RELATIONSHIP BETWEEN MOTION SICKNESS AND PERIPHERAL VESTIBULAR DYSFUCNTION: A SYSTEMATIC REVIEW

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20AUD038

A Dissertation Submitted in Part Fulfilment of the Degree of Master of Science

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August 2022

CERTIFICATE

This is to certify that this dissertation entitled "**Relationship between Motion Sickness and Peripheral Vestibular Dysfunction: A Systematic Review**" is a bonafide work submitted in part fulfilment for the degree of Master of Science (Audiology) of the student with Registration Number 20AUD038. This has been carried out under the guidance of the faculty of this institute and has not been submitted earlier to any other University for the award of any other Diploma or Degree.

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This is to certify that this dissertation entitled "**Relationship between Motion Sickness and Peripheral Vestibular Dysfunction: A Systematic Review**" has been prepared under my supervision and guidance. It is also certified that this dissertation has not been submitted earlier to any other University for the award of any other Diploma or Degree.

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DECLARATION

This is to certify that this dissertation entitled "**Relationship between Motion Sickness and Peripheral Vestibular Dysfunction: A Systematic Review**" is the result of my own study under the guidance of Dr. Sujeet Kumar Sinha, Associate Professor, Department of Audiology, All India Institute of Speech and Hearing, Mysuru, and has not been submitted earlier to any other University for the award of any other Diploma or Degree.

Mysuru **Registration No: 20AUD038**

August 2022

DEDICATED TO MY GUIDE,

TEACHERS AND MY FAMILY

ACKNOWLEDGEMENTS

As told in the Holy Scripture, **"**Those who trusts in the Lord, shall never be disappointed". The road to accomplish tasks was never easy. But I believe whatever I have achieved to the present day, is truly magical and is a gift from the Almighty. I have felt His presence in everything I have done. With every difficulty I have faced, in every waiting place, I believe I was being given a chance to trust in the process unseen and to be abundantly blessed. As I understand, I would not be here today without the Almighty walking beside me and holding my hands through all ups and downs. Therefore, I would like to begin by thanking Him for all the blessings He has showered upon me.

Secondly, I would like to thank my Guide, Dr. Sujeet Kumar Sinha, for patiently clearing my doubts and being an exemplary mentor in every aspect. Thank you Sir, for opening the doors of Vestibular Science to me, in the most creative and patient way possible. I believe I am immensely fortunate to have had a guide like you.

I would like to extend my gratitude to all the teaching faculties of AIISH who have molded me into becoming the professional I am today and enlightened me with abundant knowledge.

I would also like to express my heartfelt gratitude to my pillar of support; my Mother. Words would definitely fall short for you Mummy. You have held the ground and my mind steady, when I felt like I would slip. Thank you for believing in me. I would also like to express my gratitude to all my family for supporting me throughout this journey.

I would also like to acknowledge the tireless efforts of my seniors, Praveen and Jijinu, in guiding me through the right path.

Last but not the least, I would like to thank all my dearest friends from School, Bachelors' and IInd MSc. for keeping me sane throughout this journey and giving me all the love, moral support, care and guidance that I have ever needed in my life.

Thank you each and everyone for making my "Today" possible.

ABSTRACT

Introduction: Motion sickness can be triggered by illusions of passive motions such as, from a moving visual background, transport modalities such as cars, trains, planes and boats, as well as illusions of passive motion from video games, virtual reality and three-dimensional videos, as per the latest trend of modern life. The exhibition of signs and symptoms by these individuals vary according to the severity of motion sickness. Video head impulse test, vestibular evoked myogenic potential and caloric tests are some of the contemporary tests that have been used in the literature for the diagnosis of vestibular dysfunction in individuals with motion sickness.

Aim: The current study aims to systematically review the articles related to peripheral vestibular dysfunction in individuals with motion sickness.

Method: Initially, a review search was performed in different databases. Searches across different databases resulted in 550 topic-related articles. A total of twelve articles met the inclusion and exclusion criteria to meet the objectives of the study. The quality and potential risk associated with each article were evaluated using the QUADAS-2 risk of bias assessment tool.

Results: The results of studies that have used vHIT indicate normal VOR gain in subjects with motion sickness. However, a higher VOR gain asymmetry ratio was established in the participants with motion sickness. And there are equivocal findings in terms of presence or absence of refixation saccades in individuals with motion sickness. However, the studies reviewed here have reported a dissociation between caloric test and peripheral vestibular dysfunction in motion sickness. The results which delineated the findings of VEMP in participants with motion sickness found that, in majority of the studies, the VEMP latencies, amplitude and the interpeak amplitude and latency did not show a significant difference.

The studies also reported that individuals with motion sickness had elevated (worse) thresholds compared to the control groups. Majority of the authors have also reported, an elevated asymmetry ratio in groups with motion sickness compared to that of the control groups.

Conclusion: Therefore it can be inferred from this systematic review that a peripheral vestibular dysfunction prevails in individuals with motion sickness, and it can be found out using an appropriate test battery and test protocol.

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CHAPTER-I

INTRODUCTION

Integration of vestibular, proprioceptive and visual systems is necessary for maintaining spatial orientation. A conflict among the three systems leads to motion sickness, a condition where there is a disagreement within these sensory input systems (Reason, 1975). Motion sickness is a common disturbance or a normal physiological response generated by unexpected passive movements based on previous experience (Koch et al., 2018). There are various theories proposed on how motion sickness is caused, and one of the widely accepted theories is the sensory conflict theory by Reason (1975) which was revised later as the neural mismatch hypothesis (Reason, 1978). According to this hypothesis, motion sickness is caused due to the conflict among three sensory systems (vestibular, visual and proprioceptive) that are sensed by the central nervous system. It may also occur when there is an intra-labyrinthine conflict, commonly referred to as canal-otolith conflict (Schmäl et al., 2013).

Motion sickness can be triggered by illusions of passive motions such as, from a moving visual background, transport modalities such as cars, trains, planes and boats, as well as illusions of passive motion from video games, virtual reality and three-dimensional videos, as per the latest trend of modern life. The exhibition of signs and symptoms by these individuals vary according to the severity of motion sickness. Subjects with motion sickness mainly experience drowsiness, dizziness, discomfort, restiveness, repetitive yawning, stomach awareness, nausea, pallor, sweating, headache, malaise, bradycardia, arterial hypotension, vomiting, and apathy (Money, 1970; Reason, 1975; Murdin et al.,

2011). Individuals with motion sickness can also experience some other sign and symptoms such as lethargy, depression, and a decline in cognitive function as evidenced by deteriorated performance in several psychomotor tasks. The vulnerability to motion sickness is influenced by senescence and genetic factors (Yates et al., 1998; Tal et al., 2006; Heer & Paloski, 2006; Evans et al., 2007).

The precise root of motion sickness is not known, however as a general rule it may be set off by environmental challenges in linear or angular accelerations (Buyuklu et al., 2009). Few authors have classified the causes of motion sickness into two significant categories of sensory conflict. The first one is the incongruence between angular (from semicircular canals) and linear (from otolith organs) vestibular input, and the second one is between visual and vestibular input (Bertolini & Straumann, 2016). There are different forms of motion sickness such as car sickness (due to visual-vestibular conflict of stimuli), sea sickness (due to unfamiliar, complex linear and angular accelerations of low frequency), vehicle simulator sickness (due to optokinetic motion sickness), and space sickness (due to incongruent sensory stimuli of the otoliths, semicircular canals (Buyuklu et al., 2009).

Few studies in the literature have delineated vestibular system dysfunction in individuals with motion sickness. The video head impulse test is a contemporary tool that gauges the function of each one of the six semicircular canals in individuals with various vestibular pathologies. It has been reported that the VOR gain functions in persons with motion sickness remain normal. However, the VOR gain asymmetry is higher in motion sickness groups compared to their healthy matches (Neupane et al., 2018). The author also reported the presence of both covert and overt saccades in motion sickness individuals.

However, Kilinc et al. (2020) have described abnormal VOR gain functions for all the semicircular canals in individuals with motion sickness. Kumar and Sinha (2021) also revealed no significant discrepancy in VOR gain between healthy individuals and those with motion sickness. The authors also suggest that vHIT might not be an absolute technique to judge the vestibular system in individuals with motion sickness.

There are also reports to suggest that VEMPs findings are abnormal in individuals with motion sickness. Tal et al. (2006) described significantly higher threshold of VEMPs in motion sickness compared to their healthy counterparts. Singh et al. (2014) also reported a higher threshold and amplitude asymmetry ratio of cVEMP in motion sickness. Fowler et al. (2014) reported that subjects who were greatly susceptible to motion sickness had a larger c-VEMP amplitude than those participants in the low susceptibility group. However all the authors report that there is no significant change in terms of latency of VEMP in motion sickness. However the caloric responses are affected only in a very small proportion of the subjects with motion sickness (Mallinson and Longridge, 2002; Byukulu et al., 2009).

1.1 Need of the study

Though time-consuming, systematic reviews compile many scientific studies into a single piece of literature in a well-ordered manner. This makes the unmanageable data conveniently accessible to the researchers (Khan et al., 2003). Several authors have reported possible peripheral vestibular dysfunction in participants with motion sickness using different tests (Neupane et al., 2018, Kilinc et al., 2020, Singh et al., 2014). Therefore, a compilation of several researches shedding light on the topic, on how test results differ amongst researchers and how different tests are manifested in case of motion sickness,

would be beneficial to researchers. No systematic review has been done on this topic to date; thus, systematically reviewing and summarizing the findings regarding the possible vestibular dysfunction in motion sickness will provide the information under a single title. Hence it would be beneficial clinically and for those working in this research area. Integration of these accumulating data will also act as a quick guide that provides direct insight into the topic rather than searching all the relevant articles related to the same (Pearson et al., 2014).

1.2 Aim of the study

The current study aims to systematically review the articles related to peripheral vestibular dysfunction in individuals with motion sickness.

1.3 Review question

The review question of this study was whether individuals with motion sickness have peripheral vestibular dysfunction or not.

