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Symptomschwere, Rhinitis-bezogene Lebensqualität sowie expositionsrelevantes Verhalten bei Gräserpollenallergikern in einer Allergie-App-Studie

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DEDICATION

The dissertation is dedicated to my parents who always provided me with unconditional support without any exceptions.

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1 INTRODUCTION

1.1 POLLEN ALLERGY AND ALLERGIC RHINITIS – AN OVERVIEW

Pollen allergies represent one of the most common non-communicable diseases with an estimated prevalence of up to 40% in Europe (D'Amato et al., 2007). Due to rapid urbanization, spreading westernized lifestyle, increasing air pollution (Pawankar et al., 2013) and climate change-associated factors, the global prevalence is observed to be on the rise (Beggs, 2015). Discussed factors caused by climate change and escalating environmental pollution to contribute to this upward trend are changes in the physiology of allergenic plants, such as increased biomass production, prolonged growth- and flowering phases, enhanced anthesis, and increasing allergenicity (Beggs, 2015; Obersteiner et al., 2016; Rauer et al., 2021; Traidl-Hoffmann, 2017; Zhao et al., 2017; Zhao et al., 2016). Moreover, stratospheric ozone concentrations seem to play a role as it was found that high ozone-exposed birch trees show an increased pollen allergenicity to low ozone-exposed trees (Beck et al., 2013). However, the composition of pollen released into the atmosphere is strongly influenced by the geographic location and its according climate and vegetation (D'Amato et al., 2007). Even within the same bioclimatic region, the pollen count depends on various factors and is subject to strong fluctuations. For instance, in rural areas, pollen levels reach their peak during dawn, whereas in urban areas, they are comparatively higher in the evening (Trautmann, 2022).

In central Europe common pollen producing plants are sweet grass (Poaceae), birch (Betula verrucosa), alder (Alnus glutinosa) and hazel (Corylus avellana) (Trautmann, 2022). Grass pollen stand out as one of the most common allergens causing seasonal allergies globally, with its impact varying across different regions. Especially in Europe and North America grass pollen allergy represents the predominant form of pollen allergy (D'Amato et al., 2007; Garcia-Mozo, 2017). The high prevalence of sensitization to grass pollen seems to be related to the extensive presence of grass land, which is estimated to cover approximately 40.5% of the earth's surface. Further, grasslands are predominantly inhabited by Poaceae, which constitute the fourth largest plant family (Gibson, 2009). In Germany, the most prevalent allergen sensitization among adults is against timothy grass (a grass of the Poaceae family), showing a prevalence of 18.1%. This is closely followed by sensitizations against birch pollen and wasp venom, each with an estimated prevalence of 17.4%. Other highly prevalent sensitizations against pollen allergens were indicated to be rye (16.8%), alder (16.5%) and hazel (16.2%). Sensitizations against grass pollen were overall reported to be higher in males (22.0%) compared to females (16.9%), highest among individuals aged 18 to 29, declining with

increasing age, and sensitization increases with socioeconomic status (Haftenberger et al., 2013).

Pollen allergens are also the most common trigger of allergic respiratory diseases (Bergmann et al., 2023). The major clinical manifestation is the allergic rhinitis (AR), also known as hay fever, which affects an estimated 400 million people globally and shows an increasing trend. In Europe the prevalence of AR was estimated to range from 4% to 32% (Pawankar et al., 2013). However, the prevalence of AR highly varies between countries, depending on the geographical region and economy, among other factors. It was reported as one of the most frequent chronic medical conditions in high-income countries, showing a prevalence of up to 50% in specific areas of the world (P. J. Bousquet et al., 2008). Low-income and middle-income countries experience a comparatively low prevalence of AR, although the numbers are also gradually increasing in these areas as well (Bousquet et al., 2020). In Germany, the lifetime prevalence of AR was shown to be 16.5% for women and 13.0% for men in the DEGS1 study, which was conducted by the Robert-Koch-Institute from 2008 – 2011. According to this publication, AR is the most common allergic disease in Germany, showing the highest lifetime prevalence among all allergy-spectrum diseases (Asthma: 5.0%, Atopic Dermatitis: 2.2%, Urticaria: 1.2%, Contact Dermatitis: 2.8%, Food Allergy: 2.5%, Insect Sting Allergy: 0.5%). Allergic diseases overall were reported with a lifetime prevalence of 30.0%. Higher prevalence was observed with increasing social status, in urban areas compared to rural areas, and in females (35.8%) compared to males (24.1%). The highest lifetime prevalence (42.2%) was found among individuals aged 40 to 49, the lowest prevalence (25.8%) among individuals aged 70 to 79 (Langen et al., 2013).

