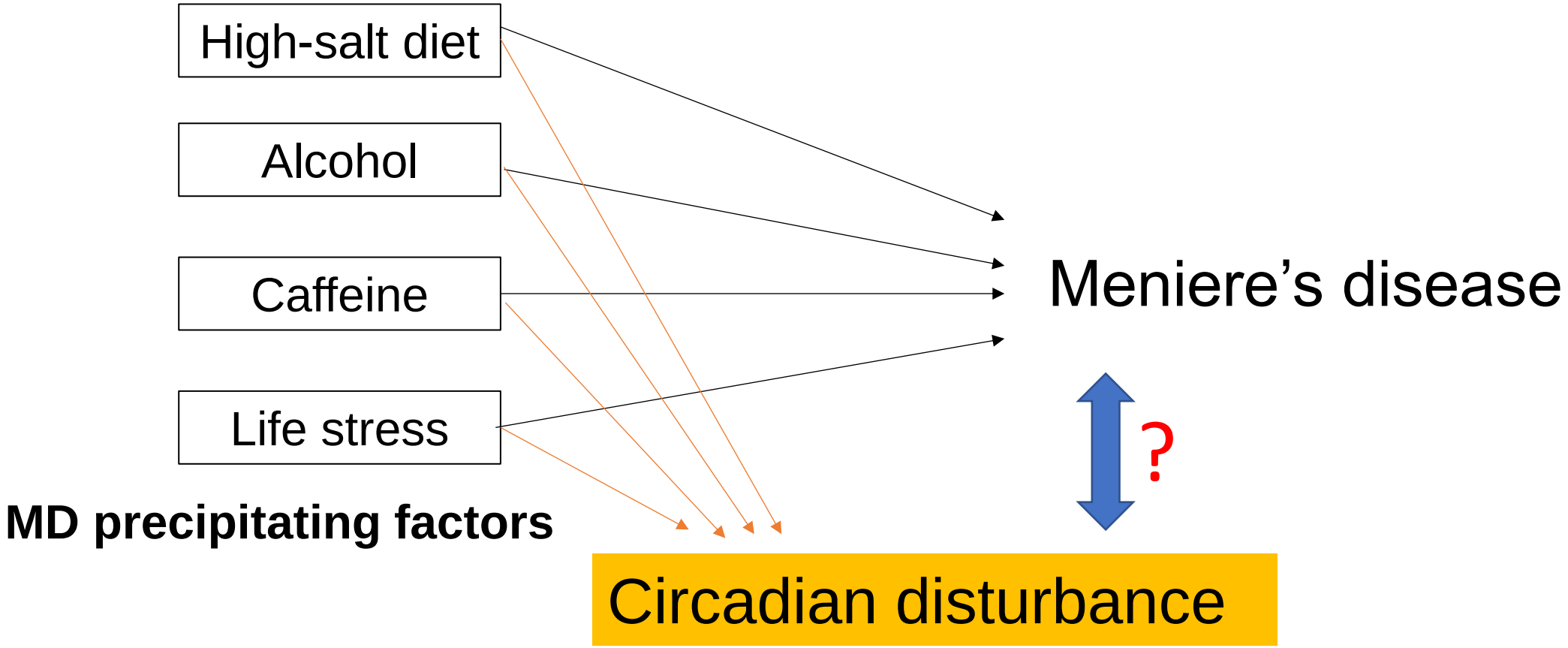
Circadian clock genes





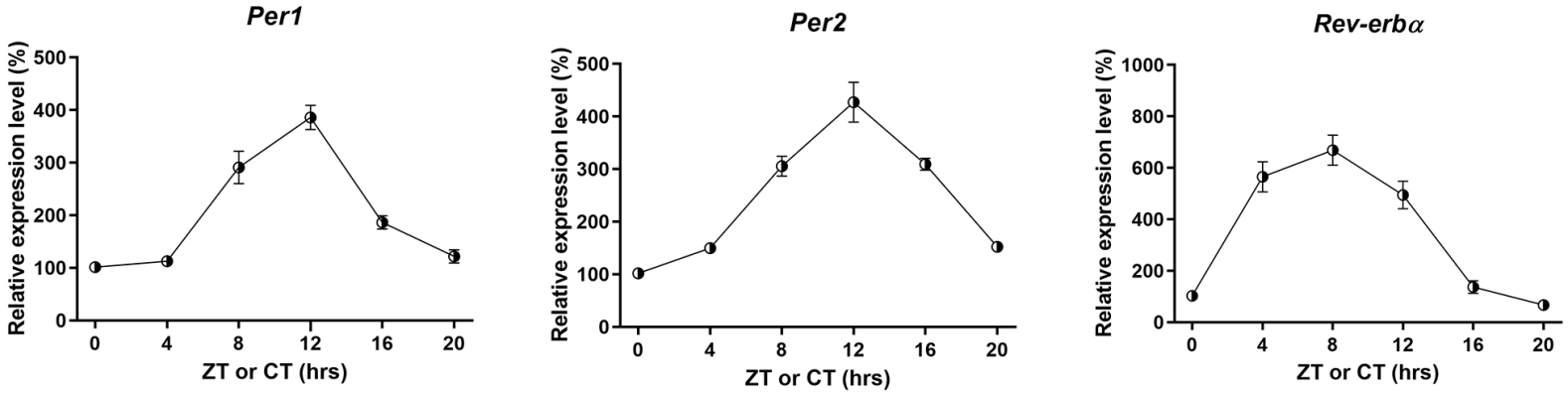
Circadian disruption and diseases

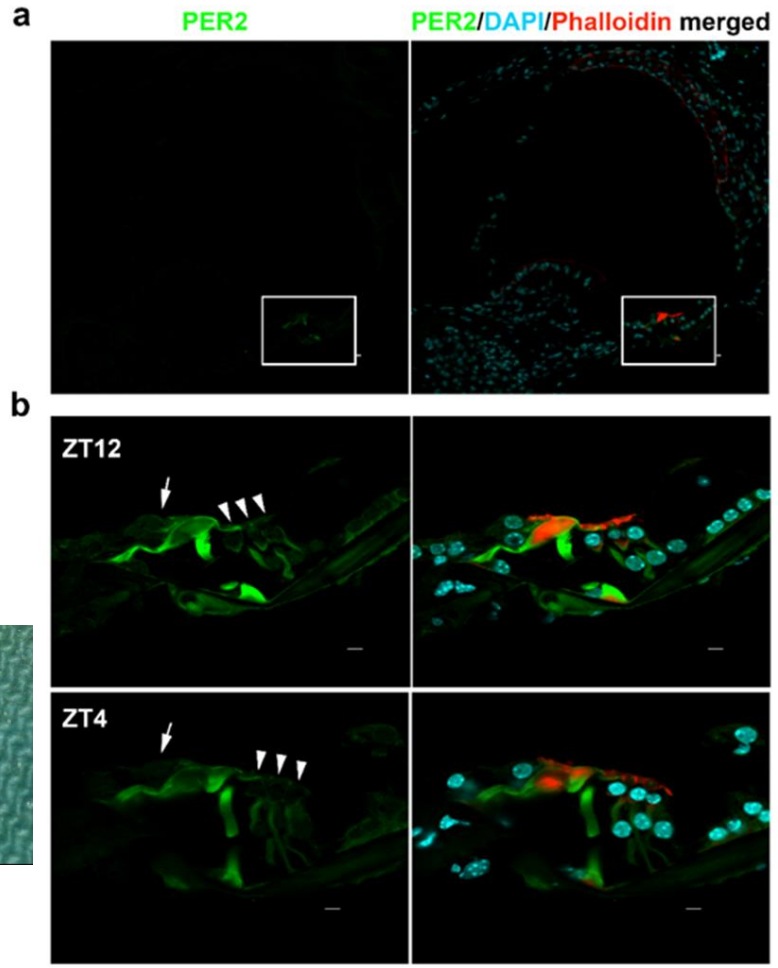




- Are there any association between circadian disturbance and MD?
- Are circadian clock genes suitable markers for MD?

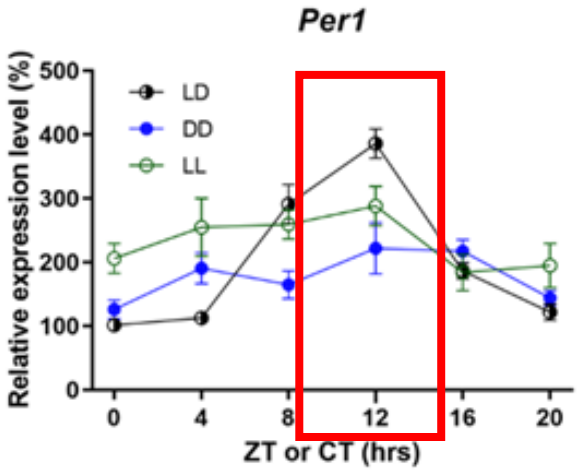
