UNIVERSITY OF
FORWARD
THINKING
WESTMINSTER

**WestminsterResearch**
http://www.westminster.ac.uk/westminsterresearch

# Sex-disease dimorphism underpins enhanced motion sickness susceptibility in primary adrenal insufficiency: a cross-sectional observational study.

**Golding, J.F.**

This is an author's accepted manuscript of an article published in Experimental Brain Research, DOI:10.1007/s00221-023-06592-y, 2023.

The final publication is available at Springer via:

https://doi.org/10.1007/s00221-023-06592-y

The WestminsterResearch online digital archive at the University of Westminster aims to make the research output of the University available to a wider audience. Copyright and Moral Rights remain with the authors and/or copyright owners.

# Sex-disease dimorphism underpins enhanced motion sickness susceptibility in primary adrenal insufficiency; a cross-sectional observational study

Yougan Saman[1*], Mishaal Sharif[1*], Abigail Lee[1], Shiza Ahmed[2], Ascensión Pagán[1], Maggie McGuirk[1], Oliver Rea[1], Rakesh Patel[3], Freya Bunting[1], Caitlin Spence[1], Ha-Jun Yoon[1], Elizabeta Mukaetova-Ladinska[1], Peter Rea[4], Amir Kheradmand[5], John Golding[6,7] & Qadeer Arshad[1,7]

(*Both authors contributed equally)

1. inAmind Laboratory, Department of Neuroscience, Psychology and Behaviour, University of Leicester, Leicester, LE1 7RH
2. Maidstone and Tunbridge Wells Hospitals NHS Trust, Tunbridge Wells Hospital, Tonbridge Road, TN2 4QJ
3. Faculty of Health and Life Sciences, De Montfort University, The Gateway, Leicester, LE1 9BH
4. E.N.T Department, Leicester Royal Infirmary, Leicester, LE1 5WW
5. Department of Neurology, The Johns Hopkins University School of Medicine, Baltimore, MD, USA
6. Department of Psychology, University of Westminster, 115 New Cavendish Street, London, W1W 6UW
7. Neuro-Otology Unit, Division of Brain Sciences, Charing Cross Hospital Campus, Imperial College London, Fulham Palace Road, London, W6 8RF

^Correspondence should be addressed to:
Dr Qadeer Arshad
inAmind Laboratory, Department of Neuroscience, Psychology and Behaviour,
George Davies Centre, Lancaster Road, Leicester,
UK,
LE1 7RH
Email: qa15@leicester.ac.uk
Phone: +447891161537
Keywords: Addison's Disease: Motion Sickness: Sex Dimorphism: HPA axis: ACTH

**ABSTRACT:**

Environmental motion can induce physiological stress and trigger motion sickness. In these situations, lower than normal levels of adrenocorticotropic hormone (ACTH) have been linked with increased susceptibility to motion sickness in healthy individuals. However, whether patients with primary adrenal insufficiency, who typically have altered ACTH levels compared to the normal population, exhibit alterations in sickness susceptibility remains unknown. To address this, we recruited 78 patients with primary adrenal insufficiency and compared changes in the motion sickness susceptibility scores from 10 years prior to diagnosis (i.e. retrospective sickness rating) with the current sickness measures (post-diagnosis), using the validated motion sickness susceptibility questionnaire (MSSQ). Group analysis revealed that motion sickness susceptibility pre-diagnosis did not differ between controls and patients. We observed that following treatment, current measures of motion sickness were significantly increased in patients and subsequent analysis revealed that this increase was primarily in female patients with primary adrenal insufficiency. These observations corroborate the role of stress hormones in modulating sickness susceptibility and support the notion of a sexually dimorphic adrenal cortex as we only observed selective enhancement in females. A potential mechanism to account for our novel observation remains obscure, but we speculate that it may reflect a complex sex-disease-drug interaction.

## INTRODUCTION:

Exposure to a provocative motion stimulus that is either externally imposed (e.g. travelling on rough seas) or internally implied (e.g. virtual reality) can induce physiological stress and trigger symptoms of motion sickness in any individual with a functioning vestibular system. The syndrome of motion sickness is typically characterised by the following symptoms: nausea, vomiting, dizziness, sweating, pallor, hypersalivation, malaise, and headache (Bronstein et al. 2020) (Lackner 2014). Susceptibility to motion sickness is known to be associated with various factors including age (i.e. decreases across the lifespan) (Dobie et al. 2001), biological sex (female preponderance) (Dobie et al. 2001), neurological disorders (i.e. migraine) (Murdin et al. 2015), phase of the menstrual cycle (Golding et al. 2005), psychological factors (i.e. neurotic personality) (Bick 1983), nicotine consumption (Golding et al. 2011) and sleep deprivation (Bronstein et al. 2020).

