Exploring headache attributed to airplane travel

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AALBORG UNIVERSITY
DENMARK

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PHD DISSERTATION

by

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DENMARK

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CV

Sebastian Bao Dinh Bui was born in Horsens on Sunday 4 August 1991 to Vietnamese parents who came to Denmark as boat refugees from Vietnam. In 2014, he completed his bachelor's degree in Medicine with Industrial Specialization at Aalborg University, where he subsequently obtained his master's degree in Medicine with Industrial Specialization in 2017. During his time as a master's student, he conducted research on headache attributed to airplane travel (airplane headache, AH), which is his main interest. Within the field of AH, he has currently published five peer-reviewed papers, one non-peer-reviewed article and presented at two international conferences. In addition, he has participated in the Danmarks Radio's (Danish Broadcasting Corporation) science program "Videnskabens Verden" and he has reviewed one scientific paper on AH.

ENGLISH SUMMARY

Background: The International Headache Society (IHS) recognized headache attributed to airplane travel (AH) as a diagnosis in 2013. In 2004, the first AH case was described, and since then the number of studies has increased. Most of the studies have been case reports, which have not provided a large enough amount of data to be able to conclude diagnosis, mechanism, and treatment. A comprehensive review of the literature is lacking on AH. Although many AH patients experience severe headache pain, treatment strategies have not yet been developed as no experimental or RCTs have yet been conducted. For a comprehensive understanding of how AH occurs and its mechanisms, the purpose of this dissertation is to describe the prevalence of AH among flight passengers in a studied population and to develop an experimental model that could provide the basis for setting up a clinical study for the purpose of developing treatment strategies for AH.

Results: Study 1 showed that from 2004 to 2017, 275 cases of AH had been reported, in which the cumulative symptoms matched the diagnostic criteria for AH as defined by IHS. AH is generally thought to be caused by sinus barotrauma, which is caused by an insufficient level of pressure equalization in the sinuses. However, this theory was only discussed at a theoretical level. In general, patients with AH had experimented most with NSAIDs and triptans. Triptans were initially noted as having the most soothing effects. Study 2 revealed that 8.3% of the studied Danish population suffers from AH and that there may be a correlation between AH and migraines. The results of Study 3 indicate that using a pressure chamber as an experimental model is useful in provoking AH and examining selected biomarkers. Cortisol levels in the control group were significantly lower than those in the AH group during the simulated flight in the pressure chamber. After the simulated flight, prostaglandin E_2 (PGE_2) levels were significantly elevated in the AH group in comparison to the control group. In Study 4, an RCT study was presented on a possible treatment for AH using triptans in real flights, which will be a first in the literature on AH.

Conclusion: The dissertation presents preliminary data on the prevalence of AH among healthy flight passengers in a studied Danish population, which indicated that 8.3% of the population are affected by AH. A form of sinus barotrauma could be implicated in the mechanism of AH by the elevation in PGE_2 levels in AH patients when compared with healthy flight passengers. This finding has never been studied before. In addition, pressure chambers can serve as a future valid experimental model for studying AH patients for specific biomarkers and parameters that can map the mechanism of AH, and also contribute to the development of a therapeutic approach.

DANSK RESUME

Baggrund: Headache attributed to airplane travel (AH) blev formelt anerkendt af Den Internationale Hovedpineorganisation (IHS) i 2013. Den første AH-patient blev beskrevet i 2004, og siden da antallet af studier været stigende. Dog har de fleste af studierne været case-rapporter, hvilket ikke har givet et stort nok datagrundlag til at kunne drage endelige konklusion vedrørende diagnosen, mekanisme og behandlingen. Der mangler et overordnet overblik over disse data grundlag for AH. Mange af AH-patienterne har angivet hovedpinesmerten til at være meget intens, og på trods af dette er der endnu ikke udviklet behandlingsstrategier, da der endnu ikke er blevet udført eksperimentelle eller klinisk randomiserede studier. Derfor har denne afhandling haft det formål at beskrive forekomsten af AH blandt flyrejsende og kortlægge mekanismerne i AH ved hjælp af en eksperimentel model, som kunne danne grundstenene for at kunne opsætte et klinisk studie med henblik på at udvikle behandlingsstrategier for AH.

Resultater: Studie 1 viste, at i perioden 2004-2017 har der været beskrevet 275 tilfælde af AH, hvor de akkumulerede symptomer stemte overens med de diagnostiske kriterier for AH, defineret af IHS. Den overordnede og gennemgående teori på mekanismen i AH er sinus barotraume, som følge af manglende trykudligning i bihulerne. Dette var dog kun diskuteret på et teoretisk niveau. De fleste af AH-patienter havde primært forsøgt sig med NSAIDs og triptaner, hvor triptaner blev rapporteret til at have den mest lindrende effekt. Studie 2 viste, at 8,3 % i en undersøgt dansk population af flypassagerer lider af AH og at der muligvis er en korrelation mellem AH og migræne. Studie 3 viste, at brugen af et trykkammer som en eksperimentel model er brugbar til at fremprovokere AH og undersøge udvalgte biomarkører. Under den simulerede flyvetur i trykkammeret var kortisol signifikant forhøjet i AH-gruppen sammenlignet med kontrolgruppen. Prostaglandin E_2 (PGE_2)-niveauet var signifikant forhøjet i AH-gruppen sammenlignet med kontrolgruppen efter den simulerede flyvetur. Studie 4 har præsenteret et RCT-studie på en mulig behandling af AH med triptaner i rigtige flyveture, som vil være det første i AH-litteraturen nogensinde.

Konklusion: Afhandlingen viser en forekomst af AH i en undersøgt dansk population af flypassagerer på 8,3 %. Teorien om en form for sinus barotraume som mekanismen for AH kan understøttes af det forhøjede PGE_2-niveau hos AH-patienter sammenlignet med raske flyrejsende. Dette er ikke tidligere blevet undersøgt før. Desuden kan brugen af trykkamre være en valid eksperimentel model til at undersøge AH-patienter for specifikke biomarkører og parametre, der kan kortlægge mekanismen i AH yderligere, og på sigt målrette en behandlingsstrategi for AH.

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The most significant person been my supervisor throughout my PhD studies, Dr. Parisa Gazerani (Associate Professor, PhD). Her extraordinary faith in me, and her unconditional support and care have been the driving forces behind all the AH studies. From the beginning of the first AH study initiated in 2014, she has always been open to my ideas and thoughts. Throughout our professional relationship, she has never rejected my ideas, but instead has always used them as a starting point and attempted to improve upon them. Her personality and professionalism have inspired me to become not only the researcher I am today, but also the person I am today. She influenced me during difficult periods of my PhD studies, encouraging me and giving me the confidence, I needed to cope. I consider Dr. Gazerani as an inspirational person. My gratitude cannot be fully expressed in words how much I appreciate Dr. Gazerani's help. I thank you from the bottom of my heart for giving me the opportunity to become your PhD student. We have always had a good working relationship and have worked well together. Our conversations in your office and on Teams have always been pleasant, and you have always created a safe research environment for me. The combination of your trust in me and my creativity has allowed me to take AH into new fields of research that have never been attempted before. It represents a unique achievement, representing the result of our collaboration and our journey.

I would like to thank the PhD committee consisting of Dr. Federico Mainardi (MD) and Dr. Flemming Winther Bach (MD) for taking the time to assess my PhD dissertation, and Dr. Andrew James Thomas Stevenson (PhD) for his role as chairman.

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by your kind and professional attitude towards patients and colleagues as well as your research approach to MOH. I would also like to thank Dr. Bibi Gram (Associate Professor, PhD), headache nurse Lena Jæger, headache nurse Maria Brunkbjerg Jepsen and Dr. Niels-Peter Brøchner Nielsen (PhD) for the warm reception I received during my stay. In particular, I will remember the headache school, the research seminar, and the lunches where I felt like a part of your research environment. I will never forget this experience.

In this dissertation, an experimental model has been developed within AH; however, this was only possible with the assistance of Senior Sergeant and flight physiologist, Erling Stengaard Jensen, who was extremely open to my first contact with Center for Flight- and Naval Medicine, Skalstrup Airbase, Danish Ministry of Defence. Senior Sergeant Erling Jensen and his colleagues have provided me with an exceptional level of hospitality and curiosity about the project; it has been a pleasure to work with them. Without your cooperation, the experimental model would never have been developed, and I cannot express my appreciation enough for your contribution.

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My unconditional love for my father (Phuoc), mother (Lan), sister (Michala), niece (Vanessa) and nephew (Stephen), who are the cornerstones of my life. Throughout my life, my mother has been a strong influence on my mental and physical well-being. She has provided me with loving care that only a mother can provide. Her attention has been constantly focused on providing me with the best healthy food possible, and she has dragged me away from the laptop whenever she saw that I was sitting too long with the dissertation. I have nearly been overwhelmed by stress several times, and she has been the key factor in preventing my collapse. My mother is my greatest supporter and has attended all of my lectures in Denmark. The completion of my dissertation would not have been possible without her love, support, and care.

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I attribute a significant part of my identity to my childhood friends Niels Vincent Næser, Christian Damgaard Kristoffersen and Maria Truong. We have been friends since we were young in primary school, and our bond has lasted since then. In general, we meet every six months - as much as possible, and it is always a pleasure to see each other. I am frequently told by my friends and colleagues that our friendship is a rarity these days and they admire our friendship. My dissertation has always been supported by you, and you have never doubted my ability to complete it. I consider you to be an integral part of my life, and you always will be.

My childhood friend Thomas Christensen and his family have always been in my thoughts during my PhD. As much as I would like to share with Thomas my joy about my dissertation, I am sure he is happy for me as well. May Thomas keep resting in peace. Since I was a child, the Christensen family has always been supportive, and

you have also asked about my PhD studies and followed along behind the scenes with great interest. The support and care you have shown me mean a lot to me.

Neha Sharma, thank you for being such a good friend to me. We have shared many good experiences together, as well as many thoughts with each other. Your presence has provided me with the opportunity to divert my attention from my dissertation, allowing me to put my thoughts aside. Michael Scott would be envious of the number of internal jokes we have developed from our experiences. In Copenhagen, you have been an invaluable component of my life, and you have provided closeness and care, which has been the catalyst for me to be able to complete it.

Following a long day at Aalborg University, I went to boxing on the fitness team in Nørresundby with Malene Steffensen as a coach, and my usual sparring partner, Michael Bødker. It was a great team environment and the community among team members was excellent. The training gave me a physical boost and a sense of joy that I was able to take on in my PhD research. I would like to thank all of the members of the training team for their energy and personalities, especially Malene and Michael. That time will never be forgotten for me.

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Last but not least, I would like to thank all my friends, colleagues, and acquaintances who have been a part of my journey.

Sebastian Bao Dinh Bui

Copenhagen, 24 May 2022

ABBREVIATIONS

AH: Headache attributed to airplane travel (airplane headache)

CGRP: Calcitonin gene-related peptide

CRF: Case report form

CT: Computerized tomography

DBP: Diastolic blood pressure

ELISA: Enzyme-linked immunosorbent assay

ENT: Ear, nose and throat

GCP: Good clinical practice

HAH: High altitude headache

ICHD: International Classification of Headache Disorders

IHS: International Headache Society

MAO: Monoamine oxidase

MRA: Magnetic resonance angiography

MRI: Magnetic resonance imaging

NRS: Numeric rating scale

NSAIDs: Non-steroidal anti-inflammatory drugs

PGE_2: Prostaglandin E_2

PVG: Pharmacovigilance

RCT: Randomized controlled trial

SBP: Systolic blood pressure

SF: Simulated flight

SF-MPQ: Short-form McGill Pain Questionnaire

VAS: Visual analog scale

VIP: Vasoactive intestinal peptide

VRS: Verbal rating scale

PREFACE

This PhD dissertation has been prepared on the basis of my research work in AH, carried out in the period 2014-2017 at Aalborg University under the supervision of Dr. Parisa Gazerani (Associate Professor, PhD). I have completed a full PhD program without enrollment and salary besides my full-time position at the Danish Medicines Agency. The dissertation was submitted for assessment for the PhD degree at the Department of Health Science and Technology, Aalborg University in September 2022.

The included three studies in this dissertation, were conducted in collaboration with Center for Flight- and Naval Medicine Skalstrup, Aalborg Airport, Sønderborg Airport, Alsie Express, Hovedpineforeningen and Migrænikerforbundet. The Danish Independent Research Council provided financial support to Study 2 and Study 3. In this dissertation, the background, discussion of the results, conclusions, and future perspectives for AH will be presented. An additional anecdotal study is also included in this dissertation.

In addition, I have conducted a research protocol that was approved for a treatment study of AH in 2017 by the local ethics committee of Region Nordjylland. The study has not yet been completed due to the COVID-19 pandemic but is likewise included in this dissertation.

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1. INTRODUCTION

The Danish author Hans Christian Andersen has a special place in the hearts of the Danish people, and almost everyone around in the world is familiar with this quote from his fairytale “Mit livs eventyr” (The Fairy Tale of My Life: An Autobiography) from 1855: “At rejse er at leve” (To travel is to live). The quote has brought inspiration to many Danes as they go on summer holidays every year. Some take the car and drive through Germany and on to the rest of Europe, but many of the Danes take the airplane when they have to travel. The flight is often the start of a joyful holiday, where most of the people can sit back and relax completely in their seat. However, this is not the case for everyone. For some individuals, this way of travel is associated with a very unpleasant, intense, and painful headache both during the flight, but mainly during take-off and landing. This kind of headache is called “headache attributed to airplane travel” or simply airplane headache (AH) [1-11].

While the flight may be uncomfortable for some passengers, the car ride is not always a joyful time either for those sitting in the back of the car or bus. These passengers will probably experience headaches and nausea, which are some of the symptoms of motion sickness; a condition that many can recognize [12-14]. Since AH is relatively unknown, many passengers may have mistakenly concluded that the cause of their headaches might have simply been motion sickness, because headache is a common symptom of motion sickness. Some passengers do, in fact, experience motion sickness on flights, but general motion sickness can be treated by using scopolamine, which can prevent motion sickness and thereby related headache [14]. However, due to the different headache mechanisms, it is uncertain whether scopolamine will have a relieving effect on AH.

1.1 HISTORICAL BACKGROUND

Having a flashback to the historical perspective of AH can help understand how it started. Humans have always been fascinated by flying. Most of us are familiar with Leonardo da Vinci, the Italian renaissance artist, who painted the famous Mona Lisa. In 1519, when he died, it was well known that in addition to his love for painting, he was also very fascinated by birds which he studied in detail and dreamed that one day we could fly just like them [15].

On 17 December 1903, the Wright brothers made their first flight [16]. The development took off. Then World War I started, where some of the world’s first fighter aircrafts were developed [16, 17]. Many of the pilots got headaches every time they had to "dive" from a high altitude due to the pressure differences between the

higher altitudes [16, 18, 19]. Ideally, we could fly at an atmospheric pressure corresponding to the sea level [16]. This is difficult to obtain as the atmospheric pressure will decrease when a higher altitude is reached and increase when below the sea level e.g. diving in deeper waters [3, 20, 21]. Cabin pressurization is necessary in order to achieve a lower pressure during flights – this option was not available during World War I, which caused problems for the pilots [16]. Over the years, advancements in the production of airplanes continued and gradually passenger airlines that are recognized today were developed [16, 22]. Usually, the flight altitude of the passenger airlines is 9-14 kilometers, but with the help of the current cabin pressurization the pressure can be regulated so it corresponds to the pressure of an altitude of 1-1.5 kilometers [16]. This means that during take-off and landing, there will be a rapid pressure change due to the high speed [1, 7, 23]. These two flight phases - take-off and landing - are known to contribute to AH and form the basis for central mechanism(s) of it [1, 2, 4-6, 9-11, 20, 21, 23-35].