Temporal expression of cochlear circadian clock genes

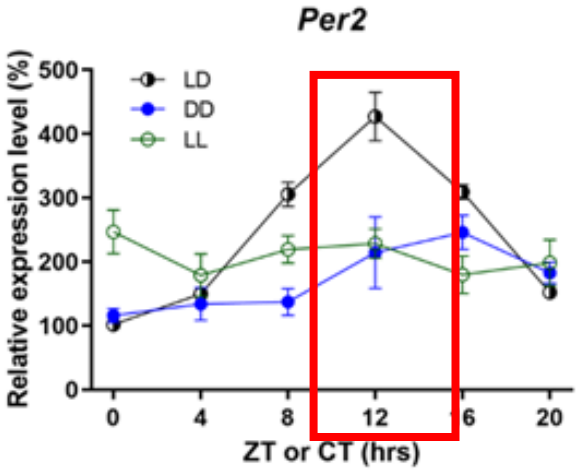


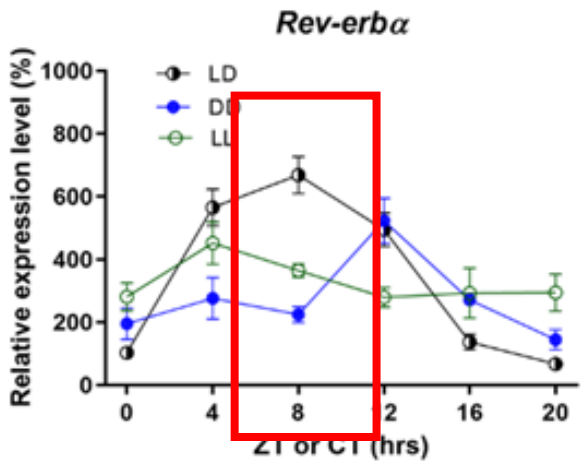


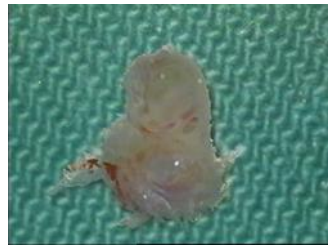
Yang et al. Int J Mol Sci. 2020 Oct 13;21(20):7535.

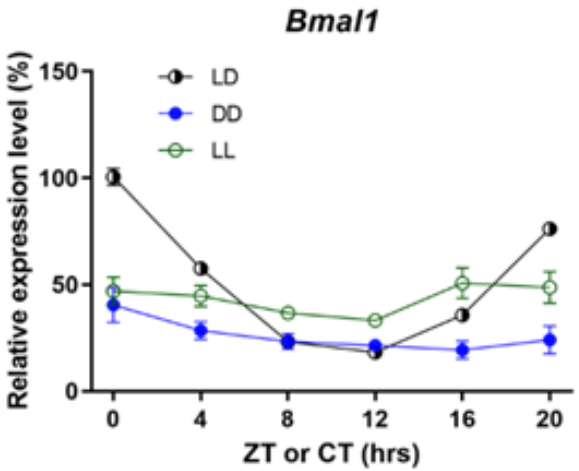
Constant light (LL) and constant dark (DD) disturb the cochlear circadian clock