1.2 ETIOLOGY AND PATHOPHYSIOLOGY OF ALLERGIC RHINITIS

Bousquet et. al and the World Allergy Organization (WAO) defined AR as “a symptomatic disorder of the nose induced by an IgE-mediated inflammation after allergen exposure of the membranes lining the nose” (Bousquet et al., 2001). Due to the novel insights in the immunology of allergies a new nomenclature for allergic diseases was recently proposed by the European Academy of Allergy & Clinical Immunology (EAACI) that classifies IgE-mediated AR into a type 1 immediate antibody-mediated hypersensitivity reaction (Jutel et al., 2023).

Depending on the timing and duration of the symptoms, AR can be categorized into seasonal and perennial AR. Typical triggers of the seasonal AR are grass pollen (typical season in central Europe from Mai until August) and tree pollen (January until May), whereas perennial AR is

mostly caused by house dust mites or constant exposure to animal dander. AR can be further classified into episodic AR (i.e. temporary exposure to animal hair) and occupational AR (i.e. grain dust) (Trautmann, 2022). Known risk factors for developing AR are a positive family history of atopic diseases, a higher socio-economic status, elevated levels of total serum IgE before the age of six, and the presence of positive immediate-type hypersensitivity skin test results (Pawankar et al., 2013). However, AR is a multifactorial disease, and whether an individual develops an AR appears to be largely determined by gene–environment interactions (J. Bousquet et al., 2008). These are a complex interplay of environmental factors, which can be either harmful or protective, and the predisposing or protective genetic background of the individual. Environmental factors like chronic exposure to inhalant pollutants, an unhealthy life-style (e. g. a diet poor in plant fibers or short-chain fatty acids, a lack of physical exercise, etc.) or chronic psychosocial stress can increase the susceptibility to allergic diseases via inducing epigenetic changes in one or multiple genes involved in innate immunity or immune regulation (Gilles et al., 2018). This epigenetic priming may already happen in utero (Lockett et al., 2015) and the sensitive phase continues throughout infancy and early childhood (Mohamad Zainal et al., 2022). The notion of environmental and host-derived microbes influencing the risk of developing an allergy is now known in the field as the so-called “hygiene hypothesis”. The scientific concept of the “hygiene hypothesis” is often erroneously associated with a harmful effect of increased communal or personal hygiene on the development of allergies (Gilles et al., 2018). The hygiene hypothesis will be addressed further in *Chapter 1.6.4 Protective Factors*.

The underlying pathophysiology of an allergic immune response that causes AR falls in two major phases: The sensitization phase and the effector phase. The sensitization can be seen as the initial and necessary, but not sufficient step required for developing an allergy. In brief, allergic sensitization is mediated by an innate immune response to a harmless antigen that leads to a production of antigen-specific IgE (sIgE) against the then so-called allergen. More specifically, the innate immune response is initiated by dendritic cells which absorb the antigen, typically proteins of common allergen sources such as pollen, in the mucosal tissue of the airways, skin or intestine. The dendritic cell then migrates to the draining lymph node presenting the antigen-derived peptides to naïve CD4+ T cells in the context of MCH II molecules. In combination with the major type 2 cytokine interleukin-4 (IL-4), this induces the differentiation of B cells to plasma cells that eventually produce sIgE antibodies, which bind to the high affinity FcεRI receptor on mast cells. This completes the sensitization process (Abul K. Abbas, 2022; Bousquet et al., 2020; Kenneth Murphy, 2018; Palomares et al., 2017; Trautmann, 2022). The sensitization phase is typically asymptomatic and can occur repeatedly against

various substances during a lifetime (Bousquet et al., 2020; Trautmann, 2022). At this point it is important to emphasize that a sensitization can, but does not necessarily have to lead to an allergic reaction (Trautmann, 2022). To provide a clear differentiation of terms, an allergy can be described as a sensitization combined with the presence of clinically significant symptoms induced by exposure to the specific allergen (Ansotegui et al., 2020). Possible risk factors that may misguide the immune system and induce a sensitization in the individual are certain genotypes, and also environmental factors such as air pollution or tobacco smoke (Trautmann, 2022). Also, factors linked to lifestyle (lack of physical exercise) and exposure to a reduced diversity of environmental and host microbes (due to nutrition behavior, antibiotic exposure etc.) are discussed (Gilles et al., 2018).