Even though AH might have been noticed earlier and discussed informally, in 2004, it was scientifically presented and attracted the attention of the headache community, and related fields to pay attention to this type of headache [3, 7]. Atkinson and Lee [7] was the first group to describe the headache back in 2004, based on a 28-year-old male patient. The man had experienced an acute and very intense headache during take-off and landing. The headache pain was localized to the eye region and disappeared shortly after onset [7]. Since then, articles on AH have been published to a limited extent [3]. But it was enough to be recognized and enrolled in the International Classification of Headache Disorders (ICHD) 3 beta version by the International Headache Society (IHS) in 2013 as a severe unilateral painful headache located in the fronto-orbital region that usually will disappear within 30 minutes [36]. It is estimated that 100 million passengers annually suffer from the headache [24].

1.2 POPULATION AFFECTED BY AH

It is reasonable to assume that some flight passengers are thinking that they suffer from motion sickness in the form of headaches, as headaches are one of the symptoms of motion sickness [12-14]. If flight passengers only experience headaches specifically related to the flight, i.e. that it disappears within 30 minutes and is without nausea, then this indicates an AH attack rather than motion sickness, as there are no accompanying symptoms during an AH attack [36].

As AH is a relatively new-defined and recognized headache, the headache is not yet known to many passengers or doctors, which may affect the number of reported AH cases in both adults and children. AH mainly affects adults [3]. So far, the literature has described 18 cases of children with AH (see Table 1) [3, 37, 38]. In these cases,

the children's AH-attacks occurred randomly during the flights, and their pain was localized to either the bilateral or the unilateral orbito-frontal region [37, 38]. Doctors performed diagnostic tests such as magnetic resonance imaging (MRI), which showed thickened mucosal membranes and a history of sinusitis in some cases, but the majority showed normal findings [37, 38]. A minority of the children were prescribed antihistamines, which relieved the headache; this immediately suggests that the antihistamines eliminated the swelling in the children and thus also accompanied AH [37]. Since the number of AH-attacks in children is very limited, it is still uncertain how the clinical picture of AH progresses in children [3, 37, 38]. This also applies to the treatment of AH in both adults and children. However, a possible mapping of the pain mechanism in adults may be a step forward in giving an overall overview of the mechanism underlying the headache.

Table 1: Demographic characteristics of AH in children.

Year, Author (reference)	Number of AH-patients	Gender (number of M/F)	Mean diagnosis age (mean ± SD) years
2018, De Carlo et al. [38]	15	3 M/ 12 F	12.4
2010, Ipekdal et al. [37]	3	1 M/ 2 F	13 ± 0.8
2010, Ipekdal et al. [39]	2	1 M/ 1 F	12 ± 1

1.3 PATHOGENESIS AND TREATMENT OF AH

It is widely accepted in the literature that sinus barotrauma may play an important role in AH pathogenesis, although the exact mechanism is not yet identified [3]. As a result of an imbalance between the pressure in the cabin and the sinuses of passengers, sinu barotrauma occurs when there is insufficient equalization of the pressures during take-off or landing [3]. As a consequence, there will be an inflammation of the nasal mucosa that will activate the trigeminal nerve in the fronto-orbital region, causing AH [3]. This proposed mechanism has not yet been definitively confirmed and it is still unclear which substances are released during the inflammation process. If the substances are identified, they can potentially act as biomarkers in the development of a strategic treatment plan for AH. So far, the treatment strategy has been based on case studies and individual patient experience, which is why there is still a need for further research within the field of AH [3]. So far, there have been examples of both

pharmacological and non-pharmacological treatments with varying effects [3, 4]. In the proportion of AH patients, who have received treatment, either pharmacological or non-pharmacological, there is a predominance of AH patients who have received pharmacological treatment [3]. However, the pharmacological treatments indicate that there may be a clinical basis for being able to support these treatments, which will also be discussed later in this dissertation. The non-pharmacological treatments for AH that have been used and described are pressing on the headache pain site and the Valvalsa maneuver as such [4]. As there is no formal treatment plan for AH and as the headache is most likely not well known by most doctors or passengers, it is conceivable that passengers may have been conflicted in trying to identify which treatment would be most beneficial to AH. Preliminary research indicates that there is a poorly clinical effect of the non-pharmacological treatments for other headache forms, such as migraines, but also for AH [4, 40].

Non-pharmacological treatments, such as neurostimulation have been used for the treatment of other headaches, such as migraine [41]. One of the neurostimulation devices is the battery powered Cefaly, which is applied to the forehead with a headband [41]. Cefaly stimulates the supraorbital nerve and is approved for migraine headaches [41]. In a previous study [42], the Cefaly device was used for three months by 67 migraine patients who reported a significant reduction in migraine attack days in comparison to those who used a sham device. Further, 53% of migraine patients reported the use of Cefaly as satisfying in a post-marketing survey consisting of 2313 migraine patients [43]. The use of Cefaly indicates that stimulation of the supraorbital nerve can somehow change brain activity [41]. In addition, the adverse effects of Cefaly have appeared to be mild and transient [43] and the device could be a considerate alternative to the pharmacological treatments of AH although the literature is very limited [3]. Conversely, the relieving effects of the pharmacological treatments are only based on reports from the passengers [3-5, 21, 25]. Therefore, there is a need to measure the biomedical effects of the drugs to compare with the non-pharmacological treatments such as Cefaly in order to map a proper treatment plan.

Considering a timeline of 2004 to 2013 from the first report to the classification of AH, and from 2013 until now, there still lacks an overview of the status of AH, and especially its underlying mechanisms, which will be discussed in this dissertation.

2. AIMS OF THE DISSERTATION

This PhD dissertation aims to advance the knowledge and evidence within the field of AH. This is achieved by focusing on the following research questions:

1. Study 2: The AH literature is limited, and the majority of the studies are conducted in the Southern Europe. Consequently, it is essential to investigate the prevalence of AH and other features of AH in a Northern European region, such as Denmark. Is AH associated with comorbidities such as high-altitude headache (HAH) and migraine?

2. Study 3: A central theory that has been discussed as a possible mechanism in AH, is sinus barotrauma. Other possible causes such as hypoxia, emotional impact as well as other physiological influences have also been mentioned. Can the development of an experimental model prove or disprove these claims?

3. Study 1 and Study 4: There is still uncertainty about the diagnosis, mechanism, and treatment. However, the evidence has been gradually increasing in recent years, so what do we know about the diagnosis and mechanism at present and how do doctors actually treat the AH patients? For example, triptans have shown promising effects on a minority of AH patients. Can the current knowledge form the foundation for clinical studies in the future in order to develop a treatment plan for AH?

The research questions have been answered in the three following peer-reviewed articles and one protocol, which are subsequently referred to as Study 1, Study 2, Study 3, and Study 4 (see Figure 1):

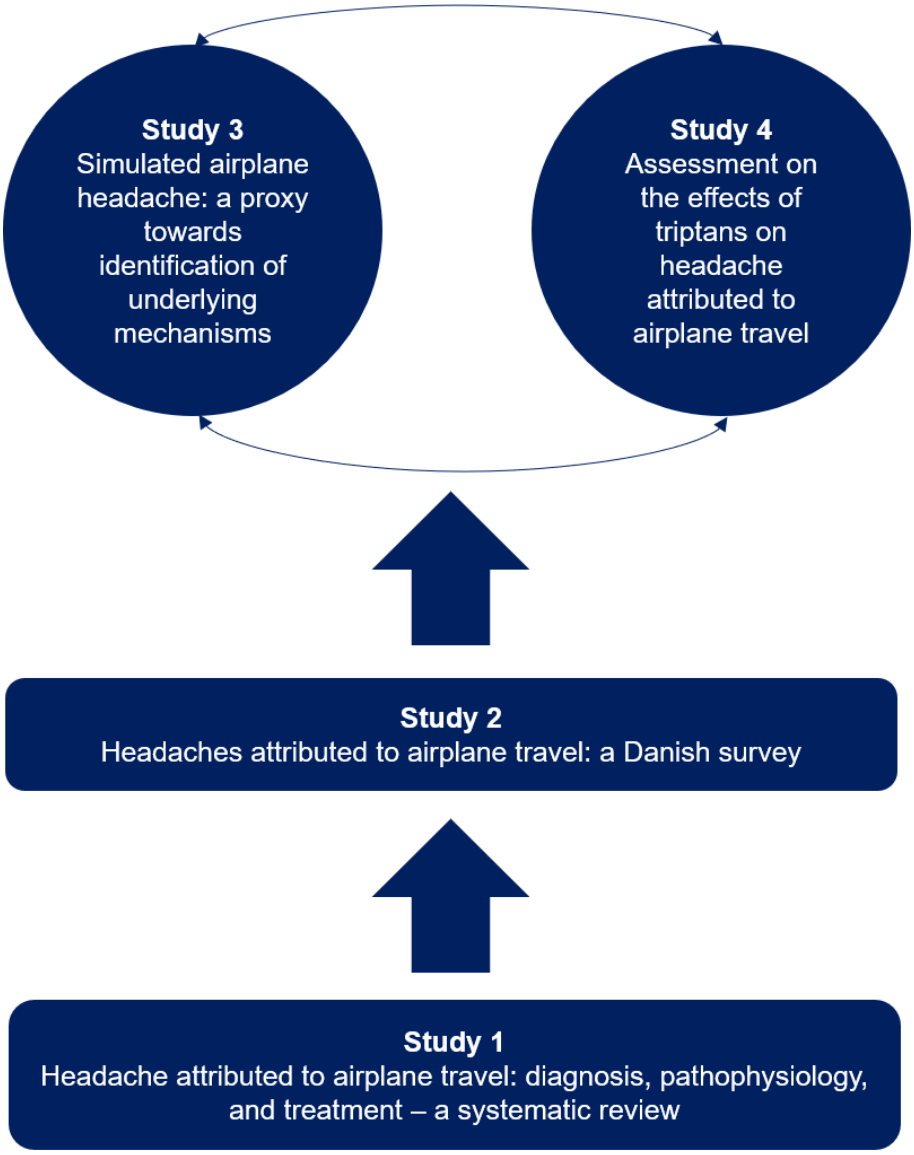


Figure 1: Overview of the PhD studies.

PAPERS INCLUDED IN THE DISSERTATION

Study 1

Bui SBD, Gazerani P. Headache attributed to airplane travel: diagnosis, pathophysiology, and treatment – a systematic review. J Headache Pain 2017;18:84-017-0788-0

Study 2

Bui SB, Petersen T, Poulsen JN, Gazerani P. Headaches attributed to airplane travel: a Danish survey. J Headache Pain 2016;17:33-016-0628-7

Study 3

Bui SBD, Petersen T, Poulsen JN, Gazerani P. Simulated airplane headache: a proxy towards identification of underlying mechanisms. J Headache Pain 2017;18:9-017-0724-3.

Study 4

Bui SBD, Gazerani P. Assessment on the effects of triptans on headache attributed to airplane travel (research protocol)

Anecdotal case

Bui SBD, Antropova O, Gazerani P (2019) An Anecdotal Case of Treatment of Headache Attributed to Airplane Travel: Are Triptans an Option? SN Comprehensive Clinical Medicine 1:527-528

AN ADDITIONAL CONTRIBUTION HAS BEEN MADE TO THE SUBSEQUENT PUBLICATIONS

Bui SBD, Gazerani P (2018) Flyrelateret hovedpine – hvad ved vi?. BestPractice 12:18-20

Bui SBD, Gazerani P (2017) Flyrejser kan give hovedpine. Ugeskr Laeger 179:2314-2317

CONFERENCE PAPERS

Bui SBD, Petersen T, Poulsen JN, Gazerani P (2017) A surrogate model to study underlying mechanisms of airplane headache. EFIC:No. 412

Bui SBD, Petersen T, Poulsen JN, Gazerani P (2015) Incidence and risk factors of flight-associated headache: a Danish study. EFIC:No. 324

3. CHARACTERISTICS OF AH

The IHS recognized AH as a formal headache for the first time in ICHD-3 beta in 2013 [36]. In addition to encouraging further research, the beta version was released in order to facilitate a final version 3 that would also include AH [36]. In 2018, AH was finally incorporated into the classification version 3 [44], which included 2 new AH studies [1, 45]. In order to create awareness of the AH, it was important that IHS recognized AH. This allowed a standardized method to determine diagnostic criteria for doctors to diagnose AH patients. The addition of two more recent studies [1, 45] to the diagnostic criteria has been beneficial since it has simplified the criteria compared to the first criteria outlined in 2013 (see Table 2).

Criteria C, 2, A, (both in 2013 [36] and in 2018 [44]) specify that the headache may occur during takeoff and/or landing. However, it is noted that the headache mainly occurs during the landing phase, where the frequency is 90% in most cases [44].

Table 2: Comparison of the diagnostic criteria on AH in ICHD-3 beta (2013) and ICHD-3 (2018).

AH diagnostic criteria, 2013 [36]	AH diagnostic criteria, 2018 [44]
A. At least two episodes of headache fulfilling criterion C.	A. At least two episodes of headache fulfilling criterion C.
B. The patient is traveling by airplane.	B. The patient is traveling by airplane.
C. Evidence of causation demonstrated by at least two of the following: 1. headache has developed exclusively during airplane travel 2. either or both of the following: a) headache has worsened in temporal relation to ascent after take-off and/or descent prior to the landing of the airplane b) headache has spontaneously improved within 30 minutes after the ascent or descent of the airplane is completed 3. headache is severe, with at least two of the following three characteristics:	C. Evidence of causation demonstrated by at least two of the following: 1. headache has developed during the airplane flight 2. either or both of the following: a) headache has worsened in temporal relation to ascent following take-off and/or descent prior to the landing of the airplane b) headache has spontaneously improved within 30 minutes after the ascent or descent of the airplane is completed 3. headache is severe, with at least two of the following three characteristics:

a) unilateral location b) orbitofrontal location (parietal spread may occur) c) jabbing or stabbing quality (pulsation may also occur)	a) unilateral location b) orbitofrontal location c) jabbing or stabbing quality
D. Not better accounted for by another ICHD-3 diagnosis.	D. Not better accounted for by another ICHD-3 diagnosis.
Notes: Not applicable	Notes: 1. Side-shift between different flights occurs in around 10% of cases. 2. Parietal spread may occur. 3. Pulsation (throbbing) may also be noted. 4. In particular, sinus disorders should be excluded.
Comments: 10.1.2 Headache attributed to airplane travel occurs during landing in more than 85% of patients. Sideshift between different flights occurs in around 10% of cases. Nasal congestion, a stuffy feeling of the face, or tearing may occur ipsilaterally, but these have been described in fewer than 5% of cases. The presence of a sinus disorder should be excluded.	Comments: A recent Scandinavian survey has indicated that up to 8.3% of air-travelers experience 10.1.2 Headache attributed to airplane travel. It occurs during landing in more than 90% of cases. Accompanying symptoms are reported in up to 30% of cases. Most frequent are restlessness and unilateral tearing; other localized parasympathetic symptoms, nausea or photo/phonophobia have been described in fewer than 5% of cases. A proportion of subjects experiencing 10.1.2 Headache attributed to airplane travel report similar headaches during free snorkeling and/or rapid descent from mountains, suggesting these headaches are due to an imbalance between intrasinus and external air pressures.

A dark blue mark indicates the change in AH criteria from ICHD-3-beta to ICHD-3.

3.1 PREVALENCE OF AH AND OTHER HEADACHES

Study 1 was based on 39 articles including in total 275 AH cases (148 men and 127 women) in the period between January 2004 and March 2017 [3]. Since this study and up until 26 January 2022, 10 new articles about AH has been published, including in total 344 cases (181 men and 159 women) [2, 46-54].

AH is a condition that is not related to other headaches or associated with other conditions. There is, however, a higher proportion of AH patients suffering from migraines (80 AH patients), tension headaches (27 AH patients), and a smaller group who suffer from HAH (13 AH patients) (see Table 4). According to the results of an initial Danish study (Study 2), there might be a correlation between AH and HAH, i.e., people who suffer from HAH are more likely to also suffer from AH [1]. Among the 21 AH passengers in Study 2, 13 AH passengers suffered from HAH (62%) (see Table 4). In addition, there were seven passengers with AH in the AH group who suffered from migraines as well (33%) (see Table 4).