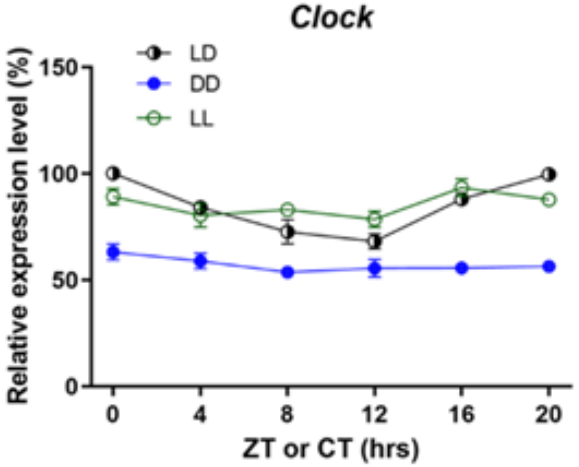










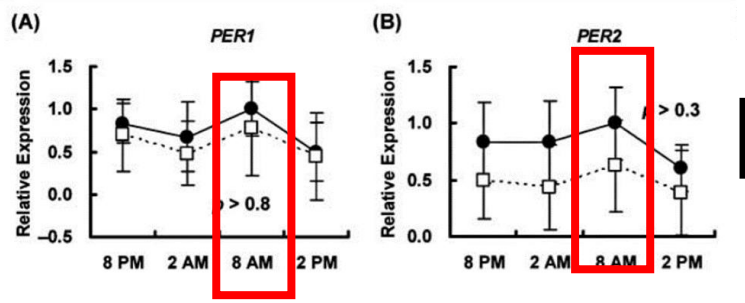


CircWave software

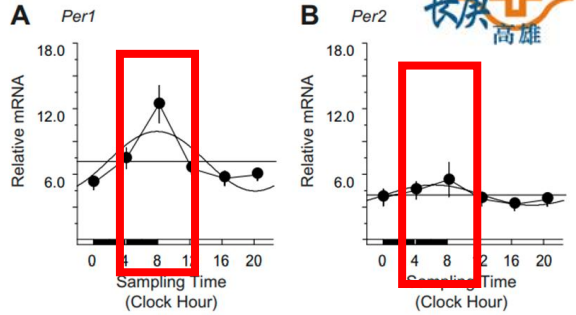
	LD Group	DD Group	LL Group
Per1	0.000012	0.023638	ns
Per2	<0.000001	0.001643	ns
Rev-erbα	<0.000001	0.008508	ns
Bmal1	0.000035	ns	ns
Clock	<0.000001	ns	ns

$p < 0.05$ indicates circadian rhythmicity, ns (not significant) means loss of circadian rhythm.

Yang et al. Int J Mol Sci. 2020 Oct 13;21(20):7535.



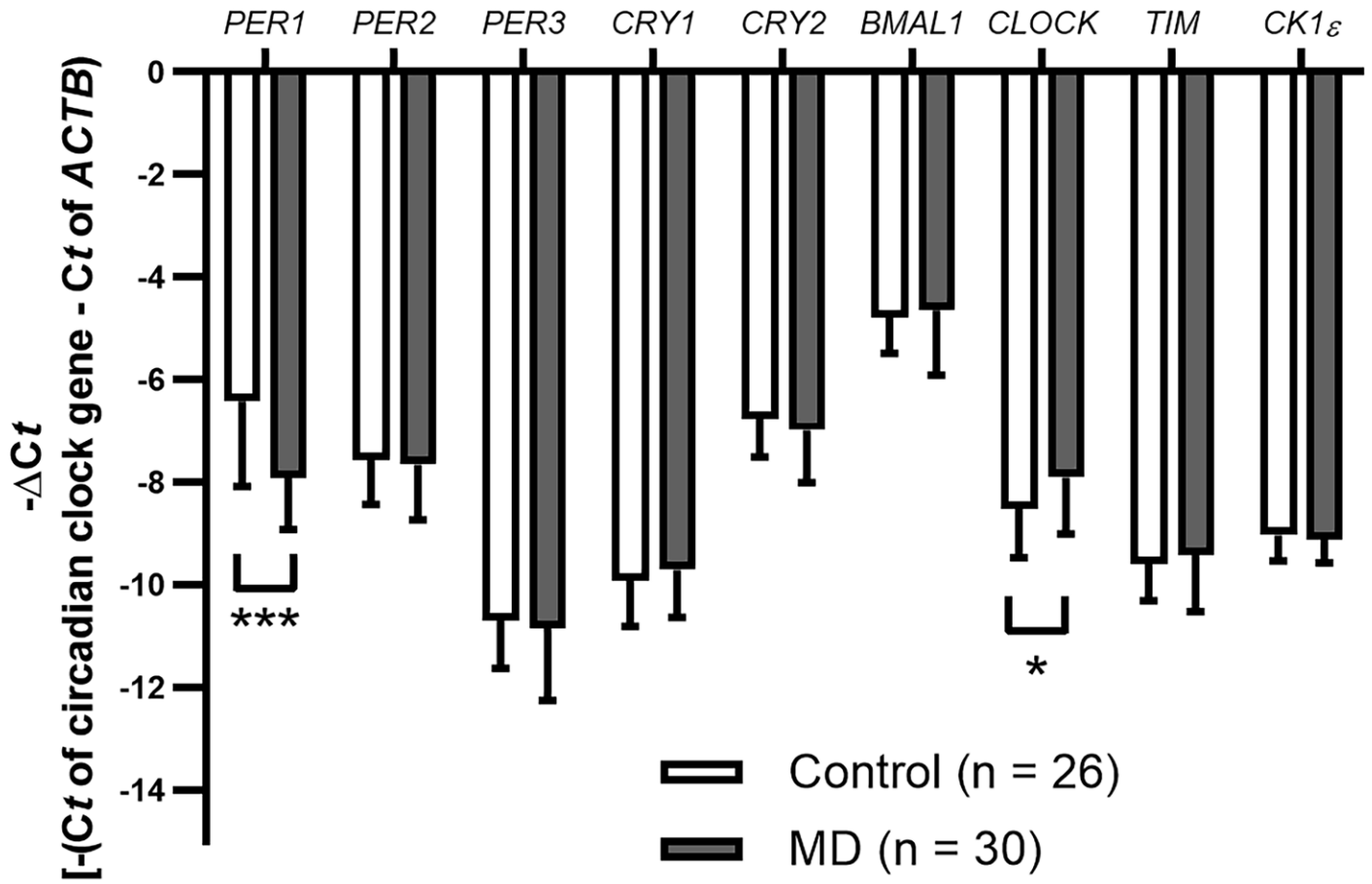
Methods



- In humans, the expression of PER1/PER2 peaked at **8:00 am** in peripheral blood leukocytes (*Yang et al, 2001; Fukuya et al, 2007*)
- Peripheral blood (PB) samples were collected from unilateral MD patients and controls in the morning (around 8:00 am)
  - **MD patients**: acute vertigo episode within one week, without steroid treatment
  - **Controls**: healthy subjects
- mRNA was obtained from leukocytes of each subject for qRT-PCR analysis