1.4 Objective of the study

The objective of the study was to systematically review and summarize the findings of articles related to peripheral vestibular dysfunction and motion sickness and to characterize the following parameters:

1) The saccades and VOR findings of vHIT in individuals with motion sickness.

2) Latency, amplitude and asymmetry ratio of VEMP findings in individuals with motion sickness

3) Caloric test findings include slow phase velocity of the nystagmus, directional preponderance and unilateral weakness in individuals with motion sickness.

CHAPTER-II

METHOD

The main aim of the study was to systematically review and summarize peripheral vestibular test findings in participants with motion sickness. To achieve this aim, in the study's first phase, a detailed electronic search was done to find out the literature related to the peripheral vestibular test findings in motion sickness. In the second phase, the results were summarized.

2.1 Searches

A literature search was conducted in the following electronic bibliographic databases: Google Scholar, Pubmed Central, Ovid Medline and Cochrane Library. The articles that defined peripheral vestibular dysfunction in individuals with motion sickness were considered for the preliminary search. No limits were placed on the date of publication. The exploration were limited to studies with full-text availability, published in English, and including human subjects. The search was also conducted just before the final analysis to identify more studies to be included. Search words such as "motion sickness, Head Impulse Test in motion sickness, VEMP in motion sickness, vestibular dysfunction in motion sickness, sea sickness and peripheral vestibular dysfunction, air sickness and peripheral vestibular dysfunction, caloric test in motion sickness, Dynamic Visual Acuity in motion sickness, etc." were entered into different databases, in various combinations with the use of Boolean operators such as AND, OR and NOT.

2.2 The types of studies included

Study designs included retrospective and prospective observational studies, cross-sectional studies, case series, and randomized clinical trials. The research included original

research data only. Any other systematic reviews and studies with less than 5 participants were excluded from the present study.

2.3 Condition or domain being studied

Evaluation of peripheral vestibular system, which included,

1. Evaluation of semicircular canal function
2. The function of otolith organs
3. Evaluation of superior and inferior vestibular nerves in individuals with motion sickness

2.4 Participants/ Population

***Inclusion Criteria*:**

Studies that describe any individuals with motion sickness, of any age range, presenting with vestibular signs and symptoms were included. Studies that described the peripheral vestibular test findings in motion sickness were particularly included.

***Exclusion Criteria*:**

Studies describing individuals with other neurological and co-morbid disorders were excluded from the study. Review studies and case studies of less than five subjects were excluded. Studies that described central vestibular tests findings in individuals with motion sickness were also excluded.

2.5 Interventions and Exposures

The studies included the individuals with motion sickness tested using:

Cervical Vestibular Evoked Myogenic Potential (cVEMP), Ocular Vestibular Evoked Myogenic Potential (oVEMP), Video Head Impulse Test (vHIT), Dynamic Visual Acuity (DVA) test and Caloric test.

2.6 Analysis

2.6.1 Data Extraction (Selection and coding)

Two review authors had screened titles and abstracts of all the obtained articles from different databases independently to narrow down the studies that most likely met the inclusion criteria. Any discrepancies or disagreements were resolved by consensus between the authors. Only the articles fulfilling the inclusion criteria were taken up for further analysis and other articles were excluded. The reference list of the included studies was further reviewed to obtain additional relevant articles. The full text of these potentially eligible articles was extracted and screened for eligibility by two review authors. Any discrepancies or disagreements regarding the methodology of the article were resolved by consensus between both the authors. The missing data were requested from the study authors. The risk of bias was considered, and the assessment for the same was carried out independently by the two reviewers. All the selected articles were screened in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards (Page et al., 2022).

2.6.2 Risk of bias (quality) assessment

Reviewer bias was overcome by involving two independent reviewers at each screening stage, and the disagreements were dealt with through discussions. Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2), an evidence-based quality analysis tool, was used to assess the risk of bias in the studies that were included, by two independent authors. QUADAS-2 was specifically developed to be used in systematic reviews of diagnostic accuracy studies, with four critical domains, including patient selection, index

test(s), reference standard, and flow and timing (Whiting et al., 2011). Studies with a higher risk of bias were excluded from further analysis and interpretation, or their results were qualified depending on the nature and potential impact of the bias.

QUADAS, was explicitly developed for systematic reviews in 2003, which was later upgraded to QUADAS-2 in 2011. It consists of four key domains: patient selection, index test, reference standard, and flow and timing. All four domains were assessed regarding their risk of bias, and the initial three domains regarding their concerns about applicability. The assessment provided the degree to which the diagnostic accuracy avoided the risk of bias and the extent to which the primary studies were applicable to this review. Each of these domains has a set of signalling questions making a total of 11 questions in the entire tool, which are listed below. Each question assessing the risk of bias was rated either yes/no or deemed unclear. If the domains have maximum 'yes' responses, it was judged as having a low risk of bias, and if it has more 'no' responses, it was considered having a high risk of bias. If the signalling questions lead to 'unclear' responses, the domain was considered to have an unclear risk of bias. Concerns regarding applicability were also evaluated as 'low/high/unclear' concerns.

Domain 1: Patient selection

1. Was a consecutive or random sample of patients enrolled?
2. Was a case-control design avoided?
3. Did the study avoid inappropriate exclusions?

Domain 2: Index test (s)

1. Were the index test results interpreted without knowledge of the results of the reference standard?

2. If a threshold was used, was it pre-specified?

Domain 3: Reference standard

1. Is the reference standard likely to correctly classify the target condition?

2. Were the reference standard results interpreted without knowledge of the results of the index test?

Domain 4: Flow and timing

1. Was there an appropriate interval between index test (s) and reference standard?

2. Did all patients receive a reference standard?

3. Did all the patients receive the same reference standard?

4. Were all the patients included in the analysis?

After obtaining the individual rating for each question, the percentage of yes was calculated for each study as a whole by finding the total number of 'yes' out of 11 questions. This was further used to categorize the studies according to the percentage of positive answers in the questions which is extrapolated from the risk of bias assessment guidelines given by The Joanna Briggs Institute (Moola et al., 2015). They considered a higher risk of bias when only up to 49% of the answers were "yes", moderate when 50%–69% of the answers were "yes", and low when more than 70% of the answers were "yes".

2.6.3 Analysis of subgroups or subsets

Correlation between different test findings were also studied.

CHAPTER-III

RESULTS

3.1 Studies selection

Searches across different databases, including Google Scholar, PubMed, Cochrane library and Ovid Medline resulted in 550 topic-related records. One hundred and ninety-eight records were identified and screened after duplicate removal. Considering the exclusion criteria, unavailability of full-text articles, studies reported in languages other than English, case reports, and reviews, 146 articles were excluded, which led to the full-text screening of 52 articles. In 32 articles, the patients were not diagnosed as having motion sickness but were only mentioned as having slight imbalance and dizziness. So these thirty-two articles were also excluded from the study. Eight articles were excluded from the remaining 20 studies as the participants had underlying neurological disorders and other co-morbid conditions. Finally, twelve articles were included for this systematic review. The process of screening and the reasons for exclusion are depicted in the PRISMA flow diagram (Figure 3.1)

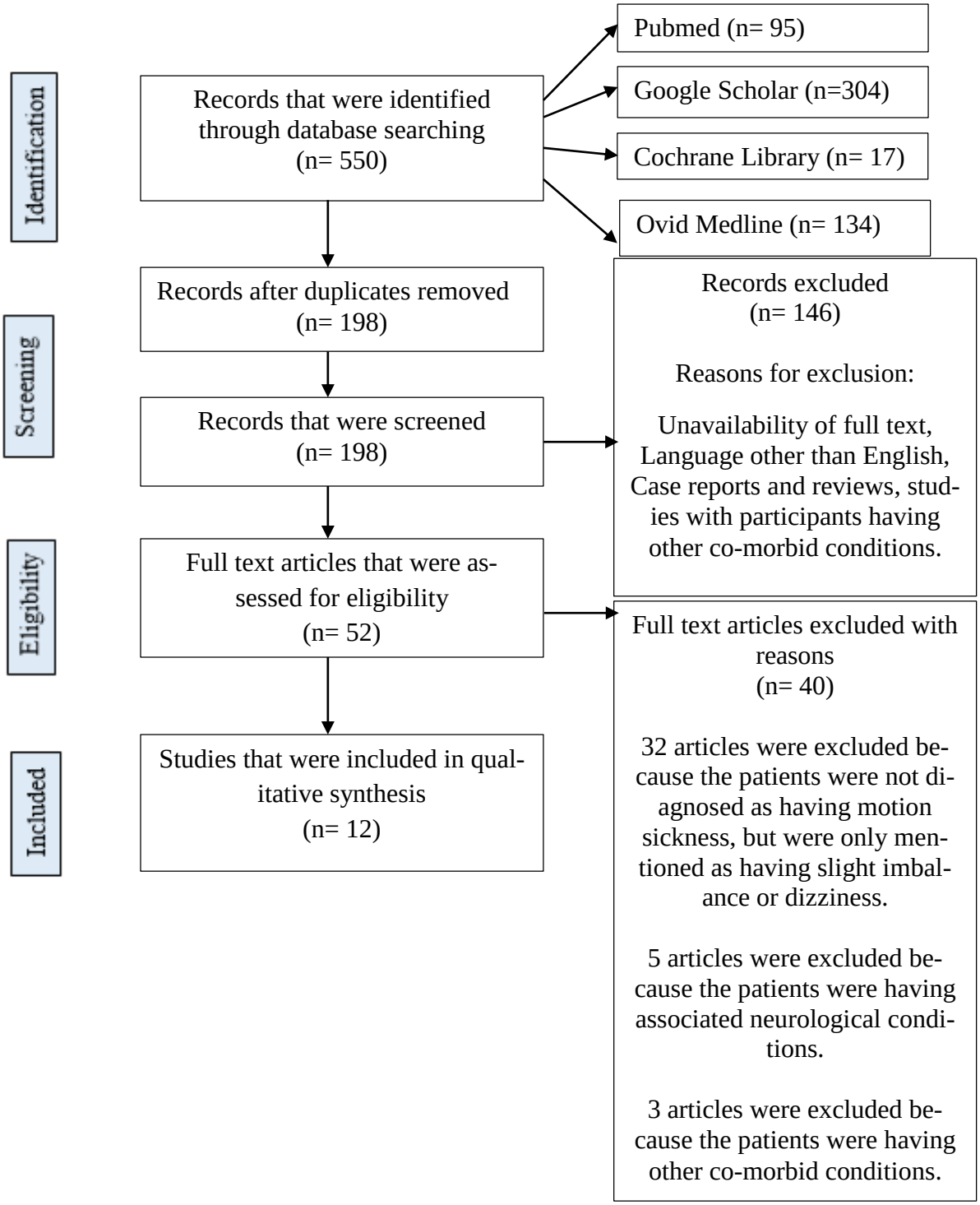

Figure 3.1

PRISMA chart for Systematic Reviews and Meta-Analyses (PRISMA)

3.2 Risk of bias

QUADAS-2 was administered finally to twelve included articles. Risk of bias involved in different domains, including patient selection, index tests, reference standard, and flow and timing were checked. The major risk was seen in the domain of 'reference standard'. The risk of bias for all the study are shown in Table 3.1.