The second phase of the allergic immune response is the effector phase, which can only occur after a prior sensitization. It is characterized by an IgE-mediated Type 1 hypersensitivity reaction, which may be caused by the renewed exposure to an allergen in the sensitized individual. The allergen exposure leads to the binding of the allergens to the sIgE-antibodies on the surface of mast cells, which are abundantly present in the nasal mucosa. This causes a cross-linking of the FcεRI-receptor which leads to an activation and degranulation of mast cells triggering the release of inflammatory mediators, such as histamines, leukotrienes, and proteases, causing inflammation, an activation of mucosal glands, vasodilatation, and increased permeability of blood vessels as well as nerval irritation (Bousquet et al., 2020; Traidl-Hoffmann et al., 2022; Trautmann, 2022).

1.3 CLINICAL MANIFESTATION OF ALLERGIC RHINITIS

Due to the above-mentioned pathophysiological changes, AR typically causes acute symptoms like rhinorrhea, sneezing, itchy nose, tingling and postnasal drip. Besides the immediate hypersensitivity reaction, AR also shows a late-phase response, which occurs after several hours and is mediated by a cellular inflammation reaction involving eosinophils, neutrophils, T-Lymphocytes, and macrophages. This causes an inflammatory nasal oedema resulting in nasal congestion as a leading symptom (Bousquet et al., 2020; Traidl-Hoffmann et al., 2022; Trautmann, 2022).

In addition to the nasal symptoms, AR is very often associated with allergic conjunctivitis (AC) (Trautmann, 2022). The combination of both, AR, and AC, is known as allergic

rhinoconjunctivitis (ARC). In patients with AR caused by pollen, approximately 70% suffer from conjunctivitis and about 50% of those are patients suffering from perennial rhinitis (Scadding et al., 2011). Typical symptoms that occur within this condition are itchy, red and swollen eyes as well as increased tear flow (Trautmann, 2022). Ocular symptoms also correlate with the severity of nasal symptoms. Further, epidemiological studies have indicated that ocular symptoms are more prevalent in patients who are polysensitized, regardless of whether they have asthma or not (Bousquet et al., 2020).

AR also frequently co-occurs with asthma and is a known risk factor to develop an asthmatic condition. Chances for patients suffering from AR are approximately three times higher to develop an asthmatic condition. Leading symptoms that occur in patients suffering from asthma are recurring dyspnea, dry cough, wheezing and chest pain (Trautmann, 2022). There appears to be a higher prevalence and greater severity of bronchial hyperreactivity in patients suffering from perennial AR, compared to patients suffering from seasonal AR (Verdiani et al., 1990). The link between asthma and AR can in part be attributed to a common genetic basis (Ferreira et al., 2017). However, AR without asthma and AR associated with asthma appear to have different genetic causes (Bousquet et al., 2020; Lemonnier et al., 2020).
Other comorbidities that can co-occur with AR are sinusitis, impairment of sleep and concentration, hyposmia, hypogeusia, hypoacusis, headaches, as well as atopic eczema (Trautmann, 2022). Headaches were identified as particularly troublesome among adults and children affected by AR (Meltzer, 2016). In addition, AR patients reported an increased overall and mental fatigue, as well as a decrease in motivation and pleasure to engage in activities. However no notable increase in physical fatigue or increased anxiety could be observed in the same study (Marshall et al., 2002).
Further studies also list increased occurrence of gastrointestinal symptoms (Powell et al., 2007) and associations of AR with thromboembolic disease during pregnancy (Wu et al., 2022).

1.4 IMPAIRMENT OF QUALITY OF LIFE AND ECONOMIC BURDEN

AR, in comparison to other diseases, is often perceived as a harmless condition by those affected, primarily because it is not usually linked to substantial mortality. However, due to the wide range of symptoms and comorbidities that can occur, it significantly impairs quality of life (QOL) in many patients (Brożek et al., 2017). Main reasons for this were reported to be e. g. limitations in activities and social interactions, sleep disorders, impaired cognitive function, as

well as fatigue. AR is also associated with reduced efficiency at home, work, and school (J. Bousquet et al., 2008; Bousquet et al., 2001; Brożek et al., 2017; Meltzer, 2001). AR was even linked to a higher decrease in work productivity (26.6%) than hypertension (8.8%) and Diabetes mellitus type II (16.7%) (de la Hoz Caballer et al., 2012). Additionally, it was shown that QOL is influenced by both, severity and duration of AR (Bousquet et al., 2012), with studies indicating a stronger impact of the severity compared to the duration on QOL (Bousquet et al., 2006). Regarding the symptom qualities, ocular symptoms appeared to have a stronger impact on QOL compared to nasal obstruction and nasal pruritus. Sneezing and rhinorrhea did not show effects on QOL (Bousquet et al., 2012).