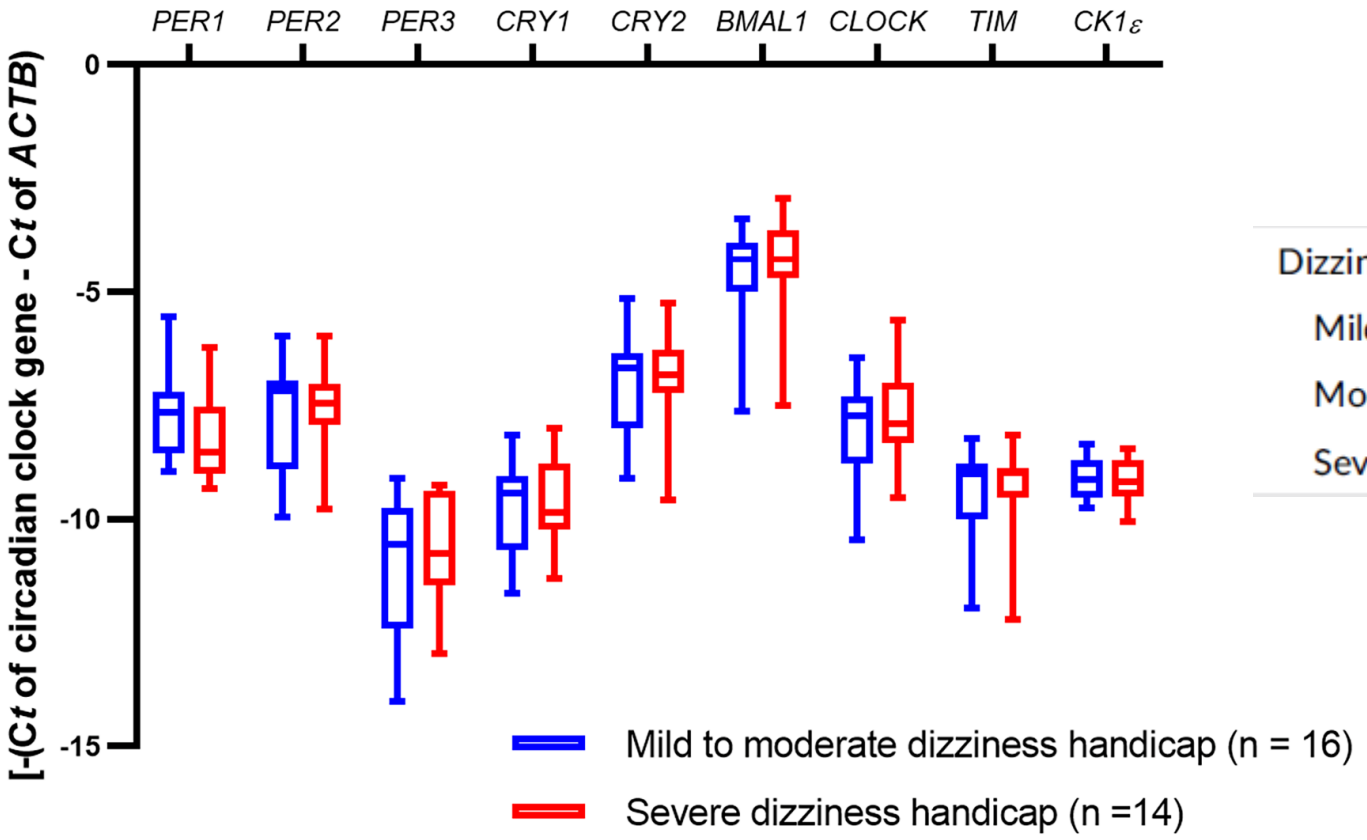
Yang et al. Laryngoscope Investigative Otolaryngology. 2022;1-8. doi:10.1002/lio2.757

Decreased *PER1* and increased *CLOCK* expression in MD



Yang et al. Laryngoscope Investigative Otolaryngology. 2022;1-8. doi:10.1002/lio2.757