Additionally, previous research has shown that the endocrine system and notably the hypothalamic–pituitary–adrenal (HPA) axis can also exert significant modulatory influences upon susceptibility to motion sickness – see for a review on this topic (Otto et al. 2006). Specifically, the initial work on endocrine changes associated with motion sickness reported a significant rise in serum cortisol levels following applications of nausea-inducing rotational stimuli (Eversmann et al. 1978). Subsequent work using stressful motion, induced by cross-coupled angular acceleration (i.e. Coriolis), illustrated a significant increase in adrenocorticotrophic hormone (ACTH) levels in placebo-treated subjects (Kohl 1985), a finding corroborated by other studies (Grigoriev et al. 1988) (Klosterhalfen et al. 2000) (Otto et al. 2006). Furthermore, such biological modulations of ACTH and cortisol levels also seem to be implicated in playing an additional role in adaptation and habituation to motion sickness. For example, ACTH levels have been reported to be increased following exposure to microgravity, which may reflect an adaptive process to suppress space motion sickness (Kohl 1985). Regarding habituation, previous findings have illustrated that repeated exposure to motion stimuli (i.e. habituation) is accompanied by an reduction in the biological responsiveness, specifically affecting ACTH levels, antidiuretic hormone secretion and cortisol levels. However, this later observation of cortisol habituation was restricted to female participants (Rohleder et al. 2006).

Based upon the above reviewed literature, it appears that ACTH and cortisol levels play a role in governing susceptibility to motion sickness, However, whether baseline (i.e. pre-motion sickness) levels of cortisol and ACTH play a role in predicting susceptibility to motion sickness remains less clear. (Kohl 1985) measured *basal* hormone levels before and after exposure to a nauseogenic motion stimuli. The results revealed that those subjects less susceptible to developing nausea following exposure to the motion stimuli displayed higher basal levels of ACTH prior to experiencing the motion. Regarding cortisol, Meissner and colleagues showed that higher baseline cortisol levels were associated with enhanced tolerability to provocative motion stimuli, but this observation was only seen in female but not male participants. However, other data obtained from parabolic flight reveals that when comparing highly susceptible versus less susceptible individuals, both baseline plasma ACTH and cortisol levels were not significantly different between both groups prior to the flight (Drummer et al. 1990). Thus, these data suggest that in contrast to the findings of (Kohl 1985) and (Meissner et al. 2009), neither basal ACTH nor cortisol levels predict susceptibility to motion sickness.

Despite the lack of consensus on the predictive fidelity of basal ACTH and cortisol levels on sickness susceptivity, there is a generalised agreement that they play a role in the evolution of motion sickness (Meissner et al. 2009) (Kohl 1985). However, precisely by which mechanism cortisol and ACTH can modulate susceptibility to sickness remains unclear. It has been suggested that it may broadly reflect responses that are peripheral neurophysiological manifestations that occur downstream from higher central nervous system events that in-turn trigger motion-sickness, or alternatively represent a generalised stress response to noxious motion stimuli (Kohl 1985). A stress response can trigger a negative feedback response mediated by the HPA axis, which starts with activation of the paraventricular nucleus (PVN) in the hypothalamus and results in the synthesis of arginine vasopressin (AVP) and corticotrophin releasing factor (CRF). These compounds then enter the hypophyseal portal system vasculature and stimulate the release of ACTH from the anterior pituitary, which then stimulates the synthesis and release of glucocorticoids from the adrenal cortex (Saman et al. 2020). Levels of these hormones are known to be altered in individuals with known dysfunction of the HPA axis and adrenal gland, as found in primary adrenal insufficiency (i.e. Addison's disease) (Alexandraki et al. 2022).