Table 3: The prevalence of other headaches among AH patients and healthy subjects in the AH literature on real flights.

AH and other headaches	WW 2004-2017 (Study 1) [3]	WW 2017-2022*	DK (Study 2) [1]
AH patients	275	54	21
AH patients with HAH	0	0	13
AH patients with migraine	47	26	7
AH patients with tension-type headache	22	5	N/A
Healthy subjects	N/A	N/A	233
Healthy subjects with HAH	N/A	N/A	42
Healthy subjects with migraine	N/A	N/A	55

AH: airplane headache. WW: Worldwide. DK: Denmark. N/A: Not applicable. *Data are based on the references: [46-48, 50, 53].

3.2 NEW CLINICAL PRESENTATION OF AH IN REAL FLIGHT AND SIMULATION FLIGHT

Even though the diagnosis of AH includes several diagnostic criteria, the clinical picture shows AH patients deviating from the criteria either because they lack characteristic symptoms or because they show additional symptoms. The diagnostic criteria do not specify at what age the headache first appears. Further, they do not describe whether there is a second phase of AH as reported in some cases. It is unknown whether the intensity of pain is described precisely on a pain scale or in which phases AH most commonly occurs in various AH patients. Finally, no mention has been made of the psychological impacts in the diagnostic criteria.

An attempt has been made to map the new clinical presentation of AH in Study 1-3 [1-3], where the diagnostic age in real flights was reported as 28.7 ± 4.8 years worldwide, while in Denmark it was reported as 39 ± 14 years in real flights, and 24 ± 1.6 in simulated flights (see Table 4). A small number of people report headaches following a flight, though this is a very small group (see Table 4). The AH attack itself occurs in most cases during landing, which is consistent with the diagnostic criteria in ICHD-3 (see Table 4). The majority of AH patients in Study 3 experience AH in the descending phase during the simulated flight, which corresponds with the landing phase in an actual flight (see Table 4).

Table 4: Overview of new additional data to the diagnostic criteria of AH.

In addition to diagnostic criteria of AH	WW 2004-2017 (Study 1) [3]	WW 2017-2022*	DK (Study 2) [1]	DK (SF) (Study 3) [2]
Age at diagnosis	28.7 ± 4.8 years	36.22*	39 ± 14 years	24 ± 1.6 years
Other headache after AH	4	4	N/A	N/A
Pain scale, (NRS 0-10)	8-10	9.5**	7-10	7-10
Onset of AH	Mostly landing	Mostly landing	Take-off and landing	Descending phase
Stress	0	0	0	1
Anxiety	1	25	0	4
Total population of AH passengers	275	54	21	7

Data are presented in the table in addition to the diagnostic criteria of AH, which were collected based on real flights. Age at diagnosis is presented as mean. Pain was measured on a scale of 0 to 10 with 0 representing no pain and 10 representing the most intense pain. NRS: Numeric Rating Scale. *Based on the references: [46-48, 50, 53]. **Data are presented as mean. AH: airplane headache. WW: Worldwide. DK: Denmark. SF: simulated flight.

Some AH studies have measured the intensity of pain. The severe pain described in the diagnostic criteria can be compared to the predominant range of pain from 7-10 on a scale from 0-10, where 0 represents no pain and 10 represents the worst imaginable pain (see Table 4) [1-5, 24, 35]. The following studies have also addressed the assessment of pain, as shown in Table 4 2017, which shows an average pain assessment of 9.5 [46, 50, 53].

Psychological effects have not yet been fully described, but worldwide there are no AH patients who experience stress, and only one AH patient who experiences anxiety upon flying (see Table 4) [6]. In Denmark, no one reported experiencing stress or anxiety when flying in real life (see Table 4) (Study 2) [1]. However, in simulated flights, 1 out of 7 people reported stress, and 3 out of 7 experienced anxieties (see Table 4) (Study 3) [2]. The emotional aspect, such as anxiety, of the research has gained significant attention after Study 3 (see Table 4). In this Italian study, it was shown that 25 out of 30 AH patients experience anxiety as a result of flying [50].

3.3 EXAMINATIONS IN THE CLINIC

Study 1 [3] has mapped the neurological examinations performed on the AH patients. Medical examinations have been conducted based on the doctors' own initiative since the diagnosis is formally determined by reviewing the medical history and comparing it to the diagnostic criteria. A total of 46 patients among the 275 AH patients in Study 3 were examined via Ear, Nose, and Throat (ENT), Computerized Tomography (CT), Magnetic Resonance Angiography (MRA), and MRI [3]. Normal conditions were found in 38 patients out of the 46 AH patients, while the remaining eight patients showed signs of thickened mucosal wall and hence inflammation in the sinuses [3].

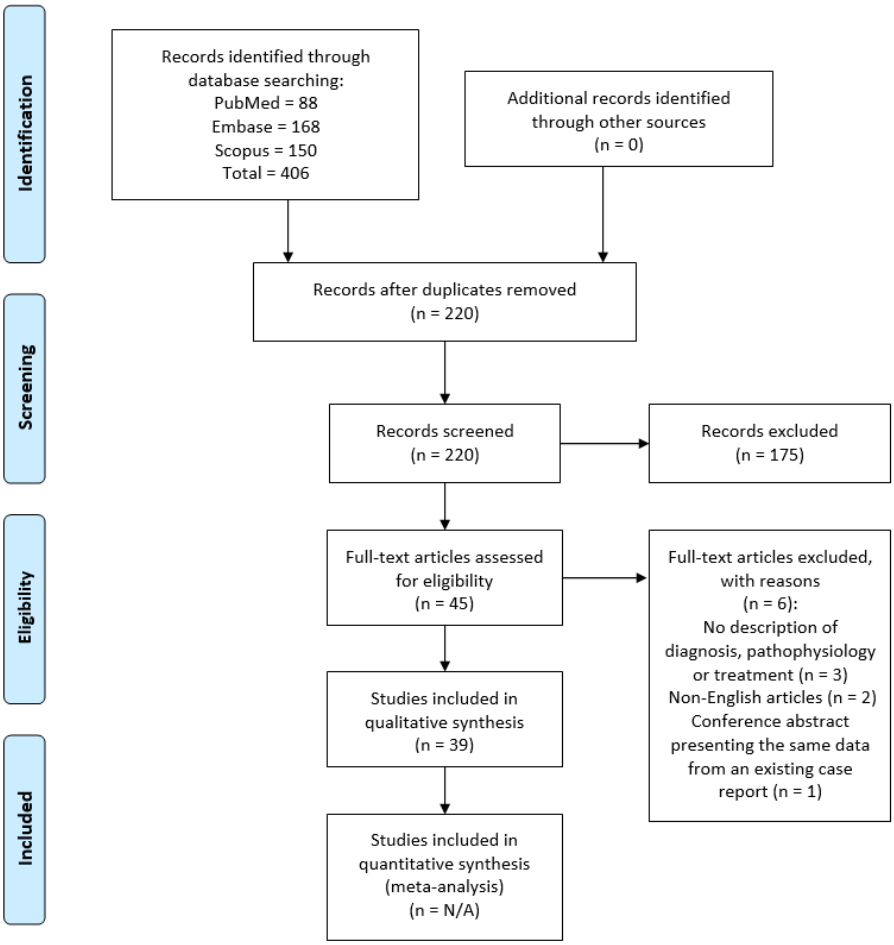
3.4 METHODS OF COLLECTION DATA WORLDWIDE AND IN DENMARK

Using the Scopus, Embase, and PubMed databases, the literature in Study 1 [3] was collected based on the search terms "airplane headache" and "aeroplane headache" (airplane OR aeroplane AND headache). The search was conducted between 2 March and 5 March 2017 and covered a period from January 2004 to March 2017. A starting point of January 2004 was chosen when the first of these studies was described in the literature. Due to the limited amount of literature available on AH, it was intended to include all types of AH studies in an attempt to provide the best possible overview of the diagnosis, mechanism, and treatment of AH. Based on the PRISMA flowchart for including data in Study 1, all types of literature were included such as conference abstracts, case reports, and case series (see Figure 2). Sorting of the literature was performed using in Excel 2010 (Microsoft Corp., Seattle, WA, USA).

The data collection on the prevalence in a studied population in Denmark on real flights was performed using a questionnaire that was created using Google Sheets and made available on Facebook with the assistance of Aalborg Airport, Sønderborg Airport, Alsie Express, Migrænikerforbundet, and Migræne- og Hovedpineforeningen in the period 15 October to the 1 December 2014. Data were stored in Excel 2010 (Microsoft Corp., Seattle, WA, USA) after the questionnaire was closed.

During the simulated flights, the subjects were asked to participate in the data collection process, which included both healthy subjects and AH subjects being given a questionnaire, which they had to complete during the simulated flight. Excel 2010 (Microsoft Corp., Seattle, WA, USA) was used to store the data after the simulated flights were over.

Figure 2: PRISMA flowchart for included AH studies in Study 1.



3.5 STATISTICAL ANALYSIS OF AGE DIFFERENCES AND RISK FACTORS FOR AH

In order to determine whether the continuous data followed a normal distribution, Shapiro-Wilk's test was used. The parametric independent *t*-test was then conducted in order to determine whether there were any age differences between the healthy flight passengers and the AH passengers on real flights in Denmark. The significance level was set at 0.05. Further evaluations were conducted using Fischer's exact test and Chi-square test to investigate whether HAH, migraines, and gender could be risk factors for AH.

4. MECHANISM OF AH

The mechanism of AH has not yet been fully determined. However, the current literature specifies a possible mechanism, sinus barotrauma, that is based on a theoretical rather than experimental basis. According to preliminary and consistently discussed hypotheses in the literature, sinus barotrauma is caused by an insufficient equalization of changes in the cabin pressure during take-off and/or landing [3].

4.1 SINUS BAROTRAUMA - A PRIMARY CAUSE OF AH?

During a flight, the cabin pressure changes during take-off and landing. According to previous research, the cabin pressure will change by 8 hPa for every 300 meters [55]. The changes in cabin pressure can be handled well by most people, however, the change can be a problem for others. The reason must be found in the individual structure of the ethmoid cells in our ethmoid sinuses, where some have such a narrow structure that it can trigger local tissue damage during flight [4, 9, 25, 56]. This type of damage is known as sinus barotrauma, in which the pressure changes in the sinuses cause local tissue damage to the surrounding mucosa of the ethmoid cells [4, 9, 25, 56]. The tissue damage will result in an inflammatory response, which will activate the branches of the trigeminal nerve that innervate the ethmoid cells [4, 9, 25, 56]. This nerve stimulation will result in the characteristic symptoms of AH [4, 9, 25, 56].

4.2 DEVELOPING AN EXPERIMENTAL MODEL

Although sinus barotrauma has been proposed as the primary cause of AH, psychological factors have also been suggested as a possible consequence of AH. A standardized experimental model can be used to test several conditions simultaneously, as these factors are difficult to describe on a theoretical level. Currently, the majority of studies summarized in AH literature are case reports and questionnaire surveys, but no experimental studies have been conducted yet [3].

An ideal scenario would be to conduct AH experiments on real airplanes in which several conditions and factors are studied, such as changes in cabin pressure, psychological aspects, and biological parameters. However, such a scheme is difficult to implement in practice, as continuous data collection during flight would require the cooperation of ordinary flight passengers and the flight staff. Considering this, it would be advantageous to investigate the same condition on the ground using an experimental setup.

AH has been studied experimentally for the first time in Study 3 [2] which is the first of its kind in the world. Currently, no studies have performed AH experiments in a pressure chamber within a controlled environment [2]. A German study [57] that investigated whether human taste buds changed during the flight was the source of inspiration for developing the experimental model in Study 3 [2]. In the German study, the experiments study were conducted in a pressure chamber during a simulated flight in order to determine whether taste buds were affected by pressure changes in the chamber. The chamber was able to simulate the pressure changes experienced during a real flight. It took a considerable amount of time to find an experimental setup in Denmark for AH, but in the end, a partnership was established with Skalstrup Airbase, which had a pressure chamber at its Center for Flight- and Naval Medicine where potential fighter pilots were being tested (see Figure 3).

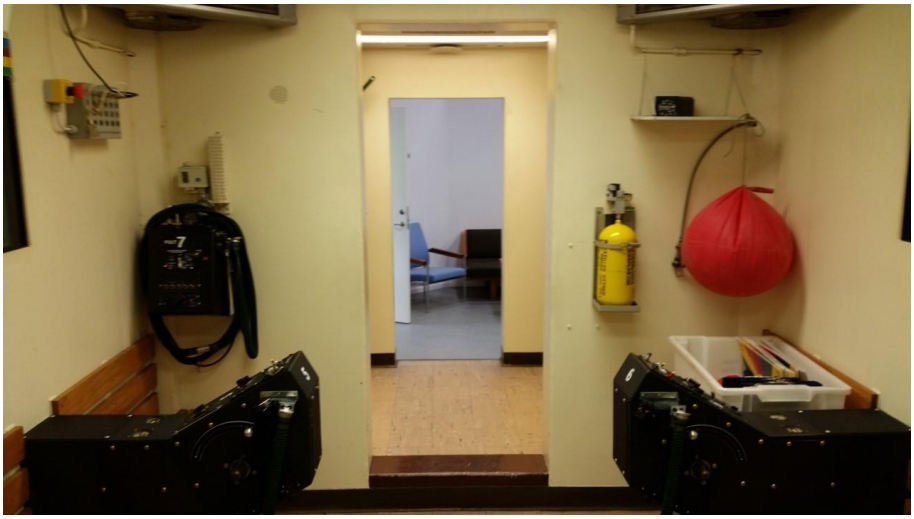


Figure 3: Inside from the pressure chamber at Skalstrup Airbase, Center for Flight- and Naval Medicine, Roskilde, Denmark. Photographer, Sebastian Bao Dinh Bui, 2016.

The pressure chamber was designed to accommodate seven subjects at a time and had a test setup consisting of two safety observers, an aviation physiologist, and a flight doctor all of which always were present during the simulation flights. The population for the simulation flights consisted of seven healthy subjects and seven subjects with AH (see Figure 4). Before entering the pressure chamber, the subjects were required to complete a questionnaire prepared by the personnel at Skalstrup Airbase.

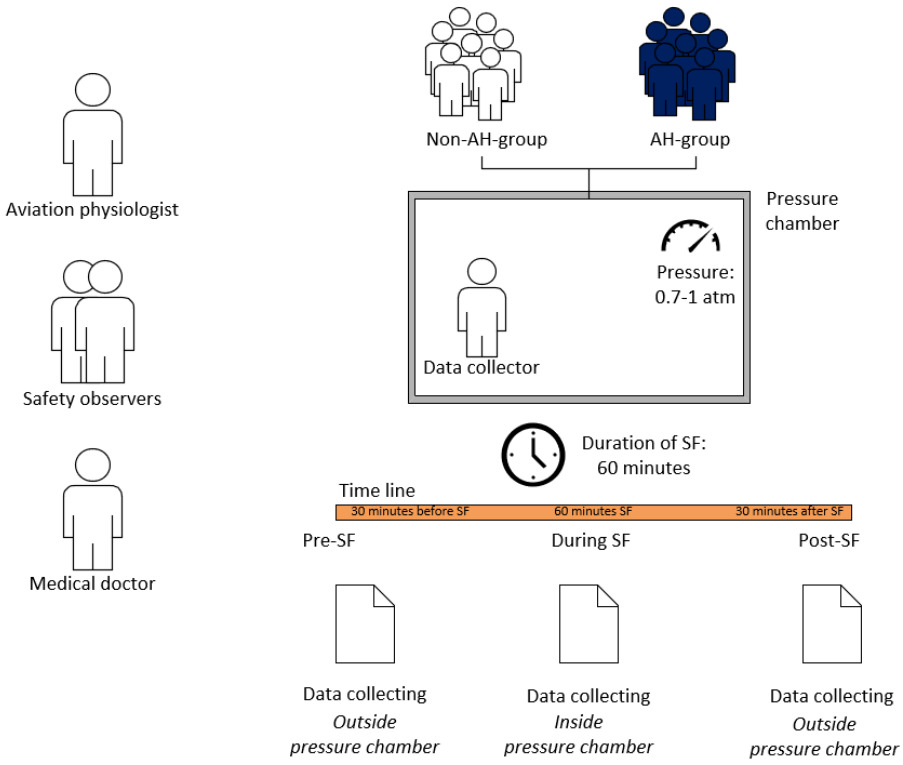


Figure 4: Illustration of the experimental setup for the simulated flights in the pressure chamber. AH: Airplane headache. SF: Simulated flight.