Gene expression did not differ between different dizziness handicap groups

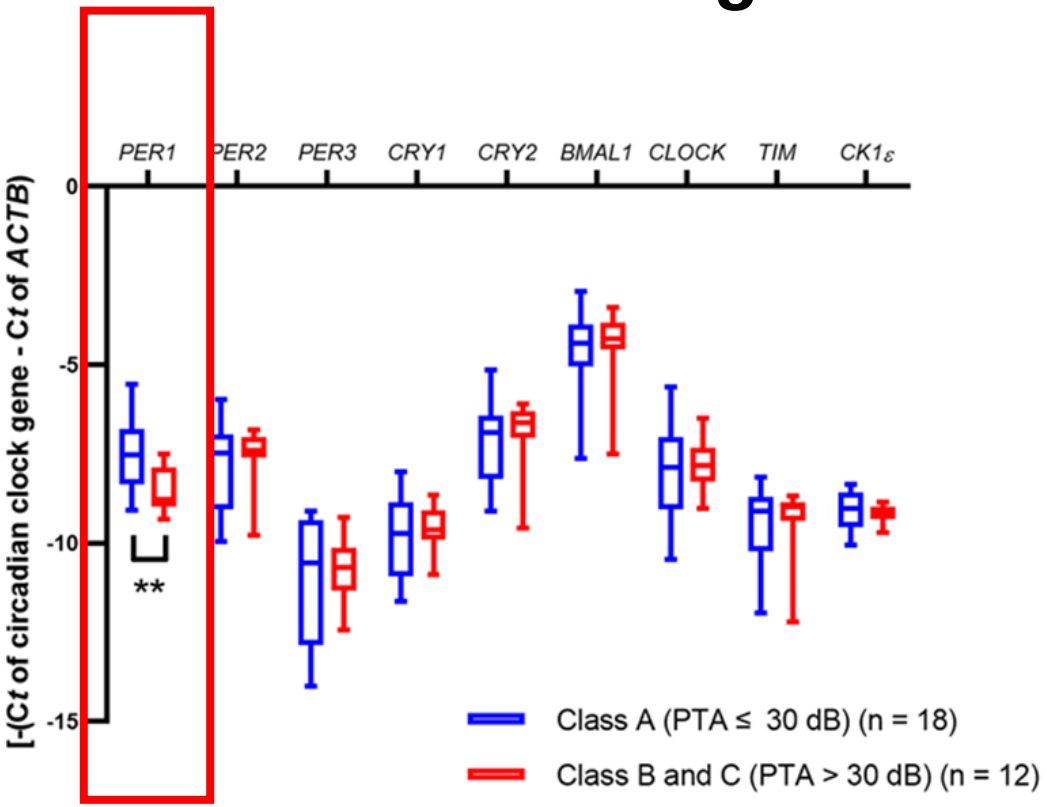


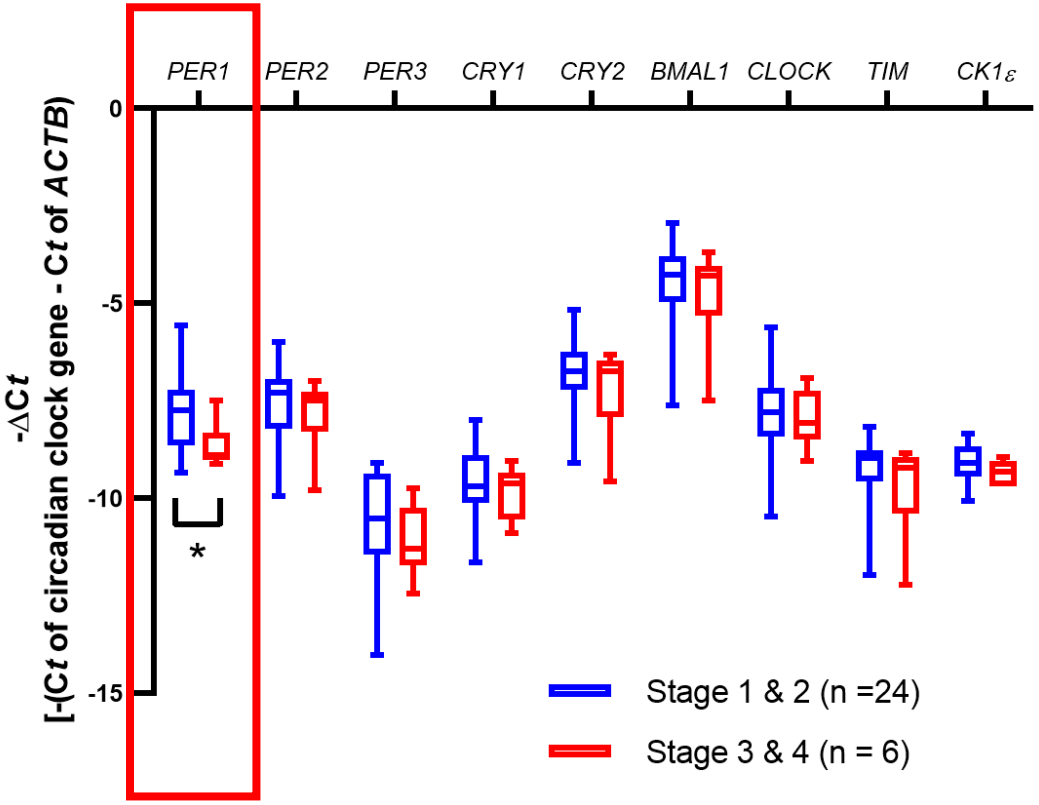
Dizziness handicap inventory (*n*, %)

- Mild (score: 16–34 points)
- Moderate (score: 36–52 points)
- Severe (score: 54+ points)

Yang et al. Laryngoscope Investigative Otolaryngology. 2022;1-8. doi:10.1002/lio2.757

Decreased *PER1* expression in MD patients with higher hearing thresholds and staging

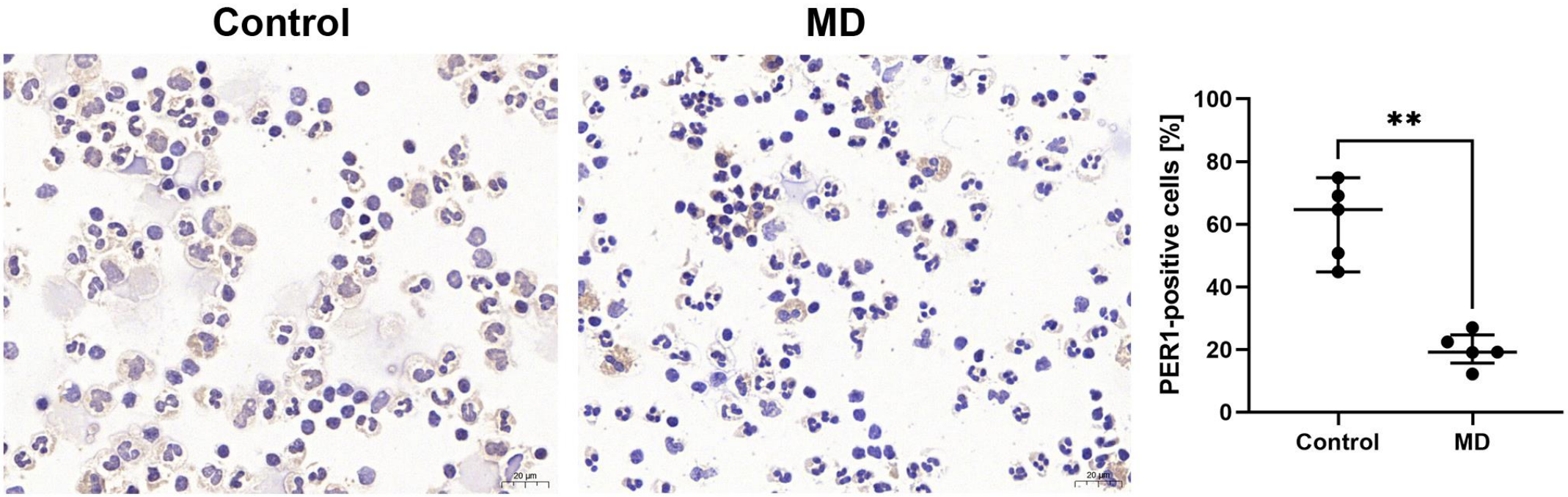




PER1 expression was significantly correlated to the PTA (r = 0.397, p = 0.03) and SRT (r = 0.371, p = 0.043).

Yang et al. Laryngoscope Investigative Otolaryngology. 2022;1-8. doi:10.1002/lio2.757