Primary adrenal insufficiency (PAI), first described by Thomas Addison, is a rare, severe life-threatening disease with a reported prevalence of about 100 to 140 cases per million and an

incidence of 4:1 000 000 per year in Western societies. It is characterised by an inability of the adrenal cortex to produce sufficient amounts of glucocorticoids and/or mineralocorticoids. Specifically, in individuals with primary adrenal insufficiency, the cortisol deficiency results in a decrease in feedback to the hypothalamic-pituitary axis which results in elevation of adrenocorticotrophic hormone (ACTH) levels to enhance stimulation of the adrenal cortex (Nematollahi and Arafah 2022)(Alexandraki et al. 2022) . Thus, primary adrenal insufficiency provides a useful disease model to further investigate the link between stress hormones, specifically ACTH and modulation of susceptibility to motion sickness. Furthermore, it can also serve to allow us to identify any potential sex-related dimorphism, as both motion sickness and adrenocortical disease are more common in females (Lackner 2014)(Bronstein et al. 2020)(Lyraki and Schedl 2021).

Here, we address these questions by recruiting patients with primary adrenal insufficiency and compared changes in motion sickness susceptibility scores for both males and females from 10 years prior to diagnosis (i.e., retrospective sickness rating) with current sickness measures (post-diagnosis), using the validated motion sickness susceptibility questionnaire (MSSQ).

## MATERIALS AND METHODS:

*Participants:* 284 patients (242F/ 42M) with acquired primary adrenal insufficiency were recruited from the Pituitary Foundation and Addison's Disease Self Help group (ADSHP), United Kingdom. Criteria for patient inclusion involved a diagnosis that was based on both the classical clinical symptoms and biochemical conformation of adrenal insufficiency in the presence of increased ACTH concentrations (> 300ng/L (66pmol/L)) and low basal early morning cortisol concentrations < 3µg/dL (80nmol/L)) (Alexandraki et al. 2022). Furthermore, other non-specific exclusion criteria were pregnancy, current nicotine consumption, and any previous or current history of alcohol or substance abuse. All participants provided written informed consent for experimentation with human subjects. Ethical approval was provided by the School of Psychology and Vision Sciences ethics committee at the University of Leicester.

Based on a medical screening questionnaire, we excluded 206 patients with the following co-morbidities due to potential interactions influencing the HPA axis either directly via the pathology or indirectly via the associated medication. These included any past or current history of i) endocrine disorders (n = 86, e.g., thyroid disease or diabetes) apart from the

primary adrenal insufficiency diagnosis in the Addisonian group, ii) cardiac disorders (n = 14) e.g. conduction defects and coronary heart disease), iii) respiratory conditions (n = 19) e.g. chronic obstructive pulmonary disease or asthma), iv) neurological disorders (n = 14 including epilepsy, brain tumours, and migraine), v) gynaecological pathologies (n = 7, e.g., pelvic inflammatory disease or ovarian cysts), vi) psychiatric disorders (n = 28) and vii) vestibular dysfunction (n = 5). Females who suffered from the early onset of the menopause were also excluded (n = 5). A brief clinical history was also taken to ensure the participant had no current or previous symptoms of dizziness due to possible vestibular dysfunction. The final part of the screening procedure involved administrating a screening questionnaire to ensure that all participants had an active travel history. Based on this, a further 28 participants were removed as they had never travelled on a plane and boat. We also recruited 200 control participants via convenience sampling. From this cohort, we excluded 122 subjects with a history of cardiac disorders, respiratory conditions, neurological dysfunction, gynaecological problems, and psychiatric disease. Further, we excluded 4 female participants due to early-onset menopause, 10 participants due to a history of vestibular dysfunction and 6 due a lack of active travel history. (N.B. Flow of participants schematically shown in Figure 1).

78 patients (20M/ 58F) with primary adrenal insufficiency and 78 healthy controls survived the above screening criteria. The mean age of the 78 patients was 42 (SD=12) whereas the mean age of the healthy participants was 43 (SD=11) – see Table for 1 for details alongside the motion sickness scores. 74.5% of patients had been diagnosed with primary adrenal insufficiency due to sporadic autoimmune disease and 6.5% due to non-autoimmune disorders (e.g. gene mutation, infection). In 19% of patients the aetiology was unknown. All the 20 male patients were taking glucocorticoids (hydrocortisone) (Mean dosage = 22.2 mg, SD = 9.8) with a mean duration of 12 years (SD = 11 years). All the 58 female patients were also taking glucocorticoids (hydrocortisone) (Mean daily dosage = 20.53 mg, SD = 6.4) with a mean duration of 12 years (SD = 10 years). 35 % of the males patients were using mineralocorticoids (fludrocortisone) (Mean dosage = 4.9 mg; SD = 5.1). 45% of females patients were using mineralocorticoids (fludrocortisone) (Mean dosage = 4.43 mg; SD = 5.4). These are summarised in Table 1. We matched these patients with respect to age, sex and retrospective MSB scores to 78 healthy controls (20M/58F) who were also recruited based on the same exclusion criteria as above (except for the absence of the primary adrenal insufficiency diagnosis) (all *p*s > 0.5).