Table 3.1

Risk of Bias assessment for the twelve studies included in the systematic review

		Risk of Bias				Applicability of Concern			
Sl No.	**Study**	**Patient selection**	**Index test**	**Reference standard**	**Flow and timing**	**Patient selection**	**Index test**	**Reference standard**	**Percentage of "yes"**
1.	**Neupane et al. (2018)**	🙂	🙂	🙂	🙂	🙂	🙂	🙂	**72.72 %**
2.	**Kumar and Sinha (2021)**	🙂	🙂	🙂	🙂	🙂	🙂	🙂	**72.72 %**
3.	**Kilinc et al. (2020)**	☹	🙂	☹	🙂	🙂	🙂	🙂	**63.63 %**
4.	**Byukulu et al. (2009)**	🙂	🙂	🙂	🙂	🙂	🙂	🙂	**63.63 %**
5.	**Fowler et al. (2014)**	🙂	🙂	🙂	🙂	🙂	🙂	🙂	**72.72 %**
6.	**Tal et al. (2007)**	☹	🙂	🙂	☹	🙂	🙂	🙂	**63.63 %**

7.	**Noiij et al. (2011)**	☹	☺	☺	☺	☺	☺	☹	**54.54 %**
8.	**Singh et al. (2014)**	☺	☺	☺	☺	☺	☺	☺	**72.72 %**
9.	**Tal et al. (2006)**	☹	☺	☺	☺	☺	☺	☹	**54.54 %**
10.	**Xie et al. (2012)**	☺	☺	☺	☺	☺	☺	☺	**72.72 %**
11.	**Fowler et al. (2020)**	☺	☺	☺	☺	☺	☺	☹	**63.63 %**
12.	**Mallinson and Longridge (2002)**	☺	☺	☹	☺	☺	☺	☺	**63.63 %**

Icon illustration: ☺ Indicates domains with a low risk of bias and ☹ or indicates domains with a high risk of bias.

The proportion of studies with a low or high risk of bias and the proportion of studies with low or high concerns regarding applicability are graphically represented in Figures 3.2 and 3.3, respectively.

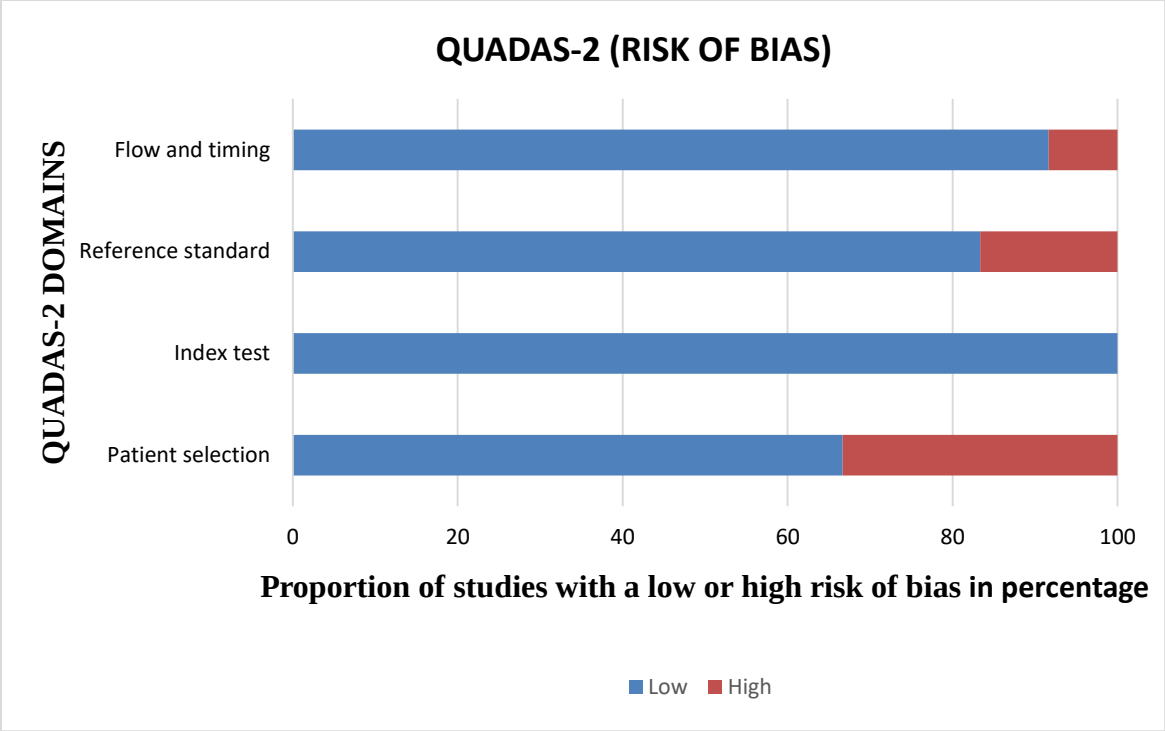

Figure 3.2

Proportion of studies with a low or high risk of bias.

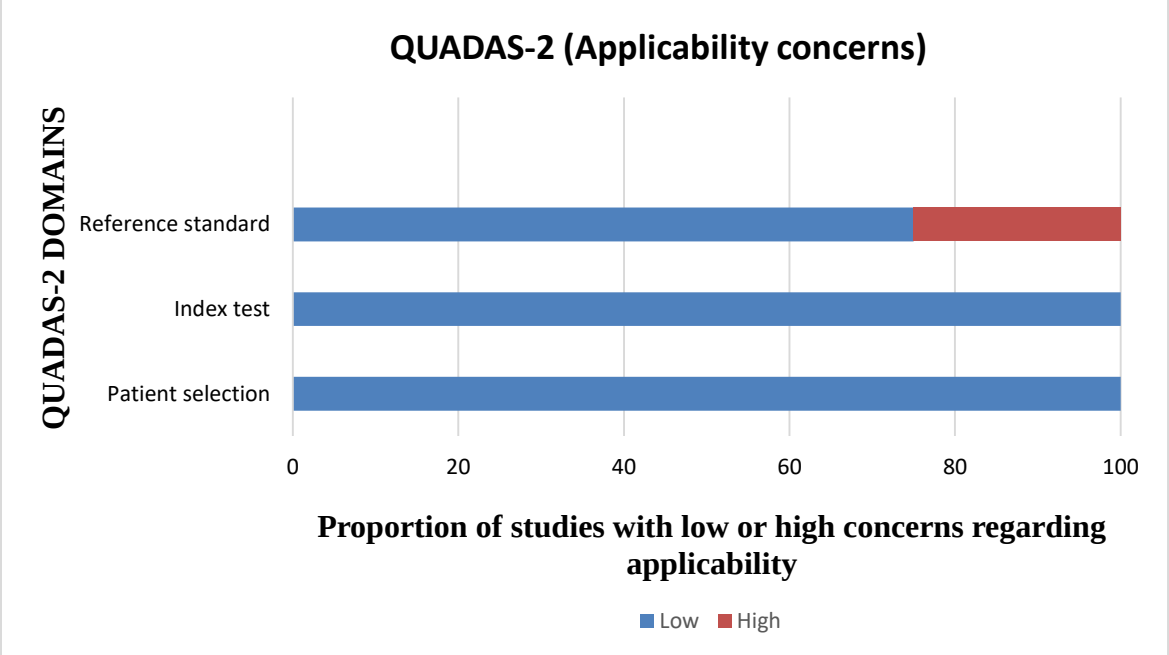

Figure 3.3

Proportion of studies with low or high concerns regarding applicability.

3.3 Characteristics of the selected studies:

All the articles included in this study have compared tests like vHIT, Caloric test and VEMP test results with either normal groups or other tests. In the area of interest, studies that used DVA testing on motion sickness individuals was unavailable. Hence it was not included. The number of participants with motion sickness varied between fifteen to two hundred in each study. The characteristics of the studies, including the number of participants, the age range of the participants, tests and questionnaires used to diagnose motion sickness and the results obtained in the groups included are mentioned in Table 3.2.