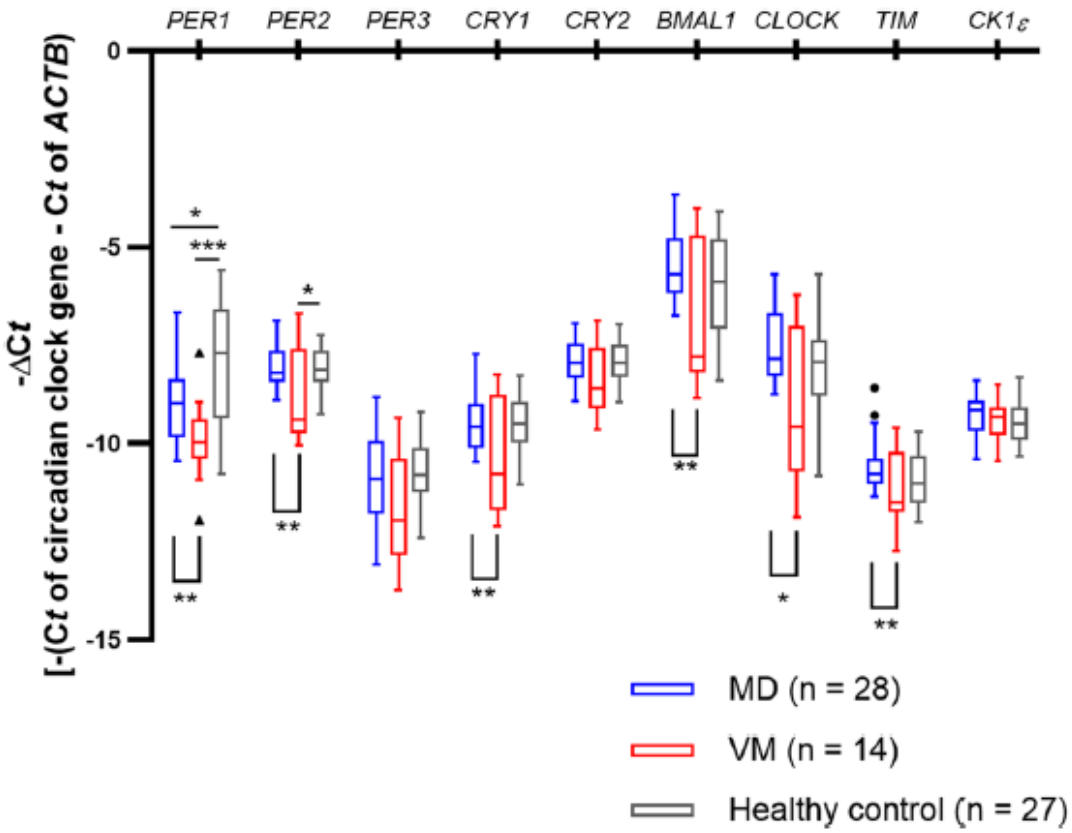
PER1 immunocytochemistry



Yang et al. Laryngoscope Investigative Otolaryngology. 2022;1-8. doi:10.1002/lio2.757

Could the CCG expression differentiate MD from VM?

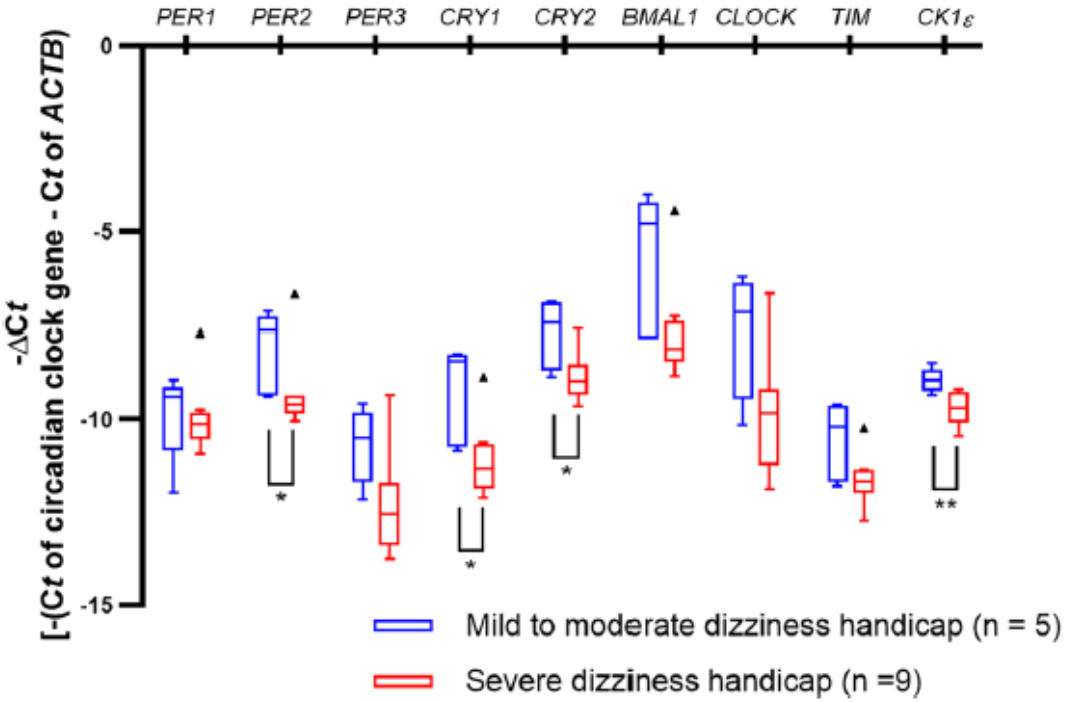
Decreased *PER1* expression in VM compared to MD



Yang et al. Otolaryngology-Head and Neck Surgery 2025.doi: 10.1002/ohn.1085

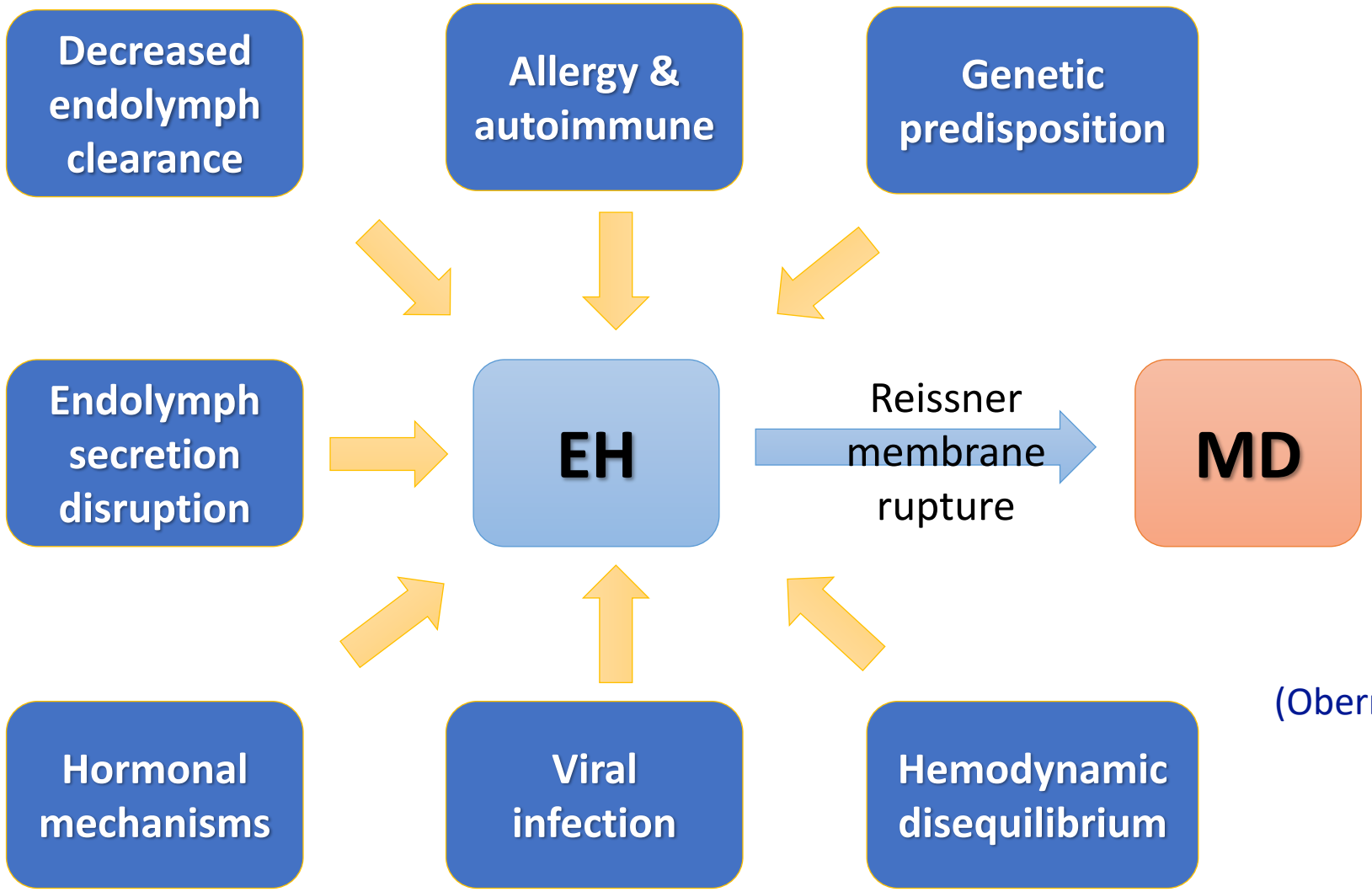
Association of Circadian clock genes with DHI in VM