The resulting economic ramifications of AR are often underestimated, primarily due to the indirect costs associated with the disease. These were shown to account for approximately 76% of the total costs, most of it caused by presenteeism. The total costs were also associated with the severity of AR but were not higher for patients suffering from AR and asthma (Colás et al., 2017). A systematic review supports this, demonstrating that indirect costs represent the major part of the total costs (76% to 93%) and that these are mostly impacted by presenteeism compared to minimal impact caused by absenteeism (Vandenplas et al., 2018). Overall, allergic diseases are estimated to impose an indirect financial burden ranging from €55 billion to €151 billion per year solely within the European Union. It is also estimated that the costs of an adequately treated AR amount to merely 5% of the expenses associated with the untreated condition (Zuberbier et al., 2014).

1.5 DIAGNOSTICS

The anamnesis of the patient plays a pivotal role in the diagnosis of AR and is more important than any other diagnostic tool. The clinical definition of symptoms characteristic for AR is indicated as experiencing at least two of the following symptoms for more than one hour per day and on most days during the relevant season: rhinorrhea, sneezing, nasal congestion, nasal pruritus, with or without symptoms of conjunctivitis. A positive family history regarding allergic diseases or atopy may also suggest an allergic genesis of a rhinitis (Scadding et al., 2011). The physical examination of the patient is another key part of the diagnostic process. It can be helpful to confirm the suspected diagnosis but may also uncover comorbidities such as atopic dermatitis and asthma. In patients experiencing moderate or severe AR, a nasal examination screening for polyps, tumors, bleeding, crusting or foreign bodies is also recommended (Bousquet et al., 2020).

Whether further diagnostic testing is necessary for patients with a clear medical history, i.e. to confirm IgE mediated sensitization with a skin prick test (SPT) or an *in vitro* diagnostic, remains a subject of ongoing debate among physicians (Bousquet et al., 2020). However, the clinical history, combined with the sensitization profile, is considered crucial for an optimal clinical management of the allergic disease (Ansotegui et al., 2020).

SPT is often the method of choice to confirm an IgE-mediated sensitization (Trautmann, 2022), especially in general practitioners' settings, and can be seen as the first level in vivo approach complementing the preceding clinical diagnosis. It is fast and simple to conduct as well as cost-effective and the most frequently used skin test to detect an IgE-mediated disease (Ansotegui et al., 2020). Most importantly it is very safe, with very low risk of causing anaphylactic or late-phase reactions. Also, its sensitivity is high, especially within inhalation allergens, and a sensitization can be reliably detected (Trautmann, 2022). A systematic review and meta-analysis supports this, indicating SPT is accurate in diagnosing AR, with sensitivities ranging from 68 to 100 % and specificities between 70 and 91 % (Nevis et al., 2016).

Besides skin tests, an *in vitro* diagnostic test can be considered which provides an in-depth analysis of the sIgE profile of the patient. The most common *in vitro* allergy test measures IgE antibodies in serum directed against allergen extracts or isolated allergen molecules (Ansotegui et al., 2020). Depending on the case, a so-called component-resolved diagnostics, i.e., a test analyzing the sensitization profile against specific allergen sources, may be helpful as it provides more information and may improve the treatment and clinical management of the patient. Benefits are, for instance, improved risk management of anaphylaxis, detection of sensitizations against allergen components without clinical relevance, or improving the indication for an AIT (Cardona & Ansotegui, 2016; Treudler & Simon, 2013).
sIgE measurements are commonly performed with a singleplex ImmunoCAP© assay (Phadia/Thermo Fisher Scientific) that provides the concentration of the sIgE in kU_A/L in the patient's serum based on the total IgE calibration system according the standard of the WHO (Trautmann, 2022; van Hage et al., 2017). As derived from the manufacturer of the ImmunoCAP© assay, the results can be interpreted for children and adults as follows (Thermo Fisher Scientific 2018):

***Table 1**: Classification of measured sIgE concentrations and its according CAP class and clinical assessment. Values of sIgE are indicated in kU_A/L.*