*Motion sickness assessment:* All participants completed an adapted version of the motion sickness susceptibility questionnaire-short form (MSSQ). Critically, the validated MSSQ questionnaire has been shown to be an effective and reliable tool in the retrospective recall of childhood susceptibility which is typically over 30 years ago for anyone over the age of 48. Furthermore, the MSSQ has been extensively validated against physiological studies and patient populations including for the specific purpose of retrospective data acquisition (Golding and Patel 2017).

The MSSQ (part B sub-section) provides a score for motion sickness susceptibility in adulthood (MSB scores) (Golding 1998). The MSSQ assesses 9 modes of transport and ranks individuals' subjective level of sickness between 0-3, with 0 being never felt sick, to 3 being frequently felt sick. The total score was the cumulative level of sickness which is a maximum of 27.

MSSQ scores were acquired for the following two time points, i) presently (i.e. after diagnosis in Addisonian patients), which we term current MSB scores, and also ii) to recall sickness susceptibility either ten years before diagnosis in Addisonian patients (average duration of diagnosis 11.8 years; SD =10.03), or 10 years ago in healthy participants. This retrospective assessment in healthy controls was implemented as a control for any potential recall bias (see Figure 1A). We termed these measures retrospective MSB scores. Retrospective and current MSB sores were calculated for each participant. Finally, all of the questionnaire assessments were performed virtually using online individual sessions.

*Data analysis:* Power calculation based on previous work investigating the role of ACTH in motion sickness indicated that we needed a sample size of 14 participants (Kohl 1985). A 2 (Group: Addisonian patient vs. healthy) x 2 (Time: before vs after diagnosis) repeated measured ANOVA was conducted on the total score for the motion sickness susceptibility scale in the whole sample.

Considering the gender bias in our sample and previous research that has shown large biological sex driven differences for both motion sickness susceptibility and adrenocortical disease, we performed a second analysis. For this analyses, we selected an equal sample (size determined maximum number of male subjects) of both sexes (n = 20) and matched (within one SD) the cohort based on all of the following parameters: age (Males: M= 42.3; SD = 15.2);

Females: M =39.6; SD =13.0), retrospective MSB scores (Males: 2.00; SD= 2.70; Females: M=3.40; SD= 3.50) (Table3), disease duration (Males: M= 11.55 years; SD =12.41); Females: M= 13.50 years; SD = 10.50), daily fludrocortisone dosage (Males: M= 3.7 mg, SD =7.9; Females = 5.8mg, SD =5.9) and daily dosage of hydrocortisone (Males: M=18.5 mg, SD =7.02); Females =22.19 mg, SD= 9.83) (all *p*s > .1). For this sample, we ran a 2 (Group: Addisonian patient vs. healthy) x 2 (Gender: male vs. female) x 2 (Time: before vs after diagnosis) repeated measured ANOVA on the total score for the motion sickness susceptibility scale in an equal number of females and males to examine whether we could observe a gender bias. In this study, Group and gender were between-subject variables, Time was a within-subject variable; and the MSSQ total score was the dependent variable.

In both analyses, Age and Duration of the treatment were included as covariates; and data were log-transformed to ensure they were normally distributed.

**RESULTS:**

Analyses for the whole sample showed the main effect of time was significant ($F(1,152)= 15.88$, $p < .001$, $\eta p^2 = .095$), such that all participants increased their motion sickness susceptibility after the diagnosis. The main effect of group was also significant ($F(1,152)= 10.32$, $p = .002$, $\eta p^2 = .064$), such that Addison patients had higher motion sickness susceptibility than healthy participants. The interaction between time and age was significant ($F(1,152)= 13.04$, $p < .001$, $\eta p^2 = .079$). The interaction between time and group was also significant ($F(1,152)= 5.23$, $p = 0.024$, $\eta p^2 = 0.033$). Bonferroni corrections post hoc comparisons revealed that the difference in motion sickness susceptibility before and after diagnosis was significant only for Addisonian patients (see Table 2 for descriptive statistics). No other effects yielded significance (*F*s < 2.3).