Table 3.2

Characteristics of the selected studies:

Sl. no	Title and Authors	Year	No. of participants & age range	MS groups diagnosed using	Tests/ parameter of interest	Results obtained
1.	Neupane et al	2018	60 17-25years	MSSQ-S	vHIT, cVEMP	Lower VOR gain in only RA and LP SCC: RA SCC Mean 0.83, SD 0.22 LP SCC Mean 0.79, SD 0.19 Higher asymmetry ratio : Lateral Mean 10.73, SD 8.75 LARP Mean 15.30 SD 9.31 RALP Mean 21.20, SD 13.36 Presence of refixation saccades in all 6 SCC in MS group. cVEMP asymmetry ratio :

						Higher in MS group Mean 34.56, SD 11.91 Non-MS group Mean 17.60, SD 13.21 No significant difference in cVEMP P1N1 latencies and amplitude.
2.	Fatma MEN KILINÇ, Mesut KAYA Tuğba EMEKC Deniz Uğur CENGİZ	2020	60 >18 years	Routine ENT examinations	vHIT	Lower VOR gain in individuals with MS : RL SCC 0.75 (±0.408) LL SCC 0.73 (±0.329) RA SCC 0.65 (±0.238) LA SCC 0.82 (±0.247) RP SCC 0.52 (±0.327) LP SCC 0.58 (±0.360) Higher asymmetry ratio for Anterior SCC in MS group : 33.80 (±26.385)
3.	Rakesh T. Kumar and Sujeet Kumar Sinha	2021	58 18–25 years	MSSQ (Golding, 2006)	vHIT HIMP & SHIMP	No significant differences in VOR gain and the asymmetry ratio between both groups : HIMP-R 1.08 SD 0.14 HIMP-L 1.03 SD 0.13 SHIMP-R 0.80 SD 0.16 SHIMP-L 0.77 SD 0.13 AR HIMP 8.36 SD 5.12

						AR SHIMP 12.93 SD 10.53
4.	Mallinson AI, Longridge NS.	2002	A prospective study with 200 individuals	Based on how long reading in a moving car is possible.	Caloric test	Caloric scores (i.e., semicircular canal [SCC] response) and motion sensitivity had no correlation between them : Group 1 mean caloric score 39.5 (not carsick) Group 2 mean caloric score 42.0 (a little carsick) Group 3 mean caloric score 44.0 (very carsick)
5.	Fowler et al	2020	50 mean age 23.9 years	MSSQ-S	SPV-Caloric test	Low susceptibility group depicted slowest slow phase velocity RC SPV (°/s) 11.3, SD 7.1 RW SPV (°/s) 10.6, SD 3.8 LC SPV (°/s) 13.5, SD 6.1 LW SPV (°/s) 13, SD 5.2 Caloric responses and the degree of MS susceptibility had positive correlations between them.
6.	Byukulu et al	2009	40 19–33 years	MSSQ	c-VEMP & bithermal caloric test	In c-VEMP no statistically significant difference was found between both groups for P1N1 latencies,

						amplitude and interpeak amplitude and latencies. No statistically significant differences for canal paresis between the two groups
7.	Fowler et al	2014	24 20-24 years	MSSQ-S	cVEMP	Larger cVEMP amplitudes in high susceptibility group and no significant between-ear difference High-Right : 98.13 (SD 34.29) Left: 95.25 (SD 47.75) Low- Right : 62.11 (SD 22.08) Left : 53.11 (SD 29.57) Asymmetry ratio and latencies were not significantly different across MS groups.
8.	Tal et al	2007	24 19–24 years	Wiker questionnaire	cVEMP	No differences were found between the groups in latencies, amplitudes, inter-peak latencies, and peak-to-peak asymmetry ratios Susceptible group had asymmetry ratios > 35% generally, but wasn't statistically significant
9.	Nooij et al	2011	15	Misery Scale (MISC)	cVEMP & caloric test	No significant differences were

			22 to 50 years			found in the absolute latencies and the peak to peak amplitude. Latency: p13: 15.8 ± 1.4 n23: 23.6 ± 2.0 Corrected peak to peak amplitude: 1.3±0.8
10.	Singh et al	2014	90 18–40 years	MSSQ-S	oVEMP cVEMP	Higher (worst) thresholds and larger asymmetry ratio in both tests. Latencies and amplitude have no significant differences.
11.	Tal et al	2006	30 19 to 23 years	Wiker questionnaire	cVEMP	p13-n23 inter amplitude significantly different between the groups : SS group - 252.50 ± 162.45 NSS group - 365.70 ± 176.73 Similar results were found for the n23 peak amplitude : SS group - 151.19 ± 96.17 NSS group - 235.01 ± 120.61 Thresholds were greater for the SS group: SS group - 84.43 ± 6.56 NSS group - 77.33 ± 4.9
12.	Xie et al	2012	54	MSSQ	oVEMP	No statistically significant differences

	19 – 24 years	between the two groups in oVEMP absolute and interpeak latencies, interpeak amplitude and asymmetry ratios. Trend towards greater asymmetry ratios in the MS susceptible group (not significant) than in the MS non-susceptible group : (18.55, SD 10.24% vs. 13.25, SD 9.47%).

MSSQ-S: *Motion Sickness Susceptibility Questionnaire- Short ,* ***vHIT:*** *Video Head Impulse Test,* ***cVEMP:*** *Cervical Vestibular Evoked Myogenic Potential,* ***oVEMP:*** *ocular Vestibular Evoked Myogenic Potential,* ***VOR gain:*** *Vestibulo Ocular Reflex gain,* ***SCC:*** *Semi Circular Canals,* ***LARP:*** *Left Lateral Right Posterior,* ***RALP:*** *Right Anterior Left Posterior,* ***MS:*** *Motion Sickness,* ***SS:*** *Sea sickness,* ***NSS:*** *Non sea sickness,* ***RA:*** *Right Anterior,* ***LA:*** *Left Anterior,* ***RP:*** *Right Posterior,* ***LP:*** *Left Posterior,* ***RL:*** *Right Lateral,* ***LL:*** *Left Lateral,* ***HIMP:*** *Head Impulse Paradigm,* ***SHIMP:*** *Suppression Head Impulse Paradigm,* ***AR:*** *Asymmetry Ratio,* ***RC:*** *Right Cold,* ***LC:*** *Left Cold,* ***RW:*** *Right Warm,* ***LW:*** *Left Warm,* ***SPV:*** *Slow Phase Velocity.*

3.4 Video Head Impulse test and Motion Sickness

Among the 12 records that was included in the study, three studies described findings of vHIT in participants with motion sickness. The parameters studied in vHIT included

VOR gain, asymmetry ratio and presence of refixation saccades. One study analyzed the VOR gain in both HIMP and SHIMP.

3.4.1 Vestibulo Ocular Reflex gain (VOR gain)

The most studied video head impulse test parameter is the VOR gain. Neupane et al. (2018) found the VOR gain in 60 participants aged 17-25 years. The participants were split into two groups, with 30 participants in each group. Group I had participants with motion sickness, and Group II had participants without motion sickness. The MSSQ-S questionnaire was used to diagnose the group as having motion sickness. Neupane et al. (2018) reported that the mean VOR gain of only right anterior semicircular canal and the left posterior semicircular canal was statistically lower in individuals with motion sickness than that of the non-motion sickness group. It was also found that the individuals with motion sickness had an elevated VOR gain asymmetry ratio than that of the non-motion sickness group in all the three planes.

Kilinc et al. (2020) studied the VOR gain in thirty individuals with motion sickness. The results suggested that the motion sickness group had statistically lower VOR gain for all semicircular canals than the non-motion sickness group. The author also reported a higher asymmetry ratio for only the anterior SCC in the motion sickness group in comparison to the non-motion sickness group. No statistically significant difference was established in the asymmetry ratio of other canals.

Kumar and Sinha (2021) studied the VOR gain in 29 individuals with motion sickness and in 29 without motion sickness. The diagnosis of motion sickness was done using MSSQ. The vHIT was done in both HIMP and SHIMP mode. The results suggested no difference in VOR gain between motion sickness and non-motion sickness individuals. It

was also reported that there was no significant difference in VOR gain asymmetry between motion sickness and non-motion sickness group.

3.4.2 Presence or absence of Refixation Saccades:

Among the three studies which used vHIT to assess the semicircular canal functioning in individuals with motion sickness, only Neupane et al. (2018) reported the existence of refixation saccades in individuals with motion sickness.

3.5 Caloric test and Motion Sickness.

Among the twelve records included in the study, only three studies described caloric test findings in individuals with motion sickness. Mallinson and Longridge (2002) studied the caloric responses of 200 participants. The participants were further subdivided into three groups. Group 0 had participants with no motion sickness in a moving car; Group 1 were individuals with a little motion sickness and Group 2 had extreme motion sickness. Group 1 mean caloric score was 39.5 (not carsick group), Group 2 mean caloric score was 42.0 (a little carsick group) and Group 3 mean caloric score was 44.0 (very carsick group). When the caloric responses were assessed, significant difference between 3 groups of individuals between the caloric scores (i.e., semicircular canal [SCC] response) and motion sensitivity, were not found.

Fowler et al. (2020) studied the slow phase velocity of fifty participants with motion sickness. Participants were diagnosed as having motion sickness using the MSSQ-S. Participants were split into three groups based on the percentile they scored. Participants who scored more than 75% were placed in the high susceptibility group and those who scored 25% - 75% were placed in the mild or moderate susceptibility group and those scoring below 25% were placed in the low susceptibility group (Golding, 2006). The results of the

study revealed the slowest slow phase velocity in low susceptibility group and vice versa. A positive correlation was obtained between the caloric responses and the degree of motion sickness susceptibility.

Byukulu et al. (2009) studied the canal paresis in forty individuals with and without motion sickness. Each group comprised of twenty participants each. Motion sickness was diagnosed using MSSQ. They found no statistically significant differences for canal paresis between the two groups.

3.6 Vestibular Evoked Myogenic Potential (VEMP) test and Motion Sickness.

Among the twelve records that was included in the study, eight studies described findings of VEMP in individuals with motion sickness. Among these eight records, only two studies have investigated oVEMP in motion sickness and the rest of the studies have used cVEMP as the assessment tool. The parameters studied in cVEMP included: threshold, P1N1 latency, P1N1 amplitude, interpeak amplitude and latency and asymmetry ratio. The parameters studied in oVEMP included N1P1 latency, N1P1 amplitude, interpeak amplitude and latency and asymmetry ratio.

3.6.1 VEMP latency

Neupane et al. (2018) found out the cVEMP latencies in sixty participants whose age ranged from 17-25 years. The study consisted of two groups with thirty participants in each group. Group I had participants with motion sickness and Group II had participants without motion sickness. The MSSQ-S questionnaire was used to diagnose the group as having motion sickness. The authors found no significant difference in the cVEMP P1N1 latencies between the two groups of individuals.