Concentration of sIgE (kU_A/L)	CAP class	Assessment
< 0.1	0	No sensitization
0.10 – 0.35	0	Low sensitization
0.35 – 0.70	1	Low sensitization
0.70 – 3.50	2	Moderate sensitization
3.50 – 17.5	3	Moderate sensitization
17.5 – 50.0	4	Strong sensitization
50.0 - 100	5	Strong sensitization
> 100	6	Strong sensitization

The testing for sIgE can follow a primary or secondary indication in the diagnostic process of AR. Primary indication means that *in vitro* diagnostic is performed instead of a skin test. Possible reasons for a primary indication may be difficulties in performing the skin test, e.g. in patients suffering from a skin disease in the test area, or in pediatric care. Other reasons include the potential risk of triggering an anaphylactic reaction in predisposed patients, or patients taking interfering medication, e.g. ß-blockers (Renz et al., 2010). However, whether skin tests or sIgE blood tests show more advantages in the diagnostics of allergic diseases and which method should be preferred in the first place is still being debated (Ansotegui et al., 2020). Indications for a secondary *in vitro* diagnostic are, for instance, discrepancies between skin test and clinical history or the requirement of a more in-depth diagnosis in preparation for specific immunotherapy (Renz et al., 2010).

It should be noted that measuring total IgE levels has limited interpretability in the context of diagnosing AR and should not be regarded as a definitive indicator of the presence of an allergic disease. Reasons are that high serum IgE levels can also be increased in other medical conditions besides atopic diseases and low to moderate IgE levels also do not rule out the presence of IgE-mediated diseases. Moreover, serum IgE concentrations decrease in the process of aging (Ansotegui et al., 2020).

In case of a discordant diagnosis despite SPT and sIgE test, further tests such as a nasal provocation can be performed (Scadding et al., 2011). Also nasal sIgE tests present a promising diagnostic tool for AR, especially in pediatrics, to avoid taking blood samples or performing a skin test (M. Gökkaya et al., 2020).
To conclude, it is important to note, that positive SPT and sIgE results, merely indicate an IgE-meditated sensitization, which may or may not be associated with allergic symptoms. The results should therefore always be interpreted by the attending physician in context of the clinical history (Trautmann, 2022).

1.6 THERAPY AND PROTECTIVE FACTORS

Subsequent to the diagnose of an AR, the treatment options should be considered. AR treatment generally consists of three cornerstones:

- Allergen avoidance
- Symptomatic medication
- Causal treatments: allergen-specific immunotherapy (AIT) and probiotic supplements

1.6.1 ALLERGEN AVOIDANCE

Depending on the patient's specific allergy profile, avoiding exposure to allergens may or may not be a feasible strategy. If the cause is an intermittent exposure i.e. animal hair, the allergen may be avoidable, whereas for airborne pollen or house dust mites, complete avoidance is hardly possible. Nevertheless, there are strategies that can be implemented to minimize the exposure to airborne allergens, including pollen: On days with high pollen counts, it is advised to limit outdoor activities. Additionally, it is recommended to sleep with windows closed, wash the hair before bedtime after outdoor activities, and regular clean the living and sleeping areas. There are also recommendations for vacation planning, as the pollen count is typically much lower in high-altitude mountainous areas (≥ 1500m above sea level) and in coastal areas with onshore wind (Trautmann, 2022). Even though the listed behavioral strategies appear reasonable, according to the International Consensus Statement on Allergy and Rhinology (ICAR-AR) there is no evidence to substantiate the clinical efficacy at this point and the recommendations are still mostly based on expert opinions (Wise et al., 2023; Wise et al., 2018).

1.6.2 SYMPTOMATIC MEDICATION

Considering pharmacological treatment there are various options available to treat AR, which can significantly alleviate the symptoms and improve QOL. First-line treatments are newer-generation oral H1-antihistamines, intranasal corticosteroids (INCS), intranasal H1-antihistamines and the combination of INCS and H1-antihistamines (Bousquet et al., 2020). The type of medication is selected based on the severity of the patient's symptoms and also based on the side effect profile of the medication. Newer-generation oral H1-antihistamines present an effective treatment for AR with fewer side effects and good safety profile. In contrast to H1-antihistamines of the first generation, newer-generation H1-antihistamines can barely pass the brain-blood-barrier and should have no or low anticholinergic and sedative side effects within the recommended dosage range (Trautmann, 2022). Regarding INCS the ICAR-AR of 2023 indicates that the effectiveness is even superior to oral antihistamines in the treatment of AR. Side effects that can occur upon the intake of INCS are, e.g., epistaxis, local burning, or local irritation. Taken together, the ICAR-AR 2023 lists newer-generation oral H1-antihistamines and INCS both with a “strong recommendation” and highest aggregate of evidence “A”. Intranasal H1-antihistamines are listed with “recommendation”, also with evidence level “A”. Oral and injectable corticosteroids are recommended against (Wise et al., 2023).