- Significant negative correlations were observed between the expression of several circadian clock genes and DHI total scores, including PER2 (r = −0.637), PER3 (r = −0.568), CRY1 (r = −0.667), CRY2 (r = −0.654), BMAL1 (r = −0.577), and CK1ε (r = −0.717) (all P < .05).



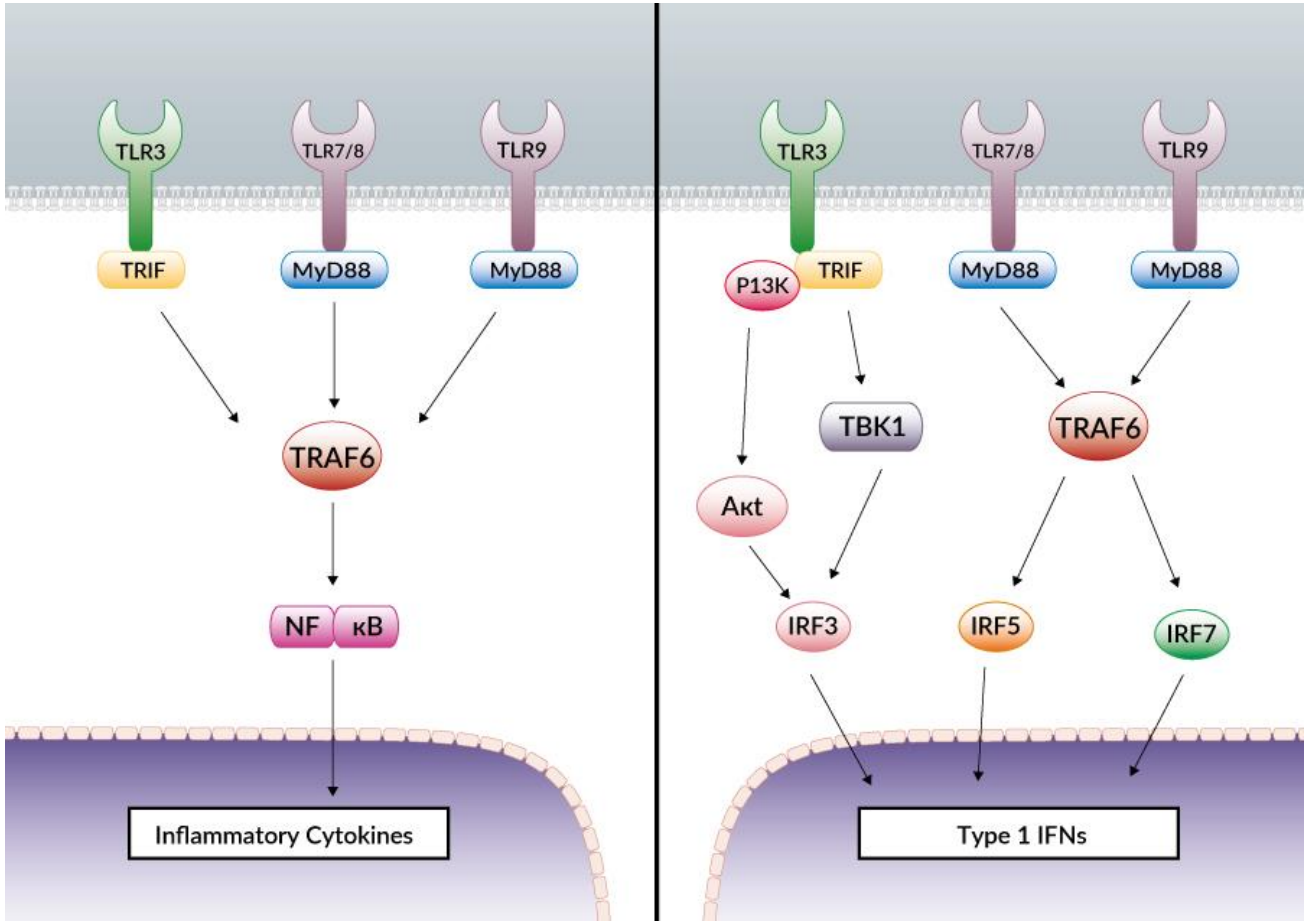
Yang et al. Otolaryngology-Head and Neck Surgery 2025.doi: 10.1002/ohn.1085