Byukulu et al. (2009) studied the P1N1 latencies in forty individuals aged 19-33 years. They were split into two groups of with and without motion sickness individuals, of twenty participants each. They were diagnosed using MSSQ. In cVEMP a statistically significant difference was not found between the two groups for P1N1 latencies.

Fowler et al. (2014) studied the cVEMP P1N1 latency in twenty four subjects aged 20-24 years. They were divided into MS susceptibility groups of low, mild/moderate and high by using the MSSQ-S. The analysis revealed that latencies were not significantly different across the MS groups.

Tal et al. (2007) studied the cVEMP P1N1 latencies in twenty four sea sickness susceptible individuals aged 19-24 years. They were divided into ten sea sickness susceptible individuals and fourteen non sea sickness susceptible individuals. Sea sickness was confirmed using the Wiker questionnaire. No statistical differences were found in P1N1 latencies between the groups.

Nooij et al. (2011) studied the cVEMP latency of fifteen participants who were in the age range of 22-50 years. They were categorized into two groups based on the Misery Scale (MISC). Eight individuals were SIC susceptible and seven individuals were non-SIC susceptible, in the study. When the results were analyzed no significant differences were found in the absolute latencies between both the groups.

Singh et al. (2014) studied both oVEMP and cVEMP latencies in ninety individuals aged 18-40 years. They were divided into three groups with thirty participants in each group. Group I consisted of thirty non susceptible motion sickness individuals, Group II consisted of professional drivers and Group III consisted of motion sickness individuals. They were diagnosed as having susceptibility to motion sickness using the MSSQ-S. No

differences were found in P1N1 and N1P1 latencies of cVEMP and oVEMP, respectively, between the groups.

Xie et al. (2012) studied the o VEMP N1P1 latencies in fifty four individuals aged 19-24 years. They were categorized into two groups wherein 1 group had thirty one motion sickness susceptible individuals and the second group had twenty three motion sickness non susceptible individuals. MSSQ was used to diagnose the group with MS. No statistically significant differences were found in N1P1 latencies between the two groups.

3.6.2 VEMP amplitude

Neupane et al. (2018) found out the cVEMP amplitude in sixty participants aged 17-25 years. The study comprised of two groups with thirty participants each. Participants with motion sickness were admitted into Group I and the participants without motion sickness were admitted into Group II. The MSSQ-S questionnaire was used to diagnose the group as having motion sickness. The authors found no significant difference in the cVEMP P1N1 amplitude.

Fowler et al. (2014) studied the cVEMP P1N1 amplitude in twenty four subjects aged 20-24 years. They were divided into MS susceptibility groups of low, mild/moderate and high by using the MSSQ-S. The analysis revealed that amplitude was significantly larger in the high MS susceptible group compared to the other groups and no significant ear difference was found in this study.

Byukulu et al. (2009) studied the P1N1 amplitude in forty individuals aged 19-33 years. They were separated into two groups of with and without motion sickness individuals, of twenty participants each. They were diagnosed using MSSQ. In cVEMP a statistically significant difference was not found between the two groups for P1N1 amplitudes.

Tal et al. (2007) studied the cVEMP P1N1 amplitudes in twenty four sea sickness susceptible individuals whose age ranged from 19-24 years. They were divided into ten sea sickness susceptible individuals and fourteen non sea sickness susceptible individuals. Sea sickness was confirmed using the Wiker questionnaire. No significant differences were found in the P1N1 cVEMP amplitudes between the groups.

Nooij et al. (2011) studied the cVEMP amplitude of fifteen participants aged 22-50 years. They were categorized into two groups based on the Misery Scale (MISC). Eight individuals were SIC susceptible and seven individuals were non-SIC susceptible. No significant differences were found in the corrected peak to peak amplitude between both the groups.

Singh et al. (2014) studied both oVEMP (N1P1) and cVEMP (P1N1) amplitude in ninety individuals aged 18-40 years. They were separated into three groups with thirty participants each. Group I consisted of thirty non susceptible motion sickness individuals, Group II consisted of professional drivers and Group III consisted of motion sickness individuals. They were diagnosed as having susceptibility to motion sickness using the MSSQ-S. No differences were found in the amplitudes of P1N1 and N1P1 of cVEMP and oVEMP, respectively, between both the groups.

Tal et al. (2006) studied the P1N1 amplitude of thirty participants aged 19-23 years. They were subdivided into two groups. The sea sickness susceptible group had fifteen sea sickness susceptible male individuals and the non-sea sickness susceptible group consisted of fifteen non sea sickness susceptible male individuals, among Navy ship crew members. They were diagnosed as having sea sickness using the Wiker questionnaire. It was found that the n23 peak amplitude was significantly different in both groups. The sea sickness

group had significantly reduced amplitude of n23 peaks than the non-sea sickness susceptible group.

Xie et al. (2012) studied the oVEMP N1P1 amplitude in fifty four individuals aged 19-24 years. They were subdivided into two groups wherein 1 group had thirty one MS susceptible individuals and the second group had twenty three motion sickness non susceptible individuals. MSSQ was used to diagnose the group with motion sickness. No statistically significant differences were found in N1P1 amplitude between the two groups.

3.6.3 VEMP interpeak amplitude and latency

Byukulu et al. (2009) studied the cVEMP interpeak amplitude and latency in forty individuals aged 19-33 years. They were subdivided into two groups of with and without motion sickness individuals, of twenty participants each. They were diagnosed using MSSQ. In cVEMP a statistically significant difference was not found between both groups for interpeak amplitude and latency.

Tal et al. (2007) studied the cVEMP interpeak latencies in twenty four sea sickness susceptible individuals aged 19-24 years. They were further subdivided into ten sea sickness susceptible individuals and fourteen non sea sickness susceptible individuals. Sea sickness was confirmed using the Wiker questionnaire. No significant differences were found in the interpeak latencies of cVEMP between the groups.

Tal et al. (2006) studied the cVEMP interpeak amplitude of thirty participants aged 19-23 years. They were subdivided into two groups; the sea sickness susceptible group had fifteen sea sickness susceptible male individuals and the non-sea sickness susceptible group consisted of fifteen non sea sickness susceptible male individuals, among Navy ship crew members. They were diagnosed as having sea sickness using the Wiker questionnaire. It

was found that the p13-n23 interpeak amplitude was significantly different between the groups. The study revealed that the sea sickness susceptible group had a significantly lower interpeak amplitude than the non-sea sickness susceptible group.

Xie et al. (2012) studied the oVEMP interpeak amplitude and latency in fifty individuals aged 19-24 years. They were further subdivided into two groups wherein one group had thirty one motion sickness susceptible individuals and the second group had twenty three non-susceptible motion sickness individuals. MSSQ was used to diagnose the group with motion sickness. No statistically significant differences were found in interpeak amplitudes and latencies between the two groups.

3.6.4 VEMP threshold

Singh et al. (2014) studied both oVEMP and cVEMP thresholds in ninety individuals aged 18-40 years. They were parted into three groups with thirty participants each. Group I comprised of thirty non susceptible motion sickness individuals, Group II consisted of professional drivers and Group III consisted of motion sickness individuals. They were diagnosed as having susceptibility to motion sickness using the MSSQ-S. Both oVEMP and cVEMP thresholds were recorded. It was found in the analysis that the motion sickness group had the significantly higher (worse) thresholds compared to the other two groups, in both oVEMP and cVEMP.

Tal et al. (2006) studied the cVEMP thresholds of thirty participants aged 19-23 years. They were categorized into 2 groups. The sea sickness susceptible group had fifteen sea sickness susceptible male individuals and the non-sea sickness susceptible group consisted of fifteen non sea sickness susceptible male individuals, among Navy ship crew members. They were diagnosed as having sea sickness using the Wiker questionnaire. It

was found that the cVEMP thresholds were significantly different between the groups. The sea sickness group had a significantly higher threshold than the non-susceptible sea sickness group.

3.6.5 VEMP asymmetry ratio

Neupane et al. (2018) found out the cVEMP asymmetry ratio in sixty participants aged 17-25 years. They were further subdivided into two groups with thirty participants in each group. Participants with motion sickness were comprised in Group I and Group II comprised of participants without motion sickness. The MSSQ-S questionnaire was used to diagnose the group as having motion sickness. When the asymmetry ratio was analyzed it was found that it was higher in the motion sickness group than that of the non-susceptible motion sickness group.

Fowler et al. (2014) studied the cVEMP asymmetry ratio in twenty four subjects aged 20-24 years. They were divided into motion sickness susceptibility groups of low, mild/moderate and high by using the MSSQ-S. The study revealed that asymmetry ratio were not significantly different across motion sickness groups.

Tal et al. (2007) studied the cVEMP asymmetry ratio in twenty four sea sickness susceptible individuals aged 19-24 years. They were divided into ten sea sickness susceptible individuals and fourteen non sea sickness susceptible individuals. Sea sickness was confirmed using the Wiker questionnaire. It was found that the susceptible group had asymmetry ratios greater than 35% generally, but wasn't statistically significant.

Singh et al. (2014) studied both oVEMP and cVEMP AR in ninety individuals aged 18-40 years. They were again subdivided into three groups with thirty participants in each group. Group I consisted of thirty non susceptible motion sickness individuals, Group II

consisted of professional drivers and Group III consisted of motion sickness individuals. They were diagnosed as having susceptibility to motion sickness using the MSSQ-S. Both oVEMP and cVEMP results revealed larger asymmetry ratio in participants comprised in the motion sickness susceptible group compared to the non-susceptible group.

Tal et al. (2006) studied the cVEMP inter-aural amplitude difference ratio of thirty participants aged 19-23 years. They were further subdivided into 2 groups. The sea sickness susceptible group had fifteen sea sickness susceptible male individuals and the non-sea sickness susceptible group consisted of fifteen non sea sickness susceptible male individuals, among Navy ship crew members. They were diagnosed as having sea sickness using the Wiker questionnaire. It was found that inter-aural amplitude difference ratio had no statistically significant difference between the two groups.