Initially, the decision was made to choose a domestic flight between Aalborg and Copenhagen as a reference point. This flight had a flight duration of 45 minutes, which was typical of a flight within Denmark. Therefore, it was chosen that the simulated flight in the pressure chamber should last one hour for all subjects with a pressure of 0.7 atm. This corresponded to a flight at an altitude of 2.48 kilometers, which was the normal cabin pressure for most passenger airlines (see Figure 4).

The staff at Skalstrup Airbase provided the data collector (Sebastian Bao Dinh Bui) with the opportunity to be inside the pressure chamber and collect biological and psychological data from the subjects during the flight. Each subject was provided with a headset that allowed them to be in constant contact with the safety observers outside the pressure chamber (see Figure 4).

4.3 SELECTION OF BIOMARKERS

In the absence of a formal treatment plan or comprehensive mechanism mapping, the use of biomarkers can provide useful insight, as well as shed light on other mechanical causes of headaches, including psychological and physiological factors which have been selected for Study 3 [2].

As sinus barotrauma is generally considered to be the main contributor to AH attacks, an examination of the local inflammatory response is necessary. PGE_2 induces headache by vasodilation after injection [58], and since PGE_2 is among the substances released during an inflammatory response, it is interesting to investigate whether PGE_2 could be selected as a biomarker for AH.

According to the AH literature, there is a group of flight passengers who are uncomfortable before boarding the plane because they know that AH attacks will occur on board [2, 6]. Therefore, it was also in the study's interest to examine cortisol levels and other vital parameters such as pulse rate, systolic blood pressure, and diastolic blood pressure in order to determine the condition of the individual passenger during the simulated flight.

PGE_2 and cortisol are selected to be collected via saliva samples, as this is considered to be less invasive when compared to blood samples. As there was a limited amount of space in the pressure chamber, it was convenient for all parties to take saliva samples during the simulated flight.

Oxygen saturation (SPO) has also been evaluated as a biomarker since it is known that cabin pressure may decrease during a flight, which could affect SPO as well [59], and therefore may be a useful biomarker to study how AH passengers will respond to this situation.

As a final biomarker, the facial skin temperature was selected, as temperature changes have been detected in migraine patients due to vasodilation of the cerebral arteries [60]. The measurement of facial temperature can contribute with insight into whether vasodilation also occurs within the cerebral arteries during an AH attack.

4.4 DATA COLLECTION OF BIOMARKERS

Study 3 [2] included both healthy subjects and subjects with AH, where all data regarding selected biomarkers were collected before, during, and after the simulated flight in the pressure chamber (see Figure 4). It was observed that the levels of biomarkers varied between the control group and the AH group at various phases during the simulated flight. Data collection took place in a nearby room before and after the flight simulation, while the data collection took place inside the pressure chamber during the simulation (see Figure 4).

Assays for PGE_2 and cortisol were performed by collecting saliva samples from the subjects in cups, collecting 1.5 mL for each subject and for each phase during the simulated flight. Subsequently, the saliva samples were frozen in a cooler bag for a short period of time, followed by further freezing at −80 °C. The concentrations of PGE_2 and cortisol were determined using an enzyme-linked immunosorbent assay (ELISA).

SPO was assessed with an Oximeter (placed on the index finger of the subjects), while vital parameters (pulse, systolic blood pressure, and diastolic blood pressure) were monitored with the BP-102 M device (Hangzhou Sejoy Electronics & Instruments Co., Hanzhou, China).

At a distance of approximately 60 cm from the subjects' faces, a thermal camera (FLIR systems E60 thermal imager, FLIR Systems, Wilsonville Oregon, USA) was located to measure the facial skin temperature with a sensitivity of <0.05 °C.

Excel 2010 (Microsoft Corp., Seattle, WA, USA) was used to store all the data from the biomarkers.

4.5 STATISTICAL ANALYSIS OF THE BIOMARKERS

To test whether the data for the biomarkers followed a normal distribution, the Shapiro-Wilks test of normality was used. Within each experimental group (control group and AH group separated) and between the experimental groups (control group vs. AH group), a two-way repeated ANOVA was performed with a significance level of 0.05 in the program SPSS 22.0 (IBM Corp., Armonk, NY, USA).

4.6 PGE_2

A significant increase (p = 0.01) in PGE_2 levels was observed in the control group after the simulated flight (52.28 ± 9.02 pg/mL) compared to before the flight (41.43 ± 6.03 pg/mL) (see Figure 5). The level of PGE_2 was almost identical in the AH group and the control group before and during the simulated flight. Considering the phase after the simulated flight, the PGE_2 level in the AH group (73.32 ± 16.87 pg/mL) was significantly elevated (p = 0.01) in comparison to the control group (52.28 ± 9.02 pg/mL) not only in this phase but also within the other two phases (before and during the simulated flight) in the AH group (see Figure 5). The significant elevated PGE_2 level in the AH group, when compared to the control group after the simulated flight, could be explained through an inflammatory response to potential sinus barotrauma.

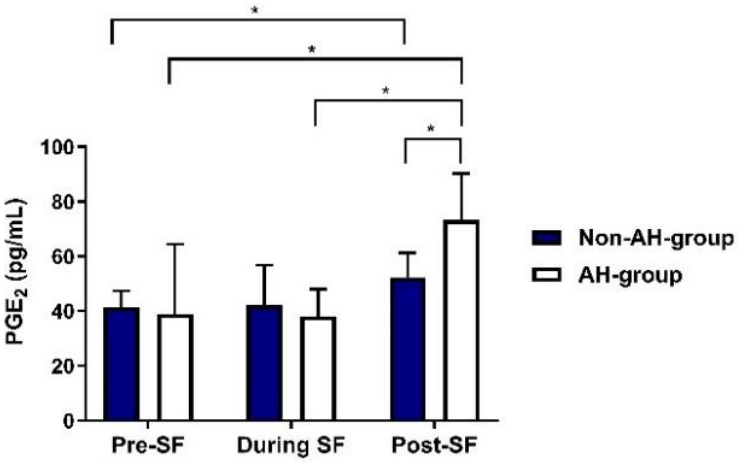


Figure 5: Comparison of PGE_2-levels during the simulated flight, presented as mean ± SD (standard deviation). SD is indicated by bars. *: $p < 0.05$. SF: simulated flight. AH: airplane headache.

4.7 CORTISOL

The cortisol level decreased gradually from before the simulated flight to after the simulated flight in the control group, where no significant differences were found between the phases. However, this was not the case for the AH group, where cortisol levels were slightly elevated before the simulated flight but increased significantly ($p < 0.001$) during the simulated flight (5.94 ± 2.03 ng/mL) compared to the control group (1.52 ± 1.16 ng/mL) (see Figure 6). The cortisol levels in the AH group decreased significantly ($p < 0.001$) after the simulated flight (2.02 ± 0.92 ng/mL), in comparison to before (4.62 ± 2.29 ng/mL) and during the simulated flight (5.94 ± 2.03 ng/mL) (see Figure 6). Cortisol levels increased significantly ($p < 0.001$) in the AH group compared to the control group during the simulated flight, indicating that the AH subjects were experiencing stress physiological reactions.

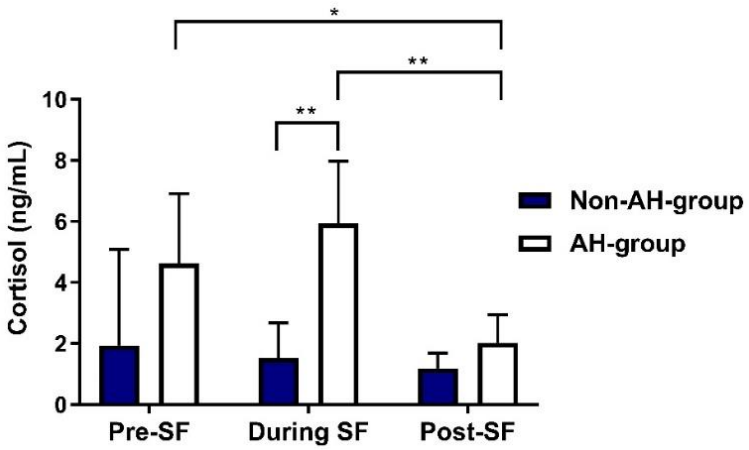


Figure 6: Cortisol levels during simulated flight, presented as mean ± SD (standard deviation). SD is indicated by bars. *: p < 0.05. **: p < 0.001. SF: simulated flight. AH: airplane headache.

4.8 OXYGEN SATURATION

The SPO of the control group remained constant throughout the flight and showed no signs of gradual changes (see Figure 7). There was, however, a significant decrease in SPO in the AH group during the flight (91.85 ± 2.48%) compared to before the

simulated flight (98.00 ± 1.00 %) ($p < 0.001$) and after the simulated flight (98.14 ± 1.06%) ($p < 0.001$), as well as compared to the control group during the flight (95.57 ± 1.81 %) ($p < 0.001$). Since the cabin pressure decreases with the oxygen concentration during a flight [61], this could indicate that the AH passengers may have less SPO when compared to healthy passengers.

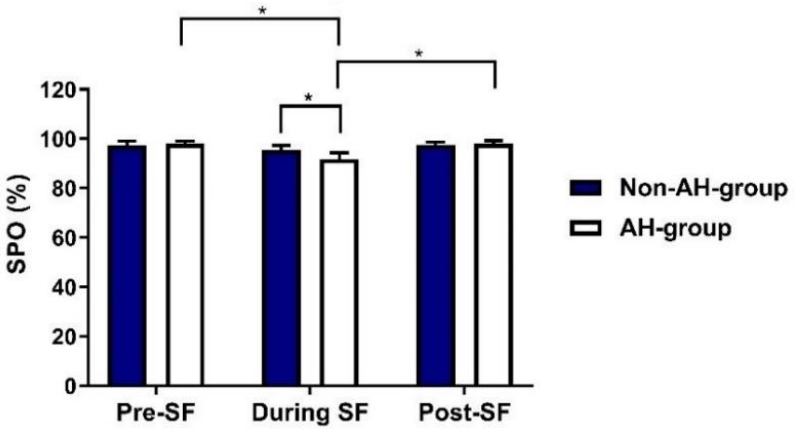


Figure 7: Comparison of oxygen saturations during the simulated flight, presented as mean ± SD (standard deviation). SD is indicated by bars. *: $p < 0.05$. SPO: saturation pulse oxygen. SF: simulated flight. AH: airplane headache.

4.9 VITAL PARAMETERS

The vital parameters pulse rate (see Figure 8, A), systolic blood pressure (see Figure 8, B), and diastolic blood pressure (see Figure 8, C) were not significantly different between the two groups. In the control group, the pulse rate gradually increased during the simulated flight before returning to its initial level before the flight. In the control group, there was a gradual decrease in diastolic and systolic blood pressure throughout the simulated flight. In the AH group, there was a gradual increase during the simulated flight, which then returned to the same level as before the simulated flight.

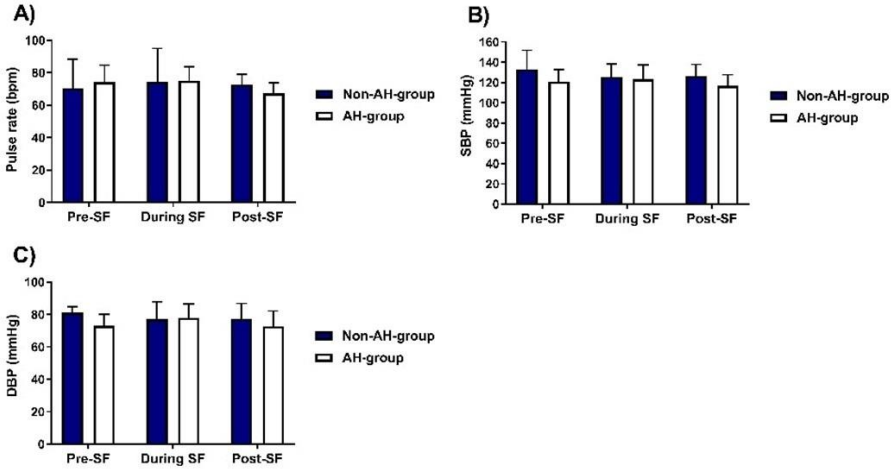


Figure 8: Comparison of the pulse rates, systolic and diastolic blood pressures during the simulated flight, presented as mean ± SD (standard deviation). SD is indicated by bars. *: $p < 0.05$. SBP: systolic blood pressure. DBP: diastolic blood pressure. SF: simulated flight. AH: airplane headache.

4.10 FACIAL SKIN TEMPERATURE

During the different phases, there were no significant differences in the facial skin temperature of the two groups (see Figure 9). For the AH group, it was essentially the same throughout the simulated flight. Contrary to this, the control group's facial skin temperature remained constant before the simulated flight and during the simulated flight but decreased gradually after the simulated flight (see Figure 9). In previous studies, facial skin temperature is higher in migraine patients in comparison to healthy subjects due to vasodilation of the cerebral arteries [60]. However, the facial skin temperatures in this study do not indicate that.

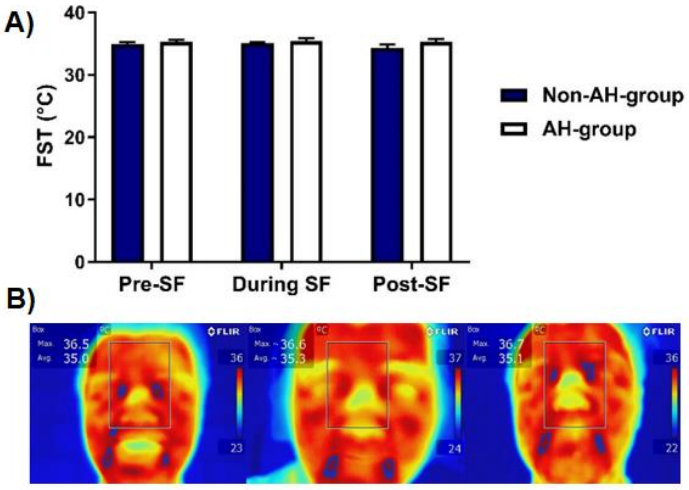


Figure 9: A): Comparison of fascial skin temperatures during the simulated flight, presented as mean ± SD (standard deviation). FST: facial skin temperature. SD is indicated by bars. SF: simulated flight. AH: airplane headache. B) Thermal pictures of a healthy subject before SF, during SF, and after SF. Written consent was obtained from the subject.

5. TREATMENT OPTIONS OF AH

Due to the lack of a proper understanding of the pathogenesis of AH [3, 50], treatments have been limited to symptomatic therapy, and ordinary analgesics have been used to mainly overcome head pain [3, 51]. The systematic review results (Study 1) revealed number of treatment strategies used by those affected by AH (see Table 5). An Italian study [50] found that despite the severity of AH, only one-third were prescribed pharmacological interventions, such as nasal decongestant spray and simple analgesics or non-steroidal anti-inflammatory drugs (NSAIDs), 30 minutes before the anticipated attack, and this strategy could reduce AH by 50-75% in subsequent flights [50].