Analyses for the matched sample showed a significant main effect of time ($F(1,74) =14.07$, $p < 0.001$, $\eta p^2 = 0.160$), such that all participants increased their motion sickness susceptibility after the diagnosis; a significant main effect of gender ($F(1,74) = 15.07$, $p < 0.001$, $\eta p^2 = 0.169$), females scored higher than males in motion sickness susceptibility; and a significant main effect of group type ($F(1,74) = 5.26$, $p = 0.025$, $\eta p^2 = 0.066$), such that Addison patients had higher motion sickness susceptibility than healthy participants (see Table 3 for descriptive statistics).

In addition, we found a significant interaction between time and age ($F(1,74) = 6.71$, $p = 0.012$, $\eta p^2 = 0.083$), a significant interaction between time and gender ($F(1,74) = 5.35$, $p = 0.024$, $\eta p^2 = 0.067$); a significant interaction between time and group ($F(1,74) = 14.64$, $p < 0.001$, $\eta p^2 = 0.165$); and a significant interaction between gender and group ($F(1,74) = 4.65$, $p = 0.034$, $\eta p^2 = 0.059$). Finally, the three way interaction between time, gender and group was also significant ($F(1,74) = 9.51$, $p = 0.003$, $\eta p^2 = 0.114$). Bonferroni corrections post hoc comparisons revealed that only Addisonian female patients increased their motion sickness susceptibility after the diagnosis (see Figures 2A, 2B & 2C).

## DISCUSSION

Our findings reveal that following treatment for primary adrenal insufficiency (i.e. current MSB scores), female but not male participants exhibited an increase in susceptibility to motion sickness. Critically, there was no difference in susceptibility for retrospective MSB scores between either, (i) male and female Addisonian patients (pre-diagnosis) or, (ii) healthy controls and Addisonian patients (pre-diagnosis). Taken together, our findings of a specific modulation of increased motion sickness susceptibility in female participants with primary adrenal insufficiency suggest a complex interaction between sex, disease, and treatment to be mediating the observed change in susceptibility.

In our cohort, all Addisonian participants were taking hydrocortisone, which is known to limit HPA activation and supress ACTH secretion (via negative feedback mechanism). Thus, theoretically this would support the observation of increased motion sickness susceptibility, based on previous work (Kohl 1985). Specifically, these findings demonstrated that in healthy individuals, increased levels of ACTH are associated with reduced susceptibility to motion sickness induced by motion stimuli (Kohl 1985). However, such a proposed mechanism cannot fully account for our current observation as we did not observe any change in sickness susceptibility in male Addisonian patients, despite them also taking hydrocortisone.

Such an observation is in line with previous research that has shown considerable sex differences with regards to both, (i) motion sickness susceptibility and, (ii) the HPA axis stress response as well as an interaction between sex*sickness susceptibility*HPA axis responsivity. Regarding motion sickness, numerous studies have found that females report

motion sickness more frequently and experience more severe symptoms than male (Dobie et al. 2001) (Golding 2006) (Kennedy and Lilienthal 1995) (Lawther and Griffin 1988), however other studies have found no significant effects of gender (Jokerst et al. 1999). Specifically using the Motion Sickness Susceptibility Questionnaire, Paillard and colleagues observed that healthy females had a higher susceptibility than males, however, this effect declined with age, potentially mediated by the menopause (Paillard et al. 2013), supporting the view that enhanced motion sickness susceptibility in females is at least partly hormone related (Golding et al. 2005).Notably, increased susceptibility to motion sickness in females is an effect that has also been observed in animals. For example, when exposing the adult *Suncis murinus* to optokinetic emesis-inducing stimuli, females were found to be more affected by the nauseogenic stimuli than males (Javid and Naylor 1999). Other work has shown that exposing male and female rats to a Ferris-Wheel rotation to induce sickness, assessed via locomotor activity, defecation, conditioned gaping, and a balance beam test resulted in no differences across different ages of rats for gaping, but there were significant effects of sex on defecation (females defecated more) as well as a three-way sex*age*rotation interaction (Zhou et al. 2017) . Furthermore, female rats were also found to exhibit less mobility in an open field maze task following rotation, however there were no significant sex differences in the balance beam test. Critically, they also observed a significant interaction between age and sex on plasma corticosterone and adrenocorticotrophic hormone (ACTH) levels following rotation (Zhou et al. 2017) . Such sex-related differences in biological responsiveness associated with motion sickness have also been reported in human participants. For example, previous work has shown that habituation of cortisol responsiveness occurs selectively in female but not male participants (Rohleder et al. 2006), and that baseline cortisol levels correlate positively with motion tolerance in women (Meissner et al. 2009). Turning to sex differences associated with the HPA axis stress response, previous findings have reported that, (i) ACTH levels to be twice as high in males compared to females in an anticipatory response to an upcoming stressful task (Kirschbaum et al. 1992), and (ii) that glucocorticoid levels are higher in females than in males after HPA axis stimulation (Rao and Androulakis 2017).