Xie et al. (2012) studied the oVEMP interpeak amplitude asymmetry ratio in fifty individuals aged 19-24 years. They were further subdivided into two groups wherein one group had thirty one motion sickness susceptible individuals and the second group had twenty three non-susceptible motion sickness individuals. MSSQ was used to diagnose the group with motion sickness. No statistically significant differences were found in interpeak amplitude asymmetry ratio between the two groups.

Table 3.3

Summary of findings

Sl. no.	Author and Year	Summary of findings
1.	Neupane et al. 2018	• Unaffected VOR gain in the MS group. • Presence of refixation saccades in all 6 SCC in MS group. • Higher cVEMP asymmetry ratio in the MS group • No significant difference in cVEMP P1N1 latencies and amplitude.

2.	Kilinc et al. 2020	• Reduced VOR gain in the MS group. • Higher asymmetry ratio for Anterior SCC in MS group
3.	Kumar and Sinha, 2021	• No significant differences in VOR gain and the asymmetry ratio between both groups
4.	Mallinson and Longridge, 2002	• No correlation exist between caloric scores (i.e. slow phase velocity) and motion sensitivity. • Slightly higher scores in more susceptible group.
5.	Fowler et al. 2020	• Slowest slow phase velocity in caloric test observed in the low susceptibility group. • Caloric responses and the degree of MS susceptibility had positive correlations.
6.	Byukulu et al. 2009	• No statistically significant difference was found between the two groups for cVEMP P1N1 latencies, amplitude and interpeak amplitude and latencies. • No statistically significant differences for canal paresis was found between the two groups in caloric test.
7.	Fowler et al. 2014	• Larger cVEMP amplitudes were reported in the high susceptibility group and no significant between ear differences was shown. • cVEMP asymmetry ratio and latencies were not significantly different across MS groups.
8.	Tal et al. 2007	• No significant differences were found between the groups in the cVEMP latencies, amplitudes, interpeak latencies, and peak-to-peak asymmetry ratios. • Susceptible group had cVEMP asymmetry ratios greater than 35% generally, but wasn't statistically significant.
9.	Nooij et al. 2011	• No significant differences were found in the absolute latencies and peak to peak amplitude of cVEMP.

10.	Singh et al. 2014	• Higher thresholds and a larger asymmetry ratio was found in both cVEMP and oVEMP in the MS group. • Latencies and amplitude were found to have no significant differences between the groups.
11.	Tal et al. 2006	• p13-n23 interpeak amplitude was significantly lower in SS group. • The n23 peak amplitude was also significantly lower in SS group. • cVEMP thresholds were greater in the SS group.
12.	Xie et al. 2012	• No statistically significant differences were found between the two groups in oVEMP absolute and interpeak latencies, interpeak amplitude and asymmetry ratios. • A greater asymmetry ratio was found in the MS susceptible group but it was not statistically significant.

CHAPTER IV

DISCUSSION

Motion sickness (MS) is a syndrome characterized with nausea and vomiting, pallor, cold sweating, headache, dizziness, increased salivation, apathy, hyperventilation, and stomach awareness. Motion sickness can occur during exposure to physical motion, visual motion, and virtual motion, and only those without a functioning vestibular system are fully immune (Lackner et al., 2014). Motion sickness disorder (MSD) is diagnosed when the sickness inducing stimulus is physical motion (Cha et al., 2021). Findings from a considerable amount of studies reveal that motion sickness manifest as a peripheral dysfunction and several tests have been carried out to support and critically analyze this hypothesis. The aim of this systematic review was to systematically review the articles related to peripheral vestibular dysfunction in individuals with motion sickness. For this purpose, twelve studies were evaluated which comprised of tests namely, video head impulse test (vHIT), vestibular evoked myogenic potential (VEMP) and caloric test. The parameters studied in the area of interest were saccades and VOR findings of vHIT; latency, amplitude and asymmetry ratio of VEMP findings and the caloric test findings included slow phase velocity of the nystagmus, directional preponderance and unilateral weakness, in individuals with motion sickness.

4.1 Video Head Impulse test and Motion Sickness

The findings of two out of the three studies indicate normal VOR gain in subjects with motion sickness. However, a higher VOR gain asymmetry ratio was established in the participants with motion sickness. Among the three studies which used vHIT to assess the

semicircular canal functioning in individuals with motion sickness, only one study reported the presence of refixation saccades in individuals with motion sickness.

Kilinc et al. (2020) have given an account of decreased VOR gain values in individuals with motion sickness. Reduced VOR gain is an indication of peripheral vestibular pathologies. Similar findings have been reported by Weber et al. (2008) and Mac Dougall et al. (2013), in other peripheral vestibular pathologies, thus indicating that people with motion sickness may have some amount of peripheral vestibular pathology. However, Neupane et al. (2018) and Kumar and Sinha (2021) reported normal VOR gain in all the individuals with motion sickness. However, Neupane et al. (2018) reported a higher asymmetry ratio of VOR gain in the motion sickness group indicating existence of vestibular dysfunction in individuals with motion sickness. Kumar and Sinha (2021) reported no difference between two groups for VOR gain asymmetry ratio and concluded that the VOR gain asymmetry ratio may not be a good indicator of deficit in peripheral vestibular system.

Again there are equivocal findings in terms of presence or absence of refixation saccades in individuals with motion sickness. Neupane et al. (2018) reported existence of refixation saccades in all the individuals with motion sickness whereas, Kumar and Sinha (2021) and Kilinc et al. (2020) reported absence of refixation saccades in motion sickness. A variation between the stimulated side and the non-stimulated side, triggers the refixation saccades. Hence the VOR generates compensatory eye movements so as to maintain gaze stability during head rotation (Bronstein & Gresty, 1991). Weber et al. (2008) reported that the presence of both covert and overt refixation saccades were symbolic of impaired semicircular canals, when the stabilization of gaze during head rotation could not be retained. The presence of overt saccades has also been reported in Meniere's disease, which is a

peripheral pathology (Blodow et al., 2013). Hence it can be inferred that refixation saccades tend to be seen in peripheral pathologies.

Oman (1982) explained it using the heuristic mathematical model for sensory conflict dynamics and motion sickness. According to the authors, before acting on the vomiting centre the sensory conflict was low pass filtered. Thus, it was inferred that low frequencies were the ones that triggered motion sickness. This finding is supported by other studies that have measured the VOR in individuals with motion sickness (Clément & Reschke, 2018). The authors also mention that, vHIT might not be an accurate test to assess the VOR gain function in individuals with motion sickness, as it assesses the high-frequency component of the VOR.

4.2 Caloric test and Motion Sickness

Two of the studies have reported a dissociation between caloric test and peripheral vestibular dysfunction in motion sickness

Mallinson and Longridge (2002) postulated the existence of a mechanism that might be suppressing excessive symptomatology under ideal circumstances, which is why no statistical difference was found between the groups. Byukulu et al. (2009) reports that the results obtained were in accordance with the findings of their study. The reason for such a dissociation could also have been due to large inter-subject variability, low statistical strength of caloric test, confounding factors namely the anatomy of the ear canal and middle ear, temperature diffusion into the surrounding tissues technique, and attentiveness of the patient, as reported by the authors (Baertschi et al., 1975). The caloric tests in the VNG test battery were usually restricted to the lateral semicircular canal and the superior vestibular nerve, but not the other semicircular canals. This limited assessment might not be able

to provide a clear picture of the whole scenario (Fowler et al., 2020). However, one study showed a result otherwise, where the slowest slow phase velocity in caloric test was observed in the low susceptibility group and the caloric responses and the degree of MS susceptibility had positive correlations between them. This could possibly be explained by resistance to motion sickness susceptibility.

4.3 Vestibular Evoked Myogenic Potential (VEMP) test and Motion Sickness

Among the eight studies which described the findings of VEMP in participants with motion sickness, majority of the studies show that the VEMP latencies, amplitude and the interpeak amplitude and latency did not show a significant difference. Two studies had reported the findings on VEMP threshold in individuals with motion sickness. Both the studies reported that individuals with motion sickness had elevated (worse) thresholds compared to the control groups. Among the eight studies, majority of the studies reported, an elevated asymmetry ratio in groups with motion sickness compared to that of the control groups.

Usually affected cVEMP latencies indicated a neural pathology rather than a labyrinthine pathology (Ochi et al., 2003; Lee et al., 2008). Neupane et al. (2018) reported that cVEMP latencies were not affected as the neural portion of the sacculocollic pathway was not involved in persons with motion sickness. This fact was in line with the results of many researches (Tal et al., 2006; Fowler et al., 2014). This reasoning has been supported by Singh et al. (2014), where the authors state the existence of a lack of neural involvement in the vestibulospinal and vestibulo-ocular reflex pathways, due to which the latencies ap-

peared to be unaffected in individuals with motion sickness. Hence the authors have suggested that latency parameters of cVEMP and oVEMP would be insensitive in differentiating the motion sickness susceptible individuals from the control groups.

Singh et al. (2014) reported that the finding of unaffected amplitude was in accordance with those obtained by Neupane et al. (2018), Tal et al. (2007) and Buyuklu et al. (2009) for cVEMP and Xie et al. (2012) for oVEMP. The authors reported that the reduced otolith amplitude might be due to the impaired signals from the otolith organs due to a peripheral involvement. Even though a smaller amplitude was obtained in few groups with motion sickness, it was not significant because of a sizeable standard deviation for the amplitude parameters. However, isolated equivocal results have also been obtained (Tal et al., 2006; Fowler et al., 2014) which could be due to a small-scale sample size taken and the high variability of cVEMP amplitudes found in even healthy populations. Hence, the different authors propose that absolute amplitudes of cVEMP and oVEMP would be insensitive in identifying motion sickness susceptible individuals.

Byukulu et al. (2009) reported that the interpeak amplitude and latency were unaffected due to uncontrolled confounding factors like heterogeneity of the type of motion sickness (e.g. car, sea, air, etc.) and the physical activity habits of their subjects included in the study. In sea sickness, Tal et al. (2007) reported that the habituation process to sea conditions might have caused the interpeak amplitude and latency to be unaffected. Takabayashi et al. (2003) investigated the functional asymmetry of the vestibular otolith organ of goldfish and carp. They did not find significant differences in utricular otolith weight

between both sides of these animals and suggested that the otolith asymmetry was negligible. The inferences from these studies could be the possible reasons why an abnormality was not manifested in VEMP interpeak amplitude and latency.