Table 5: Overview of pharma pharmacological and non-pharmacological treatments in AH patients from the period 2004 to 2017 (Study 1) [3]

Pharmacological treatment	Number of AH patients (n=79)
Naproxen	24
Triptans	12
Paracetamol	11
Dipyrone	7
Ibuprofen	6
Unspecified NSAIDs	4
Nasal decongestant	4
Aspirin	3
Antibiotics	2
Antihistamine	2
Oxymetazoline	1
Loxoprofen	1
Non-pharmacological treatment	**Number of AH patients (n=35)**
Pressure on the headache pain site	19
Valsalva maneuver	11
Relaxation methods	3
Chewing	1
Extension of the ear lobes	1/35

A total of 79 AH patients have used medications in the period 2004-2017, while 35 AH patients have used treatment without medication.

Currently, there is no formal or standard treatment strategy for AH [35, 47]. However, accumulating case studies point to the potential benefit of triptans for AH. The use of triptans derives from the proposition that AHs are caused by an imbalance between intrasinusal and external pressures that may result in mechanical stimulation of the trigeminovascular nociceptors [3, 25]. This mechanism may explain why AH may respond to triptans [54].

Tritans are a class of medications developed for the treatment of migraine attacks, of which sumatriptan was the first compound developed [62]. Other triptans include zolmitriptan, naratriptan, rizatriptan, eletriptan, almotriptan, and frovatriptan, which are agonists of the serotonin 5-HT_{1B} and 5-HT_{1D} receptor subtypes [63, 64]. According to literature [65] triptans act on 5-HT_{1B} receptors by decreasing pain induced by cranial vasodilation through vasoconstriction in the peripheral nervous system. They also inhibit the release of vasoactive peptides that trigger neurogenic inflammation by their action at the 5-HT_{1D} [65]. Triptans within the central nervous system are proposed to interfere with nociceptive signals to the trigeminal nucleus caudalis [66]. The findings of a systematic review and network meta-analysis [67] can be summarized as follows: the most effective drugs included sumatriptan subcutaneous injection, rizatriptan oral disintegrating tablets (ODT), zolmitriptan ODT, and eletriptan tablets [67]. Interestingly, this class of drug has not been approved for other indications or headaches. In 2011, Ipekdal et al. [25] presented five cases of individuals who consumed triptans 30 minutes before a flight, and none of the subjects experienced subsequent AH during the flight. The individuals presented in this report took various triptans: zolmitriptan, eletriptan, sumatriptan, and naratriptan [25]. In addition, other anecdotal cases of triptan use for AH have been reported in the literature [25, 53, 68], which collectively show that triptans have been effective and safe, with reasonable patient satisfaction. There has still been no randomized clinical trial for the use of triptans for AH. Currently, no formal treatment plan with triptans exists or is being recommended. Considering the safety and effectiveness of triptans for migraines [67], it is clinically rational to investigate whether triptans can be considered as a treatment option for AH.

There is additionally supporting evidence in the literature that indicates that the mechanisms by which triptans act [66], as well as targeting the pathogenesis of migraine [69], could further promote the idea of exploring triptans as a treatment for AH. It is proposed that overlapping mechanisms might be involved in migraine attacks and AH attacks [2], including the involvement of trigeminovascular components, which can be targeted with triptans. A study by Hansen et al. [70] shows that the concentrations of calcitonin gene-related peptide (CGRP) and vasoactive intestinal peptide (VIP) are reduced in migraine patients who received triptans and experienced headache relief [70, 71]. Vasodilation is also thought to be one of the causes of AH [2, 3, 46, 53], but the exact etiology of AH is still unknown, and barometric pressure

has been emphasized over other potential mechanisms [72]. In addition, a puzzling finding [1] shows that there is no clear link between AH and migraine, as it was assumed that people with one type might become more susceptible to the other.

Therefore, based on clinical case observations and proposed mechanisms of action of triptans, Study 4 was designed as a protocol for testing the feasibility and outcome of triptans for AH, and to investigate some of the mechanistic aspects by analyzing salivary biomarker levels (CGRP and VIP) in AH and following the administration of response to triptans.

5.1 ANECDOTAL CASE OF THE USE OF TRIPTANS IN DENMARK

Although there is no formal treatment plan for AH, it has been shown in the literature that triptans are predominately effective. Study 1 [3] showed in the period January 2004 to March 2017 that 13 AH patients out of 275 AH patients used triptans in the literature, while Study 2 [56] showed that five AH patients out of the 21 AH patients used triptans in Denmark. In the period from March 2017 to January 2022, additionally four AH patients have been reported to have used triptans in the latest literature [50, 53]. The effective use of triptans has given hope to those AH patients who want to abolish the severe AH-attacks.

In 2019, an anecdotal paper was published based on a 28-year-old man [68] who contacted the PhD fellow of this dissertation (Sebastian Bao Dinh Bui) via Facebook after reading the published papers based on Study 1-3 [1-3]. Despite only traveling 1-3 times per year, he complained of having a very intense and painful headache every time he flew, which was consistent with the symptoms of AH. He took one paracetamol tablet (500 mg) on one of his travels, but it did not affect his headache. Study 1-3 motivated him to become headache-free, and he was encouraged to visit his GP, who subsequently referred him to a neurologist. The patient had brought the papers for the interview with the neurologist, where the patient was prescribed triptans, which were advised to be taken 30 minutes before the flights. The same approach was used as described in the triptan study by Ipekdal et al. [25]. The patient was not carrying any relevant medical history, nor was he taking any other type of medication. His subsequent flights were headache-free, and he has frequently expressed how wonderful it was to travel with no AH attacks.

5.2 DEVELOPMENT OF AN EXPERIMENTAL PROTOCOL WITH TRIPTANS

The anecdote in Denmark reveals an example of an AH patient who could no longer tolerate his episodes of AH. Further research is needed to determine if there are more AH patients who have not yet consulted their doctors regarding possible treatment with triptans. A small number of AH patients have resorted to triptans with a high success rate. This phenomenon deserves further research in order to determine whether it is actually effective. The literature on AH currently lacks randomized controlled trials (RCTs) that describe potential therapeutic options. The experimental protocol (Study 4) has thus been developed, as the first in the world, to investigate whether triptans may be a possible treatment for AH patients. As an early pilot study, it may shed light on whether triptans can have therapeutic value for AH patients. In Study 3 [2], the experiment was conducted on a simulated flight, but in Study 4, the experiments will be conducted on a real flight, which will also contain healthy passengers and passengers with AH. Both groups are required to give saliva samples before, during, and after the flights. CGRP and VIP are selected as biomarkers, aiming to investigate not only the mechanism of AH, but also the effects of triptans on AH. AH patients will be administered placebos as well as triptans, which must be consumed blindly before the flights, while patients in the control group will be administered no tablets.

5.2.1 Research Questions

1. Are triptans effective for reducing head pain in AH?
2. Do triptans alter salivary levels of CGRP and VIP?

5.2.2 Hypotheses

1. Triptans can reduce head pain in adult individuals suffering from AH.
2. Triptans affect salivary concentrations of CGRP and VIP.

5.2.3 Primary objective

To determine the effectiveness of triptans for AH.

5.2.4 Secondary objective

To determine biomarker levels of CGRP and VIP before and during an AH attack, and in response to triptans.

5.2.5 Trial design

The study is designed as a randomized controlled trial with a parallel arm, blinded to the intervention, with measurement of objective biomarkers and a focus on feasibility.

This study can be considered a phase IV trial because triptans are already approved and used for migraines. It will be performed prospectively, and subjects will be observed after the intervention.

The rationale behind this trial design is that, there is no formal treatment strategy for AH, but sporadic cases demonstrate beneficial effects of triptans [25, 53, 68]. Triptans are safe and effective medicines approved for the cessation of acute migraine and can be repurposed for AH if their efficacy and safety are confirmed through a RCT. There is, however, no trial and this study protocol is considered to test whether it is feasible to conduct a RTC to test the use of triptans for relief of AH attacks. Therefore, we will measure subjective pain (numeric rating scale $(NRS)_{0\text{-}10}$), and participants' response to triptans. In addition, to shed light on the mechanistic aspects of AH and potential targeting by triptans, objective biofluid biomarkers, such as CGRP and VIP, that triptans are known to act on in migraine, will be measured, such as CGRP and VIP [71]. Saliva samples will be collected from the subjects before, during, and after their flights to identify alterations and responses to triptans.

5.2.6 Study setting

The trial will be conducted at the Department of Health Science and Technology, Faculty of Medicine, Aalborg University, Aalborg, Denmark.

5.2.7 Study population

Participants with AH and healthy matched controls showing interest in this trial will be screened for inclusion.

5.2.8 Clinical definition

The diagnosis of AH is based on the third edition of the International Classification of Headache Disorders (ICHD-3) [44].

5.2.9 Eligibility criteria

Inclusion criteria:

- Flight passengers who depart from and/or arrive at Aalborg Airport at least twice a month;
- A resident of the northern Denmark region;
- Age from 18 to 70 years;
- Flight passengers without AH;

or

- Flight passengers with AH who meet the diagnostic criteria of AH [44]:

A. At least two episodes of headache, fulfilling criterion C;

B. Traveling by airplane;

C. Evidence of causation demonstrated by at least two of these:

1. Headache developed during the airplane flight;
2. Either or both of the following:

   (a) Headache worsened in temporal relation to ascent following take-off and/or descent before landing;

   (b) Headache spontaneously improved within 30 minutes after ascent or descent was completed.

3. Headache is severe, with at least two of the following three characteristics:

   (a) Unilateral location;

   (b) Orbitofrontal location;

   (c) Jabbing or stabbing quality.

D. Headache is not better accounted for by another ICHD-3 diagnosis.

Exclusion criteria:

- Pregnancy;
- Addictive or previous addictive behaviors defined as substance abuse (e.g., cannabis, opioids);
- Epilepsy;
- Asthma;
- Migraine;
- Use of medication such as paracetamol, triptans, etc., for other types of headaches;
- Use of non-steroidal anti-inflammatory drugs (NSAIDs);
- Regular use of medication;
- Use of vasodilating/vasoconstricting medication;
- Cardiovascular disease;
- Cancer;
- Under investigation or starting treatment for human papilloma virus;
- Participation in other studies during the entire trial period;
- Previous blood clot;
- Severe hepatic impairment.

In connection with giving saliva samples before, during, and after the flight (for both groups):

- The subject must not drink alcohol 24 hours before the flight;
- The subject must not consume food 60 minutes before the flight;
- The subject must not consume caffeine, chili pepper, chocolate (including a chocolate drink), or nicotine 24 hours before the flight;
- The subject must not take headache medication at least 48 hours before the flight (however, AH subjects must take the triptan in this study as instructed).

Contraindications to the use of triptans (for the AH group):

- Ischemic heart disease;
- Prinzmetal's angina/coronary vasospasm;
- Previous myocardial infarction, previous blood clot or transient ischemic attack (TIA) in the brain, uncontrolled hypertension;
- Symptomatic peripheral vascular disorder or severe hepatic impairment;
- Co-administration of ergotamine, derivatives of ergotamine, other triptans/5-HT1 receptor agonists, or monoamine oxidase (MAO) inhibitors.

5.2.10 Participant selection, sample size, and recruitment

This study is the first of its kind in the field of AH, thus a feasibility study is required to identify practical aspects and challenges of designing and running an RCT. Therefore, the justification for the number of participants is based on the number of subjects in a previous study entitled "Salivary levels of CGRP and VIP in rhinosinusitis and migraine patients" [71], with a population of 10 subjects (five controls and five patients), comparing the concentrations of CGRP and VIP in the collected saliva samples.

The subjects will be screened, checked for eligibility criteria, and recruited. Controls and individuals with AH will be paired in the best possible way concerning age and gender to compare data between the groups. Group 1 will consist of five healthy subjects who do not suffer from AH, and Group 2 will consist of five subjects with AH, who will be taking placebo and triptans.

The subjects will be recruited by advertisements at Aalborg University, on www.forsoegsperson.dk, www.forsog.dk, Facebook, and other relevant social media websites, and by relevant recruitment companies.

5.2.11 Treatment description

This is a randomized placebo-controlled double-blind trial that aims to investigate the possible effect of triptans on AH between two groups: healthy controls (who will not take any medicines) and AH sufferers (who will take placebo and triptans in a randomized blinded crossover manner).

5.2.12 Treatment materials

- Triptans: Either two tablets of eletriptan (40 mg) or two tablets of sumatriptan (50 mg), depending on the study clinician's assessment;
- Two placebo tablets for each subject with AH.

5.2.13 Outcome measures

The outcome measurement will be made clear by one of the trial coordinators. The baseline measurement will be taken, as well as follow-up measurements at specified intervals of time . The control and AH groups will undergo investigation for three and five sessions, respectively. The first session will take place at Aalborg University,

Denmark, and the subsequent sessions will involve saliva sampling by the subjects before, during, and after their flights.

5.2.14 Primary outcome measurements

- Pain intensity rated on a numeric rating scale (NRS; from 0; no pain, to 10; most pain imaginable);
- Description of the experience of AH, including pain quality, location, and spread (reported on a questionnaire with body charts and pain descriptors inspired by the short-form McGill Pain Questionnaire (SF-MPQ)).

In headache patients, the pain NRS is a simple and reliable measure of pain intensity [73]. Subjects are instructed on how to note their pain intensity on the VAS, which is presented in the questionnaire as a line with numbers from 0 to 10.

Clinical studies have extensively utilized the SF-MPQ as a well-validated measure [74]. The questionnaire includes descriptive words inspired by this form, consisting of sensory terms (e.g., sharp or stabbing) and affective terms (e.g., sickening or fearful). The questionnaire also includes standard human body charts for reporting of location and spread of pain.

5.2.15 Secondary outcome measurements

Salivary concentrations of the biofluid biomarkers CGRP and VIP will be measured. For saliva sampling, subjects will be given Salivette® kits. Each kit contains a piece of cotton wool that the subject must chew sufficiently until saliva is produced and it is soaked. Special containers for saliva sample tubes and return envelopes will be provided and complete instructions will be given to participants. ELISA kits for CGPR and VIP (purchased from Nordic BioSite) will be used for sample analysis.

5.2.16 Study timeline and participants' schedule

Group 1: Healthy subjects who do not suffer from AH.

This group will undergo three sessions, one screening session and two flight sessions (session 1 lasts 60 minutes and sessions 2 and 3 last for the duration of each flight) (see Figure 10).

	STUDY PERIOD				
	Enrollment	Intervention period			
TIMEPOINT	*Study entry*	*Flight 1*	*Flight 2*	*Flight 3*	*Flight 4*
ENROLLMENT:					
Eligibility screen	X				
Informed consent	X				
INTERVENTIONS:					
Control group (group 1): no pills		←	→		
AH group (group 2): placebo/triptans		←			→
ASSESSMENTS:					
Salivary CGRP		←			→
Salivary VIP		←			→
AH symptoms		←			→
AH pain score (NRS)		←			→

Figure 10: Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) flow diagram for enrollment, intervention, and assessment stages in the study. AH, airplane headache; CGRP, calcitonin gene-related peptide; VIP, vasoactive intestinal peptide; NRS, numeric rating scale. Group 1 will take two flights, and group 2 will take four flights in total. All assessments will be performed for all flights.

Session 1:

The subject will go to Aalborg University, where the investigator will perform screening and provide saliva sample tubes (Salivette®), two questionnaires to collect information about the experience of AH (e.g., pain quality, pain intensity, and location, onset, and duration of headache), and envelopes for the second and third sessions.

Sessions 2 and 3 (flight sessions):

- The subject will collect their saliva in the sample tubes before, during, and after a flight (for example, between Aalborg and Copenhagen).

- After the flight, the subject will fill out the questionnaire, including pain scoring based on $NRS_{0\text{-}10}$, where 0 is no pain and 10 is the worst imaginable pain. There is no continuous rating during the flight, but the subject will note the final pain score for the overall flight at the end.

- The subject will carefully pack the saliva samples in special containers and send them with the questionnaire to Aalborg University on the same day as the flight, or the investigator will pick up the samples and questionnaire at the airport.

Group 2: Subjects suffering from AH

This group will undergo five sessions (Figure 10).