Taken together, it could be the case that in female individuals with primary adrenal insufficiency, the relatively higher glucocorticoid levels are supressing ACTH secretion to a greater extent than in males. This coupled with the sex-related pronounced reduction of ACTH levels in females may further serve to potentiate their susceptibility to developing motion

sickness. Although such an account is internally consistent with our observations and previous data, it must be tempered with the fact that we did not directly measure ACTH levels and correlate these with sickness susceptibility in the Addison's cohort (Alexandraki et al. 2022)(Lyraki and Schedl 2021). Future biochemical studies will have to directly investigate this plausible link.

To conclude, our findings provide a novel observation that there is a sex-related disease dimorphism for susceptibility to motion sickness in individuals with primary adrenal insufficiency. This observation corroborates reports of modulatory influences of the HPA axis upon susceptibility to motion sickness as well as the notion of a sexually dimorphic adrenal cortex (Kohl 1985)(Lyraki and Schedl 2021). Further research is needed to establish the mechanism to account for our novel observation, but we speculate that it may reflect a complex sex-disease-drug interaction.

**Acknowledgements:**
We would like to thank the Pituitary Foundation and Addison's Disease Self Help group (ADSHP), United Kingdom to access their database and all the participants for their time and assistance.

**Data availability statement:**

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

**Conflict of interest statement:**
None of the authors report any conflict of interest.

References

Alexandraki KI, Sanpawithayakul K, Grossman A (2022) Endotext [Internet]. MDText.com, Inc., South Dartmouth (MA)

Bick PA (1983) Physiological and psychological correlates of motion sickness. Br J Med Psychol 56:189-196

Bronstein AM, Golding JF, Gresty MA (2020) Visual vertigo, motion sickness, and disorientation in vehicles. 40:116-129

Dobie T, McBride D, Dobie Jr T, May J (2001) The effects of age and sex on susceptibility to motion sickness. Aviat Space Environ Med 72:13-20

Drummer C, Stromeyer H, Riepl RL, König A, Strollo F, Lang RE, Maass H, Röcker L, Gerzer R (1990) Hormonal changes after parabolic flight: implications on the development of motion sickness. Aviat Space Environ Med 61:821-828

Eversmann T, Gottsmann M, Uhlich E, Ulbrecht G, Werder Kv, Scriba PC (1978) Increased secretion of growth hormone, prolactin, antidiuretic hormone, and cortisol induced by the stress of motion sickness. Aviation, space & environmental medicine:53-57

Golding JF (2006) Motion sickness susceptibility. Autonomic Neuroscience 129:67-76

Golding JF (1998) Motion sickness susceptibility questionnaire revised and its relationship to other forms of sickness. Brain Res Bull 47:507-516

Golding JF, Kadzere P, Gresty MA (2005) Motion sickness susceptibility fluctuates through the menstrual cycle. Aviat Space Environ Med 76:970-973

Golding JF, Patel M (2017) Meniere's, migraine, and motion sickness. Acta Otolaryngol 137:495-502

Golding JF, Prosyanikova O, Flynn M, Gresty MA (2011) The effect of smoking nicotine tobacco versus smoking deprivation on motion sickness. Autonomic Neuroscience 160:53-58

Grigoriev AI, Nichiporuk IA, Yasnetsov VV, Shashkov VS (1988) Hormonal status and fluid electrolyte metabolism in motion sickness. Aviat Space Environ Med 59:301-305