Singh et al. (2014) reported that the significantly elevated (worst) thresholds of VEMP were in agreement with those reported previously by Tal et al. (2006). The authors stated that elevated VEMP thresholds were procured, as the functioning of the otolith organs were found to be less efficient, in those with higher susceptibility for motion sickness compared to other groups. Tal et al. (2006) reported that elevated thresholds might be due to reduced otolith responses in sea sickness groups. The reduced otolith responses would produce impaired signals from the otolith organs, which would increase the discrepancy between the information from the various sensory neural systems, thereby resulting in elevated VEMP thresholds. These findings in comparison with VEMP absolute amplitude indicated that the threshold of cVEMP and oVEMP was a better parameter for evaluating the otolith function in individuals with motion sickness.

Different authors have reported elevated cVEMP amplitude asymmetry ratio as an indication of sacculocollic pathway dysfunction in numerous vestibular pathologies (Baier et al., 2009; Taylor et al., 2011; Taylor et al., 2012). Thus, it can be inferred from this finding that even individuals with motion sickness might have a sacculocollic pathway dysfunction as a larger cVEMP asymmetry ratio was observed in them (Neupane et al., 2018). This finding coincided with the previous studies, even with both cVEMP and oVEMP (Singh et al., 2014). The authors explained that this asymmetry could be due to the variation in otoconial masses of two saccules, thus giving rise to the higher VEMP asymmetry ratio. However, a few equivocal studies also exist (Tal et al., 2007; Fowler et

al., 2014). Helling et al. (2003) reported a similar finding using an animal study where fish with difference in otoconial mass between two labyrinths showed atypical swimming behavior. This animal study supports the above mentioned findings, but was not included in this systematic review, as it did not meet the objectives.

Singh et al. (2014) described that almost all human beings had a minimal amount of otolithic asymmetry, but the difference would typically be less than twenty percentage and therefore, it was not large enough to produce discrepant information reaching the cortical areas. Moreover, one side was likely to send much higher levels of neural impulses to the central balance structures than the other side, if the otolith response was large enough. This would create a confusion in the central structures, as the impulses from one side suggested a large degree of acceleration. In contrast, the other side suggested a lesser degree of acceleration, even when the whole body was undergoing the equal acceleration. This finding could be supported with the asymmetry hypothesis of otolith function (Diamond & Markham, 1992b). Also a number of animal studies lend support to this hypothesis (Scherer et al., 2001; Helling et al., 2003). Considering these findings, it can be inferred that the VEMP asymmetry ratio can be regarded as one of the best suited parameters in detecting the motion sickness population in the vestibular test battery.

CHAPTER V

SUMMARY & CONCLUSIONS

The objective of the study was to systematically review and summarize the test findings of articles related to peripheral vestibular dysfunction and motion sickness. The following parameters: VOR gain, VOR gain asymmetry and presence or absence of saccades findings of vHIT in individuals with motion sickness; latency, amplitude and asymmetry ratio of VEMP findings in individuals with motion sickness and the caloric test findings which included slow phase velocity of the nystagmus, directional preponderance and unilateral weakness in individuals with motion sickness, were evaluated. Initially, a review search was performed in different electronic databases. Searches across different databases resulted in 550 topic-related records. A total of twelve articles that met the inclusion and exclusion criteria to meet the objectives of the study were included for the study. The quality and potential risk associated with each article were evaluated using the QUADAS-2 risk of bias assessment tool.

The results regarding VOR gain depicted that the parameter was not necessarily abnormal in all the patients with motion sickness. The individuals who exhibited reduced VOR gain further indicated a prevalence of anterior and posterior semi-circular canals getting affected more in one study, whereas another study showed all the semi-circular canals being affected unequivocally. VOR gain asymmetry ratio was found to be higher in individuals with motion sickness, in majority of the studies. The presence of refixation saccades in individuals with motion sickness was only reported in one article, among the twelve articles studied, and the authors have suggested that the presence of refixation saccade could be a good indicator in assessing individuals with motion sickness.

It can also be inferred from the findings of these studies that the VOR gain asymmetry ratio and the refixation saccades were a better indicator of peripheral dysfunction in individuals with motion sickness than the VOR gain. Most of the findings of the articles which used caloric test to assess individuals with motion sickness reported a dissociation between caloric vestibular test and peripheral vestibular dysfunction in motion sickness, thereby indicating that caloric test might not be a sensitive test to find out the peripheral dysfunction in motion sickness.

The VEMP test findings revealed that majority of the studies did not find a statistically significant difference in VEMP latency, amplitude and interpeak amplitude and latency. Two studies had reported higher VEMP thresholds in individuals with motion sickness. Similarly the VEMP asymmetry ratio was also evaluated, where it was found that it tends to be higher in the motion sickness group compared to the control groups, but not statistically significant in many studies. The trend was observed towards a higher VEMP asymmetry ratio, but more studies with larger number of participants would be needed to validate this finding. Among the VEMP parameters studied, the VEMP threshold and the asymmetry ratio better indicated the peripheral vestibular dysfunction in individuals with motion sickness.

Therefore it can be inferred from this systematic review that a peripheral vestibular dysfunction prevails in individuals with motion sickness, and it can be found out using an appropriate test battery and test protocol.

5.1 Implications of the study

1. The systematic review will add on to the information regarding the incidence of peripheral vestibular dysfunction in individuals with motion sickness.

2. The systematic review will also help in designing vestibular rehabilitation programme in individuals with motion sickness.

5.2 Research Gap

A detailed systematic review was done for twelve articles, regarding the peripheral vestibular dysfunction in individuals with motion sickness. The critical analysis of these studies throw light on the limitations of these studies as well as give future directions for researchers interested in this area. The studies included in this systematic review included sample sizes ranging from fifteen to two hundred participants. A large scale study with more number of participants was only observed in one study in this systematic review. An optimal sample should be larger and span a wider age range and include more severely affected individuals, to allow stronger inferences about the population.

There are only a limited amount of studies in motion sickness in human subjects. More studies are needed on association and causation of the peripheral pathological processes involved in motion sickness. It is also of utmost importance to bring to the readers' attention that, a considerable amount of methodological differences exist in these studies. Most of the studies does not involve a complete and definitive analysis of the peripheral and the central vestibular system, in the methodology adopted. Kilinc et al. (2020) suggested that tests like vHIT, VEMP, VNG, and posturography devices should be utilized and evaluated together to analyze both peripheral and the central vestibular system, which would help in obtaining more objective results, in individuals with motion sickness.

A research gap also exist where some studies do not employ all parameters of the test while analyzing the results, which again leads to an incomplete picture of the processes involved in individuals with motion sickness (Singh et al., 2014). Thus, a complete picture of processes involved in motion sickness could not be delineated by the authors. Another

gap that exist in the literature is the lack of a definitive and appropriate test protocol for tapping pathological processes involved in individuals with motion sickness. Therefore, an appropriate test protocol is to be formed with more future research in this particular area, as suggested by Fowler et al. (2014). Another research gap that can be brought into the notice of the readers is, the need of sensitivity and specificity measures of various tests involved in the diagnosis of motion sickness.

REFERENCES

Baertschi, A. J., Johnson, R. N., & Hanna, G. R. (1975). A theoretical and experimental determination of vestibular dynamics in caloric stimulation. *Biological Cybernetics*, *20*(3-4), 175–186. https://doi.org/10.1007/BF00342638

Baier, B., & Dieterich, M. (2009). Vestibular-evoked myogenic potentials in "vestibular migraine" and Menière's disease: a sign of an electrophysiological link. *Annals of the New York Academy of Sciences*, *1164*, 324–327. https://doi.org/10.1111/j.1749-6632.2009.03868

Bertolini, G., & Straumann, D. (2016). Moving in a Moving World: A Review on Vestibular Motion Sickness. *Frontiers in Neurology*, *7*, 14. https://doi.org/10.3389/fneur.2016.0001

Blödow, A., Pannasch, S., & Walther, L. E. (2013). Detection of isolated covert saccades with the video head impulse test in peripheral vestibular disorders. *Auris, Nasus, Larynx*, *40*(4), 348–351. https://doi.org/10.1016/j.anl.2012.11.002

Bronstein, A. M., & Gresty, M. A. (1991). Compensatory eye movements in the presence of conflicting canal and otolith signals. *Experimental Brain Research*, *85*(3), 697–700. https://doi.org/10.1007/BF00231756

Buyuklu, F., Tarhan, E., & Ozluoglu, L. (2009). Vestibular functions in motion sickness susceptible individuals. *European Archives of Oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery*, *266*(9), 1365–1371. https://doi.org/10.1007/s00405-009-0927-6

Cha, Y. H., Golding, J. F., Keshavarz, B., Furman, J., Kim, J. S., Lopez-Escamez, J. A., Magnusson, M., Yates, B. J., Lawson, B. D., & Advisors: (2021). Motion sickness diagnostic criteria: Consensus Document of the Classification Committee of the Bárány Society. *Journal of Vestibular Research : Equilibrium & Orientation*, *31*(5), 327–344. https://doi.org/10.3233/VES-200005

Clément, G., & Reschke, M. F. (2018). Relationship between motion sickness susceptibility and vestibulo-ocular reflex gain and phase. *Journal of Vestibular Research: Equilibrium & Orientation*, *28*(3-4), 295–304. https://doi.org/10.3233/VES-180632

Diamond, S. G., & Markham, C. H. (1992). Ocular torsion as a test of the asymmetry hypothesis of space motion sickness. *Acta Astronautica*, *27*, 11–17. https://doi.org/10.1016/0094-5765(92)90168-i

Evans, R. W., Marcus, D., & Furman, J. M. (2007). Motion sickness and migraine. *Headache*, *47*(4), 607–610. https://doi.org/10.1111/j.1526-4610.2007.00762.x