Session 1:

The subject will go to Aalborg University, where the clinically responsible doctor will review the diagnostic criteria for AH and investigate whether the subject can take triptans. Then, the doctor will prescribe triptans for relief of AH for two flights. The subject will be given a total of four tablets, two of which are placebo and two triptans. The tablets will be placed in blinded coded tubes and the subject will not be able to tell the difference between them. This is done to optimize the study of the possible effect of triptans.

The investigator will provide saliva sample tubes (Salivette®), four questionnaires to collect information about the experience of AH (e.g., pain quality, pain intensity,

location, onset, and duration of headache), and envelopes for the second through fifth sessions.

Sessions 2–5 (flight sessions):

- The subject will take one tablet 30 minutes before the flight.
- The subject will collect their saliva in the sample tubes before, during, and after each flight. During the flight, the saliva sample is collected immediately after the headache begins. After each flight, the subject will fill out the questionnaire, which includes pain scoring based on $NRS_{0\text{-}10}$, where 0 is no pain and 10 is the worst imaginable pain. There is no continuous rating during the flight, but the subject will note the final pain score for the overall flight at the end.
- The subject will carefully pack the saliva samples in special containers and send them together with the questionnaire to Aalborg University on the same day as the flight, or the investigator will pick up the samples and questionnaire at the airport.
- Subjects will be instructed to separate their flights with intervals of 5-7 days.

Adherence to follow-up is a contributing factor for trial maintenance and on-time closure. Adherence reminders will be sent to participants by e-mail. In case of dropouts, new subjects will be recruited to maintain the numbers in the two groups. The reasons for withdrawal will be reported for each group.

Travel expenses will not be reimbursed for this study, and the participants will be notified of this in the trial announcement.

5.2.17 Biobanking

For each session in which a flight is included, each subject will submit three saliva samples of 3-5 mL before, during, and after the flight. In order to perform the ELISA analysis, saliva samples will be centrifuged, divided into smaller units such as Eppendorf tubes, and stored at -80°C in a research biobank. Saliva samples will be handled according to current standards and safety procedures for handling human saliva. The frozen saliva samples will be stored until a sufficient number of samples

is obtained to run the relevant analyses and will not be saved after the end of the experiment. All saliva samples will be anonymous and will only be stored with a marked number. Unused samples at the end of the study will be destroyed.

5.2.18 Risks, side effects, and harm

The most common side effects (1-10 %) with triptans are weakness, nausea, and fatigue, which are all temporary. Very rare side effects (0.01%) are liver problems, heart attack, arrhythmia, and double vision. The inclusion and exclusion criteria will be reviewed for each subject with the clinically responsible doctor, who will determine the dose of triptans depending on the subject to reduce the risk of rare side effects. If a subject experiences any rare side effects, they will be informed to contact the research group immediately, after which they will be withdrawn from the experiment. The side effects will be monitored by the investigators based on the information in the survey handed out to the subjects. It will be noted that triptans are safety-approved drugs for migraine patients in Denmark but will be used in this study to assess their effectiveness in relieving AH. Flight passengers have previously used triptans to relieve AH without side effects [1, 6].

There is no risk associated with collecting saliva in sample tubes from the subjects themselves. Subjects will remove a cotton swab from the Salivette® tube and chew it for 60 seconds to stimulate salivation, and then return the swab with the absorbed saliva in the tube.

All adverse events that occur during the study period will be recorded: at each contact with study participants, investigators will seek information on adverse events with specific questions and a verbal examination.

5.2.19 Procedures for recording adverse events

The trial will record adverse effects. Evidence of adverse events will be recorded on appropriate case report forms. The clinical course of each event will be followed until resolution, stabilization, or it is determined that participation in the study was not the cause.

Ongoing serious adverse events at the end of the study will be followed to determine the outcome. The following information will be recorded: description, date of onset and end, severity, assessment of relatedness to trial medication, and other suspected drugs or devices. Then action will be taken.

Regular monitoring will be performed according to Good Clinical Practice (GCP). Data will be evaluated for compliance with the protocol and accuracy concerning

source documents. Following written standard operating procedures, the monitors will verify that the trial is conducted, and data are generated, documented, and reported in compliance with the protocol.

5.2.20 Data handling and analysis

Data handling will be conducted in Excel 2016 (Microsoft Corp., Seattle, WA, USA). The researchers will remain blinded to the analyses.

Descriptive statistics, including mean, median, standard deviation (SD), and range for continuous variables, and number and percentage for categorical variables, will be obtained for the questionnaire's variables. Subscale (affective and sensory) and total scores will be computed for the pain descriptors, similar to what is performed for analysis of the SF-MPQ. The distribution of areas where the pain is felt will be measured by VistaMetrix (v. 1.38, Publisher: SkillCrest, LLC) and assessed for comparisons with a chi-square test.

To test whether the data follows a normal distribution, the Shapiro-Wilks test of normality will be used. Two-way repeated-measures ANOVA will be used to calculate any differences in the pain scores ($NRS_{0\text{-}10}$) and concentrations of CGRP and VIP between the control group and the AH group and between the subjects in the AH group.

Based on the normality test of the data, Pearson's or Spearman's correlation will be used to assess any potential correlation between the concentrations of CGRP and VIP and the parameters in the questionnaire, such as pain intensity on the NRS.

The level of significance will be set at $p < 0.05$. Data will be presented as mean ± SD (standard deviation) or median and interquartile.

Statistical calculations will be performed with SPSS version 28.0 (IBM Corp., Armonk, NY, USA).

5.2.21 Ethical considerations

The North Denmark Region Committee on Health Research Ethics has approved to carry out the study (approval number N-20160073). The study will be conducted according to the Helsinki Declaration. Subjects will give informed consent under the current legislation, which allows subjects to withdraw from an experiment at any time. The text and content of the consent form, the use of a biobank, the participant information sheet, and advertisements for recruitment of participants have been approved by the committee in addition to the scientific protocol.

The experiment is considered ethically acceptable, as triptans mainly have no or few mild transient side effects. Subjects with AH will benefit significantly from triptans if it is shown to prevent headaches. Therefore, the risk of mild side effects, which will be monitored by a pharmacovigilance (PVG) plan, can be offset by the knowledge the researchers gain by conducting the study. This knowledge can serve as one of the keystones in developing a formal treatment plan for AH.

There will be no direct benefits for participation. It is not possible to predict whether triptans will have an effect on all subjects or how long a possible effect will last, and the subjects will not be able to continue using triptans for their AH after the end of the experiment.

The inclusion and exclusion criteria will be reviewed for each subject with the clinically responsible doctor, who will determine the dose of triptans depending on the subject. Based on this, the use of triptans will be considered ethically accepTable and safe for the subjects.

The results of this study are expected to advance our understanding of the pathogenesis of AH and our ability to target it via a mechanism-based strategy and will thus be of benefit for flight passengers in the future.

The investigator will ensure that this trial is conducted following the principles of the Declaration of Helsinki. The protocol, site-specific informed consent forms (in the subject's speaking language), participant education and recruitment materials, and other requested documents (and any subsequent modifications) will also be reviewed and approved by the regional committee. The principal investigator will ensure that this trial is conducted in accordance with relevant regulations and with Good Clinical Practice. The principal investigator shall submit an annual safety report to the committee. In addition, an end-of-trial notification and a final report will be submitted. In order to have a qualified trial, it will be conducted based on the GCP guidelines, monitored by the GCP unit at Aarhus University Hospital and Aalborg University Hospital, and registered with the Danish Medicines Agency and the EU clinical trial register.

5.2.22 Protocol amendments

Any modifications to the protocol that could impact carrying out the study or potential benefits to participants that could affect their safety, including changes in study objectives, study design, patient population, sample size, study procedures, or significant administrative aspects will be communicated to the regional ethics committee for approval.

5.2.23 Informed consent

Written and verbal versions of the participant information and informed consent form will be presented to participants. They will be allowed as much time as they wish to consider the information and the opportunity to question the researchers before deciding whether they will participate in the trial. Written informed consent will then be obtained by means of dated signatures of the participant and the person who presented and obtained the consent. A copy of the signed informed consent will be given to the participant, and the original signed form will be retained at the trial site.

5.2.24 Confidentiality

The trial staff will ensure that participants' anonymity is maintained. The participants will be identified only by an ID number on all trial documents and in any electronic database. All documents will be stored securely and accessible only by trial staff and authorized personnel. The trial will comply with the Data Protection Act, which requires data to be anonymized. Source documents, i.e., case report form (CRF) entries, will be stored safely under confidential conditions.

6. DISCUSSION

6.1 PREVALENCE OF AH IN A STUDIED POPULATION IN DENMARK

The majority of the current literature is based on populations primarily from Southern European countries such as Italy, Greece, and Turkey [3]. Despite this fact, Dr. Federico Mainardi and his Italian colleagues have contributed the most to the current literature on AH, having contributed significant and important evidence to the clinical description of AH patients [4, 11, 20, 75-79]. As part of the Study 1 [3], Mainardi and his group described 230 AH patients out of 275 cases described in the AH literature in the period 2004 to 2017 [3]. In view of these findings, PhD fellow Sebastian Bao Dinh Bui was inspired by Dr. Federico Mainardi's studies and decided to investigate the prevalence of AH in a studied population in another geographic region. Study 2 [1] has been particularly interested in identifying the prevalence in a studied population of AH in Northern Europe, particularly in Denmark. In addition, it has been of interest to investigate how many flight passengers actually suffer from AH among healthy flight passengers. It has never been investigated previously, as we only know the number of cases described in the literature. If we combine the cases described in Study 1 with published literature in the period 2017-2022 (Table 3), 329 cases have been described until January 2022, but no other studies have examined the prevalence of AH among healthy flight passengers before Study 2 [1]. In Study 2, 21 flight passengers (8.3%) of the total studied population (254 subjects) met the criteria for AH [1]. It drew the attention to an estimation around a potential prevalence of 8.3% that needs confirmation in larger cohorts.

Data were collected via an online survey on Facebook using Danish airlines and headache organizations. The intention was to make the questionnaire as open and accessible as possible to all Danish passengers in order to achieve a representative sample. Furthermore, it is plausible that healthy travelers would not tend to answer questionnaires, in comparison to those who suffer from AH. Therefore, it could be speculated that a longer period for the questionnaire or greater involvement of the airlines would have made it possible to gather a larger population, but in Study 2, the largest airlines in Denmark, Scandinavian Airlines, Norwegian, and Thomas Cook Airlines Scandinavia were contacted but declined to help due to their own resource priorities. These airlines could have distributed the questionnaire online to reach many more travelers since they have many followers on Facebook and social media. Future studies may benefit from this approach, which allows for the inclusion of AH and healthy flight passengers. It provides an overview and insight into any differences that may exist between AH and healthy flight passengers, where it is possible to consider several factors such as biomarkers and comorbidities.

In IHS's ICDH-3 definition of AH, the result of Study 3, regarding 8.3 % of flight passengers being affected by AH, is referenced under the comment section [1]. The prevalence of AH among healthy flight passengers is an important aspect to consider in future studies, where the information may indicate the proportion of flight passengers who suffer from AH, especially when the number of cases of 329 does not indicate the extent of this problem. Nevertheless, there may be an unknown number of AH patients around the world who are not seeking medical attention for their AH. Consequently, the final inclusion of AH in ICHD-3 represents a significant recognition of the headache, which may eventually help to raise flight passengers' awareness of the condition.

The purpose of Study 2 was not only to investigate and describe the AH cases in a studied population in Denmark, but also to increase the general awareness of the status of AH in Denmark. All Danish media have covered the results from studies 2 and 3, through which knowledge has been disseminated across Denmark, but also internationally. Additionally, Sebastian Bao Dinh Bui has been invited to give lectures at science festivals as well as open universities (Folkeuniversitetet) annually, which reflects the high interest in AH in Denmark.

6.2 AH IN RELATION TO OTHER HEADACHES

There is no evidence that AH is linked to other types of headaches, although some AH patients have reported other types of headaches. HAH, migraines, and tension headaches (Table 3) are the most frequently reported types of headaches. The combined data from Study 1 [3] and from the literature published between 2017 and 2022 showed that 73 of the 329 AH patients had migraine, 27 had tension-type headaches, and 13 suffered from HAH (Table 3). Study 2 examined the prevalence of the mentioned headache types in healthy flight passengers, where the proportion revealed that 42 out of 233 healthy flight passengers suffered from HAH and 55 out of 233 flight passengers had migraines [1]. The inclusion of healthy flight passengers is important because it suggests that even if you suffer from headaches and/or migraines, it is not given that you will suffer from AH. A correlation between AH and migraine was not found in Study 2, but one was found between AH and HAH [1]. There is no evidence that AH and HAH are related in other AH studies, so it could be of interest to investigate their possible relation more.

Following the current discussion that pressure differences in the cabin during take-off and landing are the most likely causes of AH, a recent study has provided a summary of AH, migraine, HAH, and tension-type headaches [72]. The study indicates that these forms of headache are all affected by changes in atmospheric pressure [72]. According to a Japanese study, a decrease in atmospheric pressure in

the range 999-1013 hPa triggered migraine attacks in 25 out of 34 migraine patients, while 3 out of 28 tension headache patients experienced headaches when atmospheric pressure decreased in the range 1001-1007 hPa. [80]. In addition to this, the study by Maini et al. [72] referred to an Austrian study, which revealed that migraine attacks increased in frequency when atmospheric pressure was elevated as well [81]. When it comes to HAH, one of its criteria is an altitude of 2,500 meters [44]. An atmospheric pressure above 3,600 meters is 480 mmHg (0.6 bar) [82], which is considerably lower than the pressure in a passenger aircraft (846 hPa (0.8 bar)) [55]. However, it is not the altitude or the atmospheric pressure itself that triggers an AH attack, but the rapid pressure changes within the cabin. In fact, cabin pressure has been shown to vary by 8 hPa per 300 meters of altitude [55].

Although there are no direct links between AH and HAH, migraines, and tension-type headaches, it is interesting to note that all three are caused by changes in barometric pressure [72]. It should be noted that even if this is the case, the pressure changes during a flight are much faster than standing on a mountain or the ground when the weather changes [55, 80]. Further, migraine sufferers have also been able to distinguish migraine attacks from AH attacks, with the biggest difference being the duration, where migraine attacks can last between 4-72 hours, whereas AH attacks last within 30 minutes [44]. Despite the absence of an associated AH comorbidity, it may still be worthwhile to investigate this aspect in the future, as it may shed light on mechanisms at AH.

6.3 OTHER HEADACHES AS A CONSEQUENCE OF AH

Approximately four AH patients experienced a so-called second-stage headache after their AH attack, according to Study 1. Reviewing the literature for the period 2017-2022, showed an additional of four AH patients, making a total of eight AH patients out of 329 (Table 3). The symptom may not necessarily change our understanding of AH until now, but it might occur after an AH attack is over. It is known that migraines and cluster headaches are preceded by different phases, but also by phases following the attack. After a migraine attack, fatigue and loss of appetite may be experienced [83], while in the event of cluster headaches, mood changes, neck pain, and decreased energy may occur [84]. Currently, no one has reported similar symptoms following an AH attack, but eight AH patients have reported mild headaches. In the anecdotally documented case (see section 5.1 Anecdotal case of triptans used in Denmark), the patient experienced mild headaches after taking the flight. The patient's headache could be relieved with paracetamol, but previously it did not affect the AH attack. Future studies should specifically examine the phase after an attack of AH if it should be ensured that AH patients do not suffer from malaise following an attack.