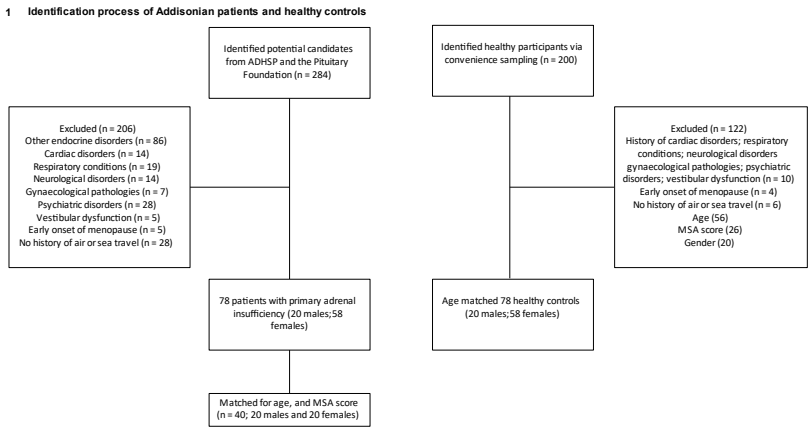
Javid FA, Naylor RJ (1999) Variables of movement amplitude and frequency in the development of motion sickness in Suncus murinus. Pharmacology Biochemistry and Behavior 64:115-122

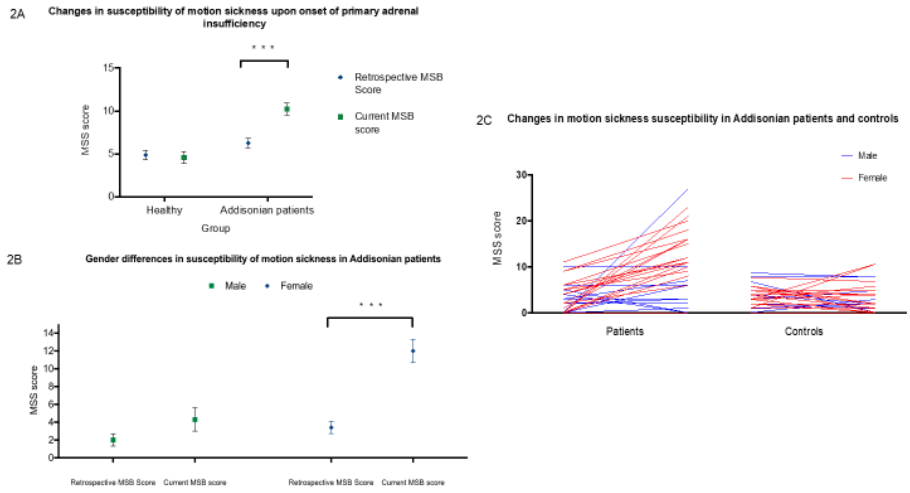
Jokerst M, Gatto M, Fazio R, Gianaros PJ, Stern RM, Koch KL (1999) Effects of gender of subjects and experimenter on susceptibility to motion sickness. Aviat Space Environ Med

Kennedy RS, Lilienthal MG (1995) Implications of balance disturbances following exposure to virtual reality systems. :35-39

Kirschbaum C, Wüst S, Hellhammer D (1992) Consistent sex differences in cortisol responses to psychological stress. Psychosom Med 54:648-657

Klosterhalfen S, Ruettgers A, Krumrey E, Otto B, Stockhorst U, Riepl RL, Probst T, Enck P (2000) Pavlovian conditioning of taste aversion using a motion sickness paradigm. Psychosom Med 62:671-677
Kohl RL (1985) Endocrine correlates of susceptibility to motion sickness. Aviat Space Environ Med 56:1158-1165
Lackner JR (2014) Motion sickness: more than nausea and vomiting. Exp Brain Res 232:2493-2510. DOI 10.1007/s00221-014-4008-8
Lawther A, Griffin MJ (1988) Motion sickness and motion characteristics of vessels at sea. Ergonomics 31:1373-1394
Lyraki R, Schedl A (2021) The Sexually Dimorphic Adrenal Cortex: Implications for Adrenal Disease. International journal of molecular sciences 22:4889. DOI 10.3390/ijms22094889
Meissner K, Enck P, Muth ER, Kellermann S, Klosterhalfen S (2009) Cortisol levels predict motion sickness tolerance in women but not in men. Physiol Behav 97:102-106
Murdin L, Chamberlain F, Cheema S, Arshad Q, Gresty MA, Golding JF, Bronstein A (2015) Motion sickness in migraine and vestibular disorders. Journal of Neurology, Neurosurgery & Psychiatry 86:585-587
Nematollahi L, Arafah B (2022) Primary adrenal insufficiency.
Otto B, Riepl RL, Klosterhalfen S, Enck P (2006) Endocrine correlates of acute nausea and vomiting. Autonomic Neuroscience 129:17-21. DOI 10.1016/j.autneu.2006.07.010
Paillard AC, Quarck G, Paolino F, Denise P, Paolino M, Golding JF, Ghulyan-Bedikian V (2013) Motion sickness susceptibility in healthy subjects and vestibular patients: effects of gender, age and trait-anxiety. Journal of Vestibular Research 23:203-209
Rao RT, Androulakis IP (2017) Modeling the Sex Differences and Interindividual Variability in the Activity of the Hypothalamic-Pituitary-Adrenal Axis. Endocrinology (Philadelphia) 158:4017-4037. DOI 10.1210/en.2017-00544
Rohleder N, Wolf JM, Maldonado EF, Kirschbaum C (2006) The psychosocial stress-induced increase in salivary alpha-amylase is independent of saliva flow rate. Psychophysiology 43:645-652
Saman Y, Arshad Q, Dutia M, Rea P (2020) Stress and the vestibular system. International review of neurobiology 152:221-236. DOI 10.1016/bs.irn.2020.03.013
Zhou W, Wang J, Pan L, Qi R, Liu P, Liu J, Cai Y (2017) Sex and age differences in motion sickness in rats: the correlation with blood hormone responses and neuronal activation in the vestibular and autonomic nuclei. Frontiers in Aging Neuroscience 9:29