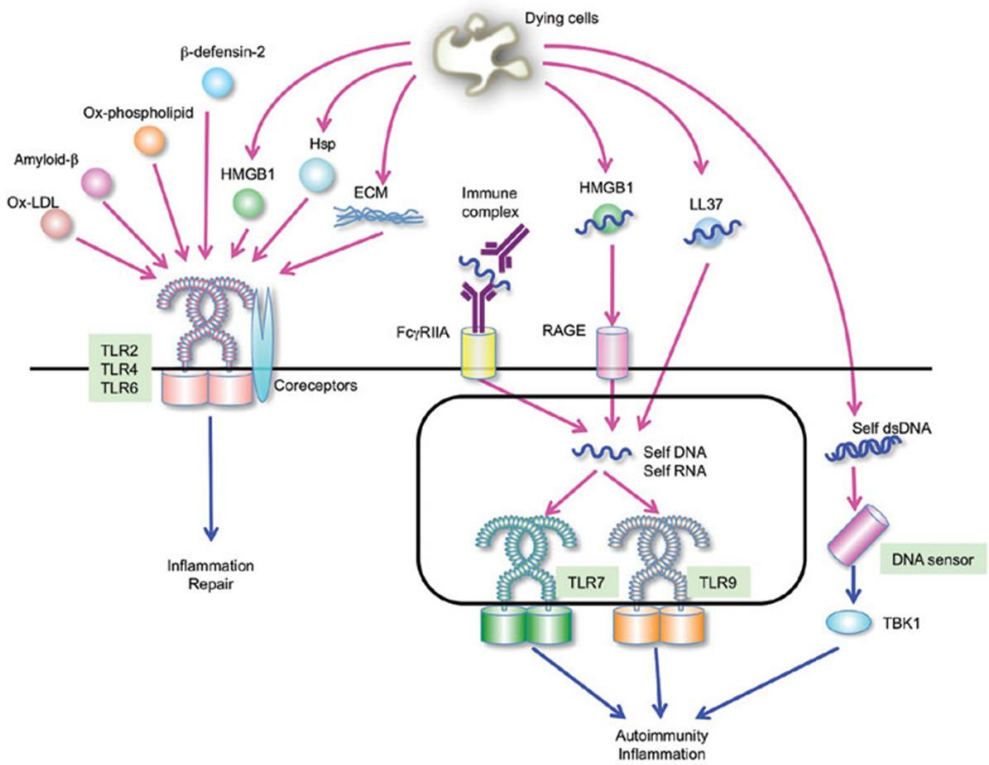
Hypotheses of MD: multifactorial



(Oberman et al, 2017)

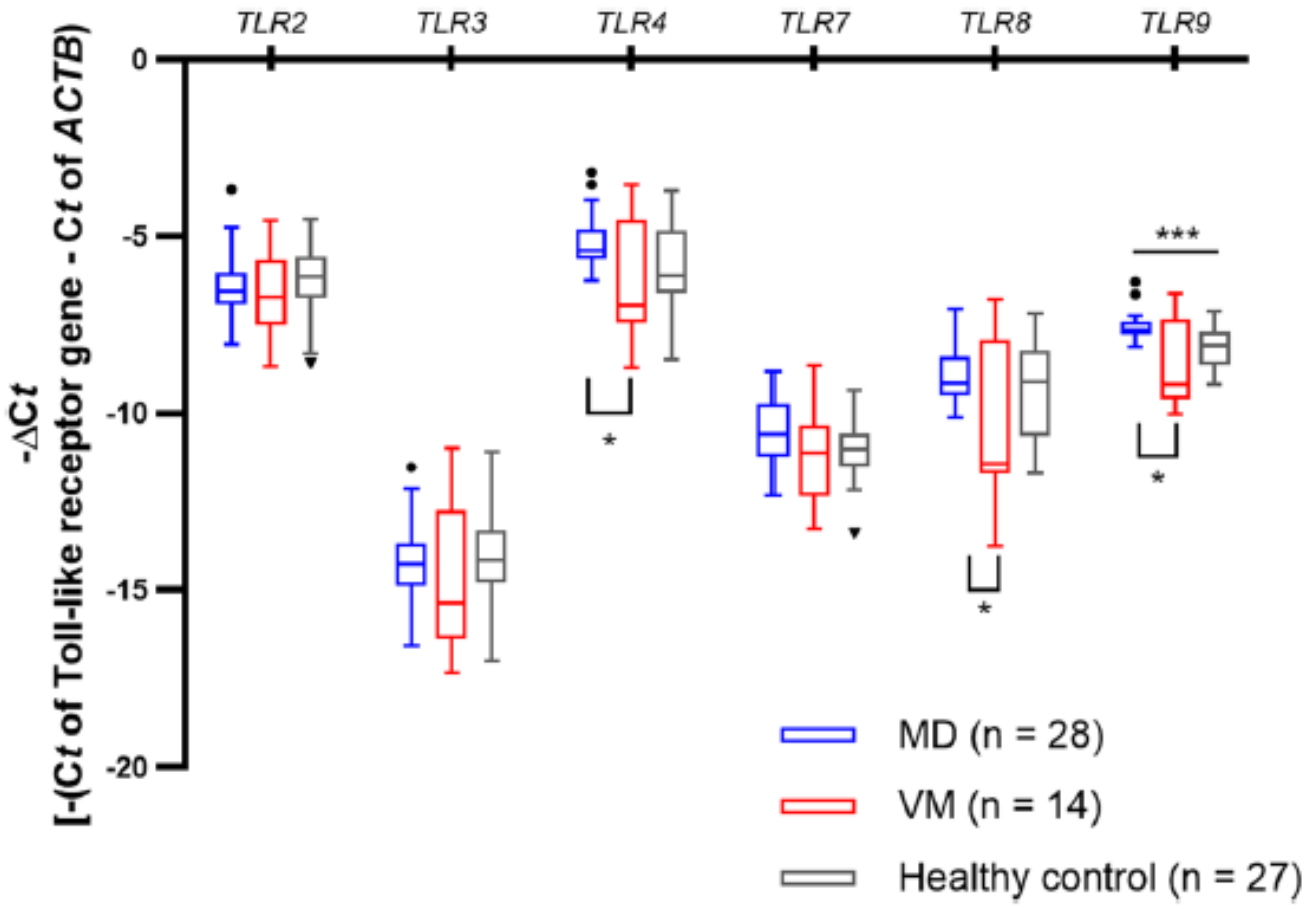
Toll-like receptors (TLRs) and inflammation





https://www.invivogen.com/review-tlr-viral-infection

Increased *TLR9* expression in MD compared to VM



Yang et al. Otolaryngology-Head and Neck Surgery 2025.doi: 10.1002/ohn.1085

Discussion

- Circadian clock may play a more significant role in the pathogenesis of migraine-related conditions.
- Circadian features have been well-documented in patients with cluster headaches and migraines. (*Benkli et al. Neurology. 2023*)
- VM patients are more likely to experience severe vertigo and headache attacks in the early hours of the day, particularly in those with a longer duration of illness or poor sleep quality (*Liu et al. Front Neurol. 2020*)

Yang et al. Otolaryngology-Head and Neck Surgery 2025.doi: 10.1002/ohn.1085

Take home message

- Sleep disturbance is prevalent in MD and VM
- VM patient may have more prevalent of sleep disturbance than MD
  - difficulty falling asleep
  - headaches upon awakening
- Sleep disturbance is correlated to severe dizziness handicap in VM
- Lower expression of *PER1* gene in MD and VM, while the expression is lower in VM compared to MD
- Higher expression of *TLR9* in MD than VM and control

Clinical implication

- The complaint of “Difficulty falling asleep” and “headaches upon awakening” may help to differentiate VM and MD
- *PER1* and *TLR9* are potential markers to differentiate VM and MD
- For therapeutic aspect
  - VM: restful sleep and keep regular circadian clock
  - MD: anti-inflammation treatment and avoid hypoxia (OSA?)

Thanks for your attention!

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