Fowler, C. G., Dallapiazza, M., & Hadsell, K. T. (2020). Vestibular Function and Motion Sickness Susceptibility: Videonystagmographic Evidence From Oculomotor and Caloric Tests. *American Journal of Audiology*, *29*(2), 188–198. https://doi.org/10.1044/2020_AJA-19-00050

Fowler, C. G., Sweet, A., & Steffel, E. (2014). Effects of motion sickness severity on the vestibular-evoked myogenic potentials. *Journal of the American Academy of Audiology*, *25*(9), 814–822. https://doi.org/10.3766/jaaa.25.9.4

Golding J. F. (2006). Motion sickness susceptibility. *Autonomic Neuroscience : Basic & Clinical*, *129*(1-2), 67–76. https://doi.org/10.1016/j.autneu.2006.07.019

Heer, M., & Paloski, W. H. (2006). Space motion sickness: incidence, etiology, and countermeasures. *Autonomic Neuroscience : Basic & Clinical*, *129*(1-2), 77–79. https://doi.org/10.1016/j.autneu.2006.07.014

Helling, K., Hausmann, S., Clarke, A., & Scherer, H. (2003). Experimentally induced motion sickness in fish: possible role of the otolith organs. *Acta Oto-laryngologica*, *123*(4), 488–492. https://doi.org/10.1080/0036554021000028121

Khan, K. S., Kunz, R., Kleijnen, J., & Antes, G. (2003). Five steps to conducting a systematic review. *Journal of the Royal Society of Medicine*, *96*(3), 118–121. https://doi.org/10.1258/jrsm.96.3.118

KILINÇ, F. M., KAYA, M., EMEKCİ, T., & CENGİZ, D. U. (2020). Evaluation of semicircular canal functions by the Video Head Impulse Test (vHIT) in individuals with motion sickness. *Evaluation*, *79*. https://doi.org/10.7176/JHMN/79-05

Koch, A., Cascorbi, I., Westhofen, M., Dafotakis, M., Klapa, S., & Kuhtz-Buschbeck, J. P. (2018). The Neurophysiology and Treatment of Motion Sickness. *Deutsches Arzteblatt International*, *115*(41), 687–696. https://doi.org/10.3238/arztebl.2018.0687

Kumar, R. T., & Sinha, S. K. (2021). Head Impulse Test Paradigm and Suppression Head Impulse Test Paradigm in Individuals With and Without Motion Sickness. *American Journal of Audiology*, *30*(3), 518–523. https://doi.org/10.1044/2021_AJA-21-00009

Lackner J. R. (2014). Motion sickness: more than nausea and vomiting. *Experimental Brain Research*, *232*(8), 2493–2510. https://doi.org/10.1007/s00221-014-4008-8

Lee, K. J., Kim, M. S., Son, E. J., Lim, H. J., Bang, J. H., & Kang, J. G. (2008). The Usefulness of Rectified VEMP. *Clinical and Experimental Otorhinolaryngology*, *1*(3), 143–147. https://doi.org/10.3342/ceo.2008.1.3.143

Macdougall, H. G., McGarvie, L. A., Halmagyi, G. M., Curthoys, I. S., & Weber, K. P. (2013). The video Head Impulse Test (vHIT) detects vertical semicircular canal dysfunction. *PloS One*, *8*(4), e61488. https://doi.org/10.1371/journal.pone.0061488

Mallinson, A. I., & Longridge, N. S. (2002). Motion sickness and vestibular hypersensitivity. *The Journal of Otolaryngology*, *31*(6), 381–385. https://doi.org/10.2310/7070.2002.34575

Money K. E. (1970). Motion sickness. *Physiological Reviews*, *50*(1), 1–39. https://doi.org/10.1152/physrev.1970.50.1.1

Moola, S., Munn, Z., Sears, K., Sfetcu, R., Currie, M., Lisy, K., Tufanaru, C., Qureshi, R., Mattis, P., & Mu, P. (2015). Conducting systematic reviews of association (etiology): The Joanna Briggs Institute's approach. *International Journal of Evidence-Based Healthcare*, *13*(3), 163–169. https://doi.org/10.1097/XEB.0000000000000064

Murdin, L., Golding, J., & Bronstein, A. (2011). Managing motion sickness. *British Medical Journal (Clinical research ed.)*, *343*, d7430. https://doi.org/10.1136/bmj.d7430

Neupane, A. K., Gururaj, K., & Sinha, S. K. (2018). Higher asymmetry ratio and refixation saccades in individuals with motion sickness. *Journal of the American Academy of Audiology*, *29*(02), 175-186. https://doi.org/10.3766/jaaa.16175

Nooij, S. A., Vanspauwen, R., Bos, J. E., & Wuyts, F. L. (2011). A re-investigation of the role of utricular asymmetries in Space Motion Sickness. *Journal of Vestibular Research : Equilibrium & Orientation*, *21*(3), 141–151. https://doi.org/10.3233/VES-2011-0400

Ochi, K., Ohashi, T., & Watanabe, S. (2003). Vestibular-evoked myogenic potential in patients with unilateral vestibular neuritis: abnormal VEMP and its recovery. *The Journal of Laryngology and Otology*, *117*(2), 104–108. https://doi.org/10.1258/002221503762624521

Oman C. M. (1982). A heuristic mathematical model for the dynamics of sensory conflict and motion sickness. *Acta Oto-laryngologica Supplementum*, *392*, 1–44. https://doi.org/10.1007/BF00232780

Page, M. J., Moher, D., & McKenzie, J. E. (2022). Introduction to preferred reporting items for systematic reviews and meta-analyses 2020 and implications for research synthesis methodologists. *Research Synthesis Methods*, *13*(2), 156–163. https://doi.org/10.1002/jrsm.1535

Pearson, A., & Aromataris, E. (2014). The systematic review: an overview. *The American Journal of Nursing*, *114*(3), 53–58. https://doi.org/10.1097/01.NAJ.0000444496.24228.2c

Reason J. (1975). Motion sickness: Some theoretical and practical considerations. *Applied Ergonomics*, *9*(3), 163–167. https://doi.org/10.1016/0003-6870(78)90008-x

Reason J. T. (1978). Motion sickness adaptation: a neural mismatch model. *Journal of the Royal Society of Medicine*, *71*(11), 819–829. https://doi.org/10 .1177/014107687807101109

Scherer, H., Helling, K., Clarke, A. H., & Hausmann, S. (2001). Motion sickness and otolith asymmetry. *Uchu Seibutsu Kagaku*, *15*(4), 401–404. https://doi.org/10.1177/0333102411439644

Schmäl F. (2013). Neuronal mechanisms and the treatment of motion sickness. *Pharmacology*, *91*(3-4), 229-241 https://doi.org/10.1159/000350185

Singh, N. K., Pandey, P., & Mahesh, S. (2014). Assessment of otolith function using cervical and ocular vestibular evoked myogenic potentials in individuals with motion sickness. *Ergonomics*, *57*(12), 1907–1918. https://doi.org/ 10.10 80/00 14013 9.2014 .952683

Takabayashi, A., & Ohmura-Iwasaki, T. (2003). Functional asymmetry estimated by measurements of otolith in fish. *Uchu Seibutsu Kagaku*, *17*(4), 293–297. https://doi.org/10.2187/bss.17.293

Tal, D., Gilbey, P., Bar, R., & Shupak, A. (2007). Seasickness pathogenesis and the otolithic organs: vestibular evoked myogenic potentials study--preliminary results. *The Israel Medical Association Journal : , 9*(9), 641–644. https://doi.org/10.4324/9780203834091

Tal, D., Hershkovitz, D., Kaminski, G., & Bar, R. (2006). Vestibular evoked myogenic potential threshold and seasickness susceptibility. *Journal of Vestibular Research : Equilibrium & Orientation*, *16*(6), 273–278. https://doi.org/10.3233/ves-2006-16604

Taylor, R. L., Wijewardene, A. A., Gibson, W. P., Black, D. A., Halmagyi, G. M., & Welgampola, M. S. (2011). The vestibular evoked-potential profile of Ménière's disease. *Clinical Neurophysiology: official journal of the International Federation of Clinical Neurophysiology*, *122*(6), 1256–1263. https://doi.org/10.1016/j.clinph.2010.11.009

Taylor, R. L., Zagami, A. S., Gibson, W. P., Black, D. A., Watson, S. R., Halmagyi, M. G., & Welgampola, M. S. (2012). Vestibular evoked myogenic potentials to sound and vibration: characteristics in vestibular migraine that enable separation from Meniere's disease. *Cephalalgia: an International Journal of Headache*, *32*(3), 213–225. https://doi.org/10.1177/0333102411434166

Weber, K. P., Aw, S. T., Todd, M. J., McGarvie, L. A., Curthoys, I. S., & Halmagyi, G. M. (2008). Head impulse test in unilateral vestibular loss: vestibulo-ocular reflex and catch-up saccades. *Neurology*, *70*(6), 454–463. https://doi.org/10.1212/01.wnl.0000299117.48935.2e

Whiting, P. F., Rutjes, A. W., Westwood, M. E., Mallett, S., Deeks, J. J., Reitsma, J. B., Leeflang, M. M., Sterne, J. A., Bossuyt, P. M., & QUADAS-2 Group (2011). QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Annals of Internal Medicine*, *155*(8), 529–536. https://doi.org/10.7326/0003-4819-155-8-201110180-00009

Xie, S. J., Chen, W., Jia, H. B., Wang, Z. J., Yao, Q., & Jiang, Y. Y. (2012). Ocular vestibular evoked myogenic potentials and motion sickness susceptibility. *Aviation, Space, and Environmental Medicine*, *83*(1), 14–18. https://doi.org/10.3357/asem.3101.2012

Yates, B. J., Miller, A. D., & Lucot, J. B. (1998). Physiological basis and pharmacology of motion sickness: an update. *Brain Research Bulletin*, *47*(5), 395–406. https://doi.org/10.1016/s0361-9230(98)00092-6