## Figure legend:

**Figure 1A: Changes in susceptibility of motion sickness upon onset of primary adrenal insufficiency**. On the x-axis we represent the two sex, age and retrospective MSB matched group; healthy controls and Addisonian patients. Repeated measures ANOVA revealed a significant difference in motion sickness scores (i.e. retrospective MSB and current MSB scores) in the Addisonian group ($p<0.001$). Significance levels represented are * = $p<0.05$, ** = $p<0.01$, ***=$p<0.001$, ****= $p<0.0001$. Error bars represent standard error of the mean (SEM). **Figure 1B: Gender differences in MSS in Addisonian patients** On the x-axis we represent the two sex, age and retrospective MSB matched group; male and female Addisonian patients. Repeated measures ANOVA revealed a significant difference in motion sickness scores (i.e. retrospective MSB and current MSB scores) in the female Addisonian group ($p<0.001$). Significance levels represented are * = $p<0.05$, ** = $p<0.01$, ***=$p<0.001$, ****= $p<0.0001$. Error bars represent standard error of the mean (SEM). **Figure 1C: Individualised changes** Here we plot the individual change in susceptibility for the matched group of patients with primary adrenal insufficiency. The red line represents the female participants, and the blue line represents the males. **Figure 1D: Individualised changes** Here we plot the individual change in susceptibility for the healthy group. The red line represents the female participants, and the blue line represents the males.

Table 1. Clinical characteristics of patients with primary adrenal insufficiency.

| | Males (n =20) | | Females (58) | |
|---|---|---|---|---|
| | Mean (SD) | Range | Mean (SD) | Range |
| Age at diagnosis in years | 29 (12) | 18-64 | 30 (11) | 18-53 |
| Duration of treatment | 12 (11) | 1-38 | 12 (10) | 1-38 |
| Dose in mg (fludrocortisone) | 4.9 (5.1) | 0.2-20 | 4.43 (5.4) | 0.1-10 |
| Daily dose in mg (hydrocortisone) | 22.2 (9.8) | 0.2-75 | 20.53 (6.4) | 6-40 |

Table 2. Means (Standard Deviations) for each participant group on age, and the MSSQ total score before and after diagnosis.

| | | MSB | |
|---|---|---|---|
| Groups | Age | Before | After |
| Addison patients (n =78) | 42 (12) | 6.27 (5.70) | 10.2 (7.46) |
| Healthy participants (n =78) | 43 (11) | 4.87 (4.40) | 4.58 (4.62) |

Table 3. Means (SD: Standard Deviations for each participant group on age, gender and the MSSQ total score before and after diagnosis.

| | | | MSB | |
|---|---|---|---|---|
| Groups | Gender | Age | Before | After |
| Addison patients | Male (n =20) | 42.3(15.2) | 2.00 (2.7) | 4.3 (6.4) |
| | Female (n = 20) | 39.6 (13.0) | 3.40 (3.5) | 12.9 (5.4) |
| Healthy participants | Male (n =20) | 44 (14) | 2.66 (2.9) | 2.31 (2.5) |
| | Female (n = 20) | 40 (12) | 3.51 (2.0) | 3.46 (3.3) |