6.4 STRESS, ANXIETY, AND CORTISOL – IS THERE A CONNECTION?

Study 3 examined cortisol levels among healthy air passengers by comparison with AH patients, a comparison that has never been performed before in the English based literature on AH [2, 3]. However, salivary cortisol is increasingly being used as a biomarker for stress and anxiety [85-87]. In previous research, it has been demonstrated that anxiety disorders are associated with elevated levels of cortisol [88], but these levels have not been measured during flights. The mechanism for elevated cortisol in AH patients is presently unclear, but it may result from the flight (lack of pressure equalization) or from the thought of having to travel and getting a headache along the way. The AH patient may be experiencing some kind of short-term anxiety during the flight and not an anxiety disorder. It can be speculated that the actual feeling of anxiety may differ from person to person, and that the body reacts physiologically differently. These differences can be seen as elevated cortisol levels in Study 3, where 1 out of 7 AH subjects experienced stress and 4 out of 7 AH subjects experienced anxiety [2].

An examination by Merz et al. [89] has found that students are experiencing short-term anxiety in the form of state anxiety when they are exposed to academic stress through an oral presentation. Specifically, saliva samples were collected before the presentation on control days and after the presentation on the presentation day, where state anxiety and cortisol were significantly higher after the presentations than during the control days [89].

In a recent study, Tammayan et al. [90] also measured cortisol levels in saliva before and after oral presentations in front of an audience in two different groups, those who would be presenting and those who would be part of the audience but would not be presenting. The cortisol levels of the two groups did not differ before the oral presentation, but afterward, the presenters had significantly higher cortisol levels than the control group due to the experience of stress related to the oral presentations [90]. According to Tammayan et al. [90], their findings are in accordance with the current literature on academic stress [90]. The Tammayan et al. study only collected saliva samples of cortisol before and after the oral presentation [90]; therefore, a sample collected during the presentation would have been interesting and could have correlated with the samples taken in Study 3 before, during, and after the flight [2]. However, the presentation group showed higher cortisol levels than the control group, while after the simulated flight, there was no significant difference in Study 3 [2, 90]. It could be speculated that the students exhibited elevated cortisol levels due to their desire to perform well, but also the stressful event, which may have explained the elevated level of cortisol when compared to the control group. AH features a different

scenario where it is not about performing well, but rather that the headache attack itself has triggered a stress reaction in the body with elevated cortisol levels, which had been significantly reduced after the simulated flight. There may have been some relief for the subjects as the flight and headache were now over.

Psychological influences are an important area to focus on since they influence the individual passenger's flight experience. Combining cortisol measurements and the presence of anxiety and stress can give insight into their well-being. Cortisol may not stand alone as a central cause of AH, but it is a consequence of AH. Passengers are aware that a headache will be encountered during the flight, but they may feel psychologically impacted by it since they will know they are in for very intense pain. A major psychological aspect has not been previously studied in AH studies, except for the Greek case report by Kararizou et al. [6]. However, in a recent study by Mainardi et al. [50] published in 2019, it was found that 25 out of the 34 AH patients in the study exhibited anxiety before the flight, and 2 out of 34 AH patients would not travel again due to fear of an AH attack. The AH area is still developing, and emphasis should be placed on the psychological aspect for the well-being of AH patients.

6.5 PAIN MEASUREMENT IN AH

As defined by the diagnostic criteria for AH, the headache pain is severe [44]. It is sometimes difficult to determine when pain is severe. There have been several AH studies that used pain scales in the form of the numeric rating scale (NRS), with a scale of 0-10, where 0 indicates no pain and 10 indicates the worst imaginable pain. Evans et al. [5] were the first to notice the pain intensity, and other studies have followed since then [3]. In Study 1, the most dominant pain range was 8-10 (0-10) for the pain intensity [3], whereas literature data from 2017-2022 indicated an average of 9.5 for the pain intensity (see Table 4). Additionally, Study 2 and Study 3 showed a dominant interval of 7-10 (0-10) on the scale [1, 2]. This could indicate that headache pain is categorized predominantly at the high end of the scale. Study 2 showed that 43% of the 21 AH patients experienced moderate pain [1], while Study 3 revealed that 2 out of 7 AH patients scored 3 on the scale (0-10), and 1 out of 7 AH patients scored 4 on the scale (0-10) [2]. Based on the severe pain criteria in AH [44], a score of 3-4 on the pain intensity scale (0-10) from Study 3 [2] and a moderate score on the pain intensity from Study 2 [1] may not fulfill the diagnostic criteria. If we take a closer look at the criteria for AH, we see that severe pain falls under point C, which is one of three criteria, at least two of which must be experienced in order for point C to be met. The concept of subjective experience is an important aspect since severe pain can be perceived as very painful by one patient while being perceived as mild by another [91].

As a preliminary consideration, most AH patients indicate their pain to be on the high end of the scale (see Table 4). Furthermore, further use of the NRS will be beneficial for maintaining diagnostic criteria for AH, which has appeared in some AH studies that have used the NRS [3]. If the NRS is compared with other scales for measuring the intensity of headache pain, such as a visual analog scale (VAS) or verbal rating scale (VRS), it is also the most preferred scale for measuring pain due to its ease of use and adjustment [73]. In order to develop a standard treatment for AH, the painful experience must be considered. It might not seem necessary or desirable for patients who experience mild AH attacks to seek treatment, but those who suffer a severe attack will do anything to alleviate their suffering. Additionally, this was observed in the anecdote about the patient (see section 5.1 Anecdotal case of triptans used in Denmark) who was willing to try a treatment based on Study 1, 2 and 3 [1-3]. Therefore, it would be a positive development if more future studies of AH would include NRS in their studies participating to an increased evidence base for the intensity of pain in AH and form a higher incentive to develop a treatment strategy.

6.6 IS AGE A RISK FACTOR OF AH?

The diagnostic age interval for Study 1-3 [1-3] and the literature from 2017-2022 is between 24 and 39 years (see Table 4) and for children, it is approximately 12-13 years (see Table 1). In the first instance, it appears very uncertain and all too early to identify a typical debut age for AH. AH usually occurs only in connection with the flight, so if you were to make your first flight as an 80-year-old and then develop AH on your first flight, the age of diagnosis would be 80 years old. This requires the 80-year-old patient to consult his general practitioner so that it can be registered, which applies to all patients with AH. It is possible that it may provide insight into when AH tends to occur and which age group is most susceptible, however, that will require the establishment of a national, and possibly a global registry of AH patients. In the current research literature, there are only 329 patients with AH, and perhaps there are more who have not been diagnosed, either because they are unaware that the condition exists. Currently, 19 children have been diagnosed with AH (see Table 1), but it is not known whether the number of children with AH is similar to the number of adults with AH. Data collection would require children and adults to visit the doctor for their AH in order to collect the necessary information regarding age. However, focusing on the nature of AH as a fundamental problem of pressure equalization, it may be suggested that age is irrelevant since it essentially depends on the first flight of a person's life and its subsequent development.

6.7 DIAGNOSTIC APPROACH TO AH

The results of neurological examinations performed days after the flight will not provide an accurate picture of the condition of the sinuses during the trip, especially if the concept that grade 1 sinus barotrauma is the most common cause of AH is followed, which may not show thickened mucous membranes in most cases [2, 3, 10, 92]. Therefore, an examination that can be conducted during a flight might be more appropriate. Study 3 demonstrated that saliva samples can shed light on the causes of AH. The method can also be used in the future to diagnose AH. AH is diagnosed based on the medical history according to the diagnostic criteria of IHS [3, 44]. Is it possible that doctors could complement their diagnosis with the addition of a biomarker test? The majority of neurological examinations have shown normal conditions in the overview in Study 1 [3], but the PGE_2 biomarker in Study 3 revealed that some kind of inflammation may occur as a result of an AH attack [2]. Saliva tests are easily accessible to passengers who can take them before, during, and after flights and receive a result immediately following the flight.

In Copenhagen Airport, for example, there is a medical clinic known as Airport Doctor, where various tests can be conducted in connection with flights and entry requirements for destination countries. This type of clinic will be able to receive the saliva samples and analyze them, which will be able to provide the results to the patient's own physician, which will serve as an additional component to the physician's medical records. As part of this setup, some kind of standard reference value must be defined with which the saliva samples can be compared. AH studies will be required over many years before reference values can begin to be observed. Nevertheless, it is worth mentioning that the necessary equipment and facilities are in place, which would enable AH to be investigated further, including the diagnosis and the subsequent treatment. By using a biomarker to diagnose AH, it is possible to monitor the course of the headache when we can target the treatment so that it targets the right mechanisms.

AH may be diagnosed using saliva samples at airports more as a "wishful thinking" scenario rather than a realistic scenario, since it requires that AH is prioritized in a society where resources are allocated for this purpose. The future studies on AH and the dissemination of information about AH can, however, be an invaluable step towards creating optimal conditions for diagnosis and treatment, even if they are small ones.

6.8 MECHANISTIC ASPECTS OF AH

Study 3 [2] is the first English study in the current AH literature to incorporate biomarkers in a pressure chamber to examine the mechanism physiologically. Study

3 presents support for the discussions about mechanisms regarding AH and opens the door to considering biomarkers in a broader context in future AH studies. Currently, no control group has been included in any AH literature. It is lacking to that extent, making it impossible to differentiate the AH group from the control group and identify the potential differences that can be investigated further.

A recent study from 2017 [93] examined approximately the same parameters as Study 3 [2]. In the study, only healthy volunteers were included, in which one group was the control group, living their normal day-to-day routine, while the other group underwent a simulated flight in a pressure chamber [93]. The study examined the parameters blood pressure, heart rate, interleukin-6, and SPO as “biomarkers” and no differences were observed in blood pressure, heart rate, or interleukin-6 levels between the control group and the pressure chamber group [93]. Similarly, no significant differences were observed in the blood pressure, pulse rate, and PGE_2 except for one pulse rate measurement that was lower in the AH group than the control group after the simulated flight [2]. The study conducted by University College London, however, took place both within and outside the pressure chamber, with only healthy subjects being used [93]. This is in contrast to Study 3, where both groups were examined in the pressure chamber, with AH and healthy subjects [2]. Nonetheless, by considering the healthy subjects, the studies can be beneficially compared with each other. The average pulse rate during the flight in Study 3 was 74.43 bpm (altitude: 2.4 km) [2], while the rate was 76.2 bpm (altitude: 2.4 km) in the study of University College London [93], which is approximately similar. University College London used interleukin-6 in their study because they wanted to examine whether some form of inflammatory response occurred during the simulated flight, which did not occur [93]. Interleukin-6 and PGE_2 are among the inflammatory substances that constitute the inflammatory response [94]. It can, however, be assumed that healthy individuals do not experience an inflammatory condition during a flight. This is also evident in Study 3, where reported PGE_2 levels for the control group were significantly lower than that of the AH group, and where the control group did not report headache or AH [2].

The final "biomarker" that was common to the two studies was oxygen saturation [2, 93]. It has been shown that oxygen saturation decreases by approximately 7% at 2.4 km altitude [93]. The average oxygen saturation level for the healthy subjects in Study 3 was 95.57 % (altitude: 2.4 km) [2]. The examination by University College London found that it was between 92% and 93% during the simulated flight at an altitude of 2.4 km [93]. Consequently, oxygen saturation can therefore be expected to decrease during a flight in healthy flight passengers without causing problems. The oxygen saturation level in the AH group during the flight in Study 3 was 91.85%, which was lower than in the AH group before and after the simulated flight [2]. The study by University College London has shown that of 5900 oxygen saturation

measurements, 268 measurements were between 79% and 89% without causing malaise, a finding that was also valid for subjects with cardiopulmonary diseases [93]. There may be no direct relationship between this and AH, where the oxygen saturation was 91.85% in Study 3 [2]. Alveolar oxygen tension decreases during flight [93], and consequently hypoxia may also occur [95, 96]. Furthermore, hypoxia can itself cause headaches in migraine and HAH patients [97]. Although Study 3 shows that oxygen saturation in the AH group is significantly lower during the simulated flight as compared to before and after the simulated flight [2], the evidence is too little to conclude whether hypoxia is the main cause of the AH. The current AH literature suggests that sinus barotrauma is more common due to the inability to equalize pressure than hypoxia.

The elevated PGE_2 levels found in the AH group in Study 3 may be indicative of an inflammatory condition occurring during an attack of AH [2]. It was previously demonstrated that the injection of PGE_2 caused headaches in healthy subjects [58], and that the presence of higher levels of PGE_2 caused headaches in AH patients compared to the control group in Study 3 [2]. PGE_2 has been shown to cause vasodilation of the cerebral arteries and consequent headaches in the study by Wienecke et al. [58], which could be corroborated by the thermal camera in Study 3 [2]. However, measurements of the facial skin temperatures showed no significant differences between the AH group and the control group or throughout the simulated flight (see Figure 9) [2]. Additionally, there is a huge amount of uncertainty associated with these thermal images, and it is not possible to determine whether there is vasodilation or not based on the images and the temperature measurements, but it is an interesting method to investigate further in future AH studies. Furthermore, it may be very beneficial to examine cerebral blood flow in an AH patient in a pressure chamber, which could indicate as to whether there is vasodilation during an AH attack, as occurred in the study by Wienecke et al. [58]. This should be compared with the level of PGE_2, since as Wienecke et al. point out that vasodilation alone cannot explain the cause of headaches, but the symptoms are due to activation and sensitization of the meningeal nociceptors [58].

According to a study by Funakubo et al., AH patients may be more susceptible to barometric pressure changes. A pressure chamber was used for experiments and the study included only healthy subjects [98]. In the pressure chamber, 3 out of 15 subjects developed mild to moderate headaches as the pressure was reduced by 0 hPa, 20 hPa (0.02 bar) and 40 hPa (0.04 bar) [98]. As a result, the pressure was lower than that in Study 3, which had a pressure of approximately 0.8 bar, as the purpose of the study was to mimic a flight [2]. There was only one headache subject who reported headache pain to be approximately 4 on the VAS (0-10), where 0 was no sensation and 10 was maximal sensation [98]. As compared to AH, the pain intensity was lower, with an NRS score in the dominant range of 7-10 (range: 0-10) [2, 98]. However, the basis for comparison is skewed, as only three of the healthy subjects experienced headaches, while seven AH patients experienced AH attacks [2, 98]. Biomarkers could be considered to be evaluated in the study by Funakubo et al. [98] as it seems reasonable to assume that a mild headache was not caused by sinus barotrauma as in AH [98]. Nevertheless, the potential and further development of the pressure chamber as an experimental model is quite intriguing, and it may be a pathway for further investigation of biomarkers for AH.

Mainardi et al. [4] has previously suggested that anatomical structure cannot stand alone as an explanation, but rather AH is the result of a combination of factors including environmental factors as well. This is an important point to consider, nevertheless, this study (Study 3) has not investigated whether the participants suffered headaches on every flight, as the main purpose was to investigate the mechanism [2]. It may nevertheless be interesting to examine the level of PGE_2 during all flights for AH patients to determine whether the level is normal during flights when the AH patients do not experience AH attacks. The results will then indicate whether there is a tendency for an inflammatory response. There is an obvious question of whether seven patients can confirm the mechanism of AH, as seven AH subjects is a very small number, but they have served as a pilot study that was necessary to initiate [2]. Based on the results of the pilot experiment, it indicates that an experimental model in the form of a pressure chamber can be used since it is the pressure itself that triggers the headache [2]. In this case, there are several parameters to consider, such as the design of the pressure chamber and its acoustics and comfort. It is possible to imagine a similar setup in the German study, in which they used a real plane as a pressure chamber [57].

As shown in Study 1 and the current literature (Table 4), AH attacks occur primarily during landing, despite the diagnostic criteria indicating that they can occur during takeoff or landing [44]. Further, the ICHD-3 also states that AH generally occurs during landing in approximately 90% of cases [44]. This may well make sense if we focus on sinus barotrauma as the underlying mechanism [2]. It is known that earplugs are used on airplanes when they take off or land. It is often during landing that earplugs are received, however, this can be alleviated by chewing gum or making swallowing movements [99-102]. The purpose of this is to keep the Eustachian tube open in order to equalize pressure in the ears [99]. Similarly, it would be ideal if the same principle applied to our sinuses, but this is not possible. It could be speculated that the sinus openings are passively open during takeoff as the Eustachian tube, as the symptoms for ear problems related to pressure changes are more dominant during the landing phases compared to the take-off phases [100]. The sinuses need to be actively opened upon landing, just as the eustatic tube must be actively kept open upon landing. As an active opening of the sinus ostia is not possible, AH patients with a narrow structure will be unable to equalize pressure changes, which will result in tissue damage. Despite this, some patients with AH also experience symptoms during take-off. Therefore it would not be fair to state only the landing phase as an onset symptom in the diagnostic criteria for AH, which is not the case since both phases are included in the ICHD-3 [44]. However, it provides an interesting opportunity to focus on the landing phase in future AH studies.

Mainardi et al. have already initiated an interesting and relevant discussion regarding descent in their brief communication regarding their 36-year-old female patient who experienced headaches while driving down a mountain [20]. The headache was described as a mountain descending headache (MDH), and it had approximately the same symptoms as AH [20]. It was discussed by Mainardi et al. that both AH and MDH are induced by a rapid descent, which is caused by a pressure imbalance between the sinuses and the ambient pressure [20]. In comparison, the descent from a mountain in a car is much slower than that of an airplane, which is considerably quicker. It is possible to reduce the speed of the car to the point where MDH can be avoided partially, which is impossible in an airplane [20]. Assuming that AH and MDH share the same mechanism, it is reasonable to assume that AH patients will also experience MDH. One of Dr. Federico Mainardi's other studies found that 8 out of 85 AH patients experienced headaches when they were driving down a mountain [4]. The descent alone may cause both types of headaches in a subset of patients suffering from AH. In their brief communication, Mainardi et al. emphasize that anatomical variations in the ethmoid sinuses cannot stand alone as the primary cause of AH, since not all AH patients experience AH attacks on each flight [20]. According to the current literature [3], it has not been studied whether all AH patients experience AH when flying, which could be a focus point of future AH studies. In spite of the absence of sufficient evidence at present, a possible association between

non-narrowed sinuses and headache pain triggered by barometric pressure has been demonstrated.

In a study by Laury et al. [103], it was shown that dilation of the sinus ostia reduced headache pain in patients with sinus pressure headaches during barometric pressure changes, but no research has been conducted on whether opening the sinus ostia will have any effect on headache pain for patients with AH. Even though the results are still speculative, it is interesting that the method appears to have reduced headache pain for some patients with sinus pressure headaches [103]. However, this might be an overly violent intervention for patients with AH-considering that triptans have been able to prevent AH completely in most cases [3]. Furthermore, the potential benefits of triptans will outweigh the interventions of balloon dilation of sinus ostia, which will only reduce headache pain, but it is still an interesting method to consider in future studies of AH to present several possible treatment options.

In summary, studies 1-4 attempted to offer an overall proposal for diagnosis, mechanism, and treatment within the AH literature (see Figure 11). In particular, the mechanism and the treatment are interconnected, since the treatment can only be strategically developed if the mechanism has been mapped. Study 3 showed an increase of PGE_2 levels during an AH attack in comparison to healthy flight passengers. This might be correlated with inflammation that may be caused by a lack of pressure equalization and subsequent sinus barotrauma due to AH attacks [2]. Other biomarkers of inflammation may also be investigated in future AH studies, such as other prostaglandins and interleukin, which also play a role during inflammation [104]. Furthermore, psychological factors were also addressed in Study 3, where elevated levels of cortisol were found in the AH patients compared to the healthy passengers. Considering that lysozyme and melatonin have previously been used as biomarkers in stress and depression [85], further investigation into this aspect would be interesting in future AH studies. In general, treatment of AH is not necessarily limited to triptans, since the actual effect of triptans is not yet known, but this study may serve as motivation for other AH researchers to conduct RCTs within various treatment options. A prospective study should examine the effect of NSAIDs in larger RCTs and investigate whether neuro stimulation may be effective in reducing or eliminating the pain in AH, recognizing the importance of offering a variety of treatment options.

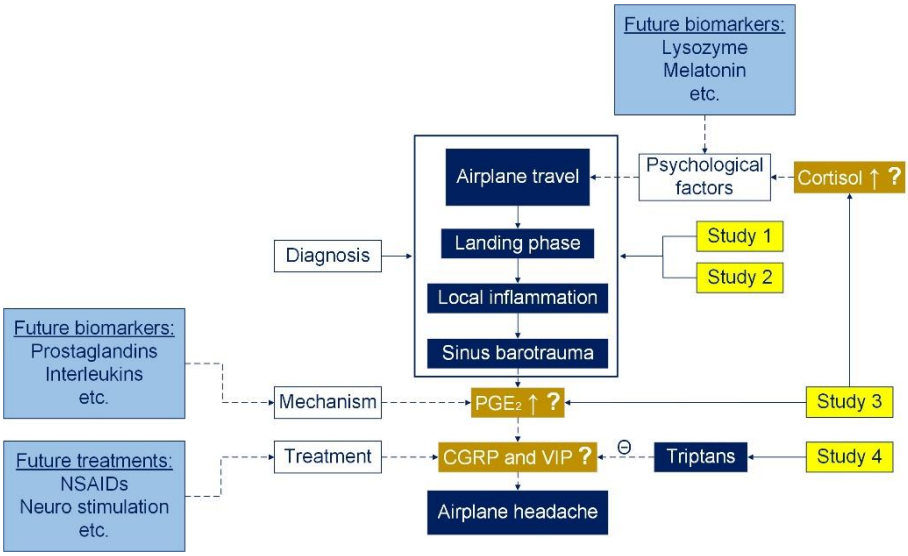


Figure 11: Overview of the AH mechanism based on Study 1, Study 2, Study 3 and Study 4 in this dissertation. NSAIDs: non-steroidal anti-inflammatory drugs. CGRP: calcitonin gene-related peptide. PGE_2: Prostaglandin E_2.

6.9 THE IMPORTANCE OF RCT FOR TREATMENT STUDIES

As a part of Study 4, a feasibility study is being prepared to examine the effectiveness of triptan for AH through a randomized controlled trial with double-blinding. Evidence-based research is required to provide qualified data that can guide the design of large RCTs. Qualified evidence then forms the basis for clinical practice recommendations. With AH, only scattered and anecdotal case studies currently exist that collectively point to potential beneficial effects of triptans. However, triptans are not approved for this kind of headache, and large RCTs are required to provide sufficient data. This small trial was considered to investigate the feasibility and adjust the study outcomes at one step before conducting a large multicenter RCT on the use of triptans in AH. Practical issues of this pilot study, from patient recruitment to selection of triptan preparations for intervention, blinding and randomization processes, and primary and secondary outcome measures, will help identify the limitations and strengths of the protocol and provide guidance for adjusting the protocol with proper changes. The available studies, based on cases of triptan use for AH, are not comparable due to different methodologies and measures applied. Therefore, there is a need for a standard and transparent protocol to follow to measure the efficacy and safety of triptan for use in AH. In addition, studying the underlying mechanism of AH and how triptans can target it is of great value.

Even though almost all patient cases in the literature are presented with effective relief of pain following the use of triptans, there has not yet been a clinical study comparing the use of triptans with placebo or considering accompanying biomarkers such as CGRP or VIP. It is hypothesized that if there was a common cascade of events that promoted attacks of migraine or AH, e.g., neurogenic inflammation or trigeminal nerve sensitization, this could help explain why triptans are beneficial in both migraine and AH. Biomarkers were limited to a few key substances to study the potential underlying mechanisms of effects. Future studies could expand the biomarker range, specifically considering other potential drugs for pain relief in AH, such as NSAIDs. This is based on the fact that prostaglandin E_2 (PGE_2) is increased during an AH attack and the observation that AH patients have used NSAIDs with soothing effects. A further investigation of PGE_2 and NSAIDs would have been obvious. However, it has not been the focus of this dissertation due to the current four-year follow-up period on triptans in the Turkish study [25]. It is possible that NSAIDs could have been included in Study 4 if there had been a longer follow-up period in the AH literature [3]. NSAIDs and CGRP may be examined as part of future RCTs in order to assess their potential effects. Considering that CGRP is released and regulated by PGE_2 [58, 105] and that triptans have a soothing effect on AH, there is a need to investigate whether CGRP plays a role in AH. Can CGRP or PGE_2 be the primary causes of the headache, or do both of these substances interact to cause it? We are unable to answer this question since there have been no studies conducted in this area to shed further light on the subject. The biological effect triptans have on AH is still unknown, which applies also to NSAIDs, but Study 4 may be the first step in describing the effect of triptans.

Collectively, we believe that the protocol offers several strong points in terms of its design, including that it is randomized, controlled, and blinded, with a parallel arm and measurement of both objective and subjective markers for the efficacy of triptans against pain. However, there are limitations and challenges in the design and implementation of the study. Depending on the results of this pilot study, the sample size could be justified and adjusted accordingly for the larger RCT. Practical issues may arise when collecting and storing saliva samples from subjects after their flight sessions, depending on where they are departing from. The flight characteristics are factors that could influence the findings. The current literature indicates that the length of the flight does not have an impact on the development of AH. However, for future studies, travel within or outside Europe might be considered.

It is worth mentioning that Study 4 follows a protocol based on actual flights. The use of experimental models can be used to provoke AH; however, it is also interesting to investigate how AH develops during real flights. It is possible that Study 4 could also be conducted in pressure chambers, however, real flights provide other clinical aspects in real-time, such as psychological effects. A small pressure chamber may

cause some people to feel claustrophobic, but this can be compensated with a real plane on the ground [57].

Due to the COVID-19 pandemic, and ban of traveling for a long time, Study 4 could not be completed within time-frame for this dissertation. In addition, collecting saliva samples after a flight, would have increased risk of infection at the airport because of the large number of travelers from all over the world for the PhD fellow (Sebastian Bao Dinh Bui), who would be collecting the samples. Study 4 is intended therefore to be published as a study protocol, which is an accepted practice for randomized controlled trials. For instance BMC public health has stated clearly that "*BMC believes that publishing Study protocols will help to improve the standard of medical research"* [106].The purpose of this protocol is to motivate and encourage other researchers to conduct clinical trials using triptans. There is a clear emphasis that triptans should not be the only treatment option, as patients with cardiovascular problems may not be able to use them; instead, triptans should be one of the possible treatments. In regards to COVID-19, RCTs have been essential when it comes to developing and testing vaccines against the disease, for example, the vaccines developed by Pfizer and Moderna [107-109]. Even though AH and COVID-19 can never be compared, neither pathophysiologically nor in terms of mortality [110-112], it is more the principle that RCTs conducted within AH are crucial for developing an effective treatment strategy. It will be a crucial step towards providing treatment options based on a high level of evidence if we can conduct a sufficient number of randomized controlled trials. In the future, it may also be possible to develop a drug that will specifically prevent AH, so that triptans will no longer be necessary. There are currently motion sickness pills that can be purchased over the counter in pharmacies and airports. In the future, maybe it will be possible to purchase AH pills over the counter. The treatment of AH may not be sufficient to solve the problem of pressure equalization in the sinuses if we maintain this as the general understanding of the mechanism [3]. This treatment will, nevertheless, treat the AH, but the underlying trauma related to the sinuses will persist, but for the individual, it will overall be a significant improvement when it comes to flight travel.

Additional quantitative outcome evaluation might be considered in a larger RCT to further clarify the effects or to assess participants with AH. The follow-up period might also need to be adjusted, but this might lead to some attrition in terms of participation. Last but not least, with the pandemic situation and its impact on traveling, in addition to the changes taking place around the globe in re-thinking the flight industry, and global climate changes, it is not clear if substantial changes will be required for studies within the AH domain in general. However, from a scientific and clinical perspective, the research question of whether and how triptans can target AH pathogenesis to reduce head pain remains valid.

7. FUTURE PERSPECTIVES

In the form of a three-stage rocket, this dissertation provides an overview and new knowledge in three distinct stages: 1) diagnosis, 2) mechanism, and 3) treatment (see Figure 11). Studies 1 and 2 provide a comprehensive overview of the AH symptoms related to diagnosis and prevalence in a studied population in Denmark and worldwide, as well as among healthy flight passengers. Study 3 focused on the mechanism, where the most important findings were that AH patients have elevated blood levels of PGE_2 and cortisol during AH attacks compared to healthy subjects. Because PGE_2 is believed to be triggered by sinus barotrauma, this provided fertile ground for Study 4, which is investigating the possible soothing effect of triptans on AH, possibly utilizing CGRP or VIP as potential biomarkers in future studies. Thus, studies 1-4 address all aspects of AH, and studies 4, in particular, may provide benefits for AH patients if AH researchers can move beyond the current studies. AH research will be important in the future for several target groups:

1. **AH researchers**: In future studies, researchers in AH may focus on various aspects, which may be psychological or physiological in nature. Based on Study 4, several RCTs can be conducted in order to develop a treatment strategy.
2. **AH patients**: AH patients have a bright future ahead of them, since the foundations of AH research are being established now. It is important to keep in mind that triptans should not necessarily be the only treatment option, but they should be included among other options. There is also the possibility that another medication will be developed for AH. Some patients may also not want treatment due to the short duration of AH, but would prefer to have certainty of their AH attacks, which is now possible for them.
3. **Clinicians**: Clinicians will be able to gain a deeper understanding and be prepared if AH patients attend the clinic. The diagnosis of AH can be performed according to the diagnostic criteria established by IHS and possibly Study 1 to complete an overall assessment. This could be beneficial for the clinicians, as well as for the patients if they experience AH while flying.
4. **Airline companies**: If AH patients are discouraged from seeking treatment in connection with their flights, then it is reasonable to think that some passengers will not feel comfortable traveling on an airplane. Consequently, airlines also have an interest in providing passengers with a comfortable travel experience. This could be provided in the form of offering water on board, cabin pressure, noise cancellation, and new improved comfortable seats, so that position and posture of passengers can be adjusted and helpful to reduce the risk of headache development. In addition, if AH researchers can develop a treatment that can be bought at the airport, similar to the

medicine for motion sickness, we will create a more comfortable travel environment for AH passengers in this segment.

5. **Society**: A media campaign has generally proven to be an effective way of raising awareness for a specific issue. It has also been the case here in Denmark, where most Danes are now familiar with AH because almost all Danish media outlets have reported the results of this dissertation. Furthermore, it has been able to create international awareness among researchers, academics, and citizens interested in finding out more about AH. The results of this dissertation have been reported in the "Oxford Textbook of Headache Syndromes", published by Oxford University [113], as well as "Case Studies in Uncommon Headache Disorders", published by Ambar Chakravarty [114]. It may be the beginning of creating international awareness of AH in other media around the world, where ordinary citizens, as well as healthy passengers, will gain an understanding of this headache.

8. CONCLUSION

Based on three different methods applied in this PhD dissertation: systematic review, online survey, qualitative study + research-based study (simulation), and treatment strategy (triptans), it was found that preclinical biomarkers such as PGE_2 can be used to indicate a barosinusitis condition that is influenced by inflammation. The use of pressure chambers appears to be a valid experimental model for the investigation of both mechanism and treatment options, where for example triptans can be evaluated in interaction with selected biomarkers in the future. This dissertation also incorporates a unique methodological combination, where psychological aspects are combined with cortisol samples from saliva, a measure of well-being that has never before been measured in AH patients. The results and methods in this dissertation have raised awareness about AH, especially in Denmark, as more Danish flight passengers have become familiar with AH. There exist several medical and lay websites in Denmark and outside Denmark that discuss AH and refer to the PhD studies in this dissertation. Danish citizens are provided with an easy and accessible method of obtaining scientific information, which is important to the advancement of the AH research field. In addition, the dissertation indicates that the area of AH is still relatively underexamined, and that the publication of this dissertation will encourage further AH research being conducted in the future, preferably in conjunction with experimental studies and RCTs in order to develop future treatment strategies. It may be possible to accomplish this through collaboration between AH researchers across the world, whereby a multi-center survey may be conducted across Europe and outside of Europe. The Italian study by the group Mainardi et al. [50] has performed a multi-center study in Italy, which highlights the possibility for international studies that could contribute with knowledge from different parts of the world to the AH literature.

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