1.6.3 CAUSAL TREATMENT

1.6.3.1 ALLERGEN-SPECIFIC IMMUNOTHERAPY

Allergen-specific immunotherapy (AIT) describes a treatment for IgE-mediated Type 1 hypersensitivity reactions, which aims to change the misguided response of the immune system to an allergen by administering increasing amounts of the allergen within a specified time period. Considering pollen allergies, the treatment is usually performed as a subcutaneous immunotherapy (SCIT) or sublingual immunotherapy (SLIT). The expected positive outcome is absent or reduced symptoms and, concurrently, reduced medication use, when exposed to the allergen subsequent to AIT. It is assumed that in patients suffering from AR, AIT also reduces the probability of developing an asthmatic condition or further sensitizations to other allergens. However, the long-term effectiveness of AIT treatment has not always been demonstrated consistently and may differ between allergens (Trautmann, 2022). The ICAR-AR 2023 gives a strong recommendation (evidence-level “A”) for SCIT in reducing symptoms and medication intake for patients suffering from AR and recommends it specifically for patients who continue

to suffer from symptoms despite getting adequate symptomatic therapy. SCIT is recommended over SLIT, which is also listed with a “strong recommendation” (Wise et al., 2023).

1.6.3.2 PROBIOITC SUPPLEMENTS

Another causal treatment approach for AR is the administration of probiotic supplements. A recent systematic review and meta-analysis evaluated the efficacy of this treatment, concluding that there appears to be a positive effect regarding symptoms and QOL. However, overall, the evidence is considered weak and the authors recommend to remain cautious with applying probiotic supplements to treat AR until further data from high-quality randomized, controlled trials (RCTs) are available (Luo et al., 2022).

1.6.4 PROTECTIVE FACTORS

Due to limited causal therapeutic approaches except AIT and a persistently high prevalence of allergic diseases in Western industrial nations, the authors of the German S3 guideline for allergy prevention appeal for the necessity of evidence-based primary prevention strategies for the development of allergic diseases (Kopp et al., 2022).

In the prevention of allergies, the “hygiene hypothesis”, or the newer terms “biodiversity hypothesis” and “microflora hypothesis” play a vital role. Taken together, these hypotheses suggest that the observed increase in the prevalence of allergic sensitizations and -diseases is due to a reduction in the microbial diversity in humans and their environment (Wise et al., 2018). It is also suggested that the rise of chronic inflammatory diseases stems from the decreased exposure to microbial diversity, causing dysregulated immune system function, showing the broadest evidence regarding allergic diseases (Rook, 2009).

The “hygiene hypothesis” originated from David P Strachan in 1989 who observed a decreased risk of AR in children who had more siblings. Additionally, it appeared that being the youngest child among siblings had a protective effect. The cause for this was assumed to be more frequent infections during early childhood due to unhygienic contact with the siblings or prenatally (Strachan, 1989, 2000). Over time, the hypothesis was developed and expanded, with further studies introducing additional evidence for its validity. The main protective factors involved are summarized in the ICAR-AR 2023 and include an increased diversity in the gut and skin microbiome during childhood, the presence of siblings, and growing up on a farm with

contact to stable animals. The aggregated evidence for the hypothesis is rated as “B”, with the ICAR-AR 2023 appealing for a necessity of studies investigating causal relationships (Wise et al., 2023).

The German guideline of allergy prevention also indicates an increased risk of developing allergies due to active and passive exposure to tobacco smoke and an increased risk, especially for asthma, due to exposure to nitrogen oxides, ozone, and fine particles (PM 2.5). Recommended as being protective is exclusive breastfeeding for the first four to six months after birth, along with the introduction of diverse complementary foods. As for keeping pets, there is no reasonable basis for recommending restrictions for families without a positive family history. Some studies even showed protective effects when keeping a dog. In contrast, given a positive family history of allergic diseases, it is recommended to avoid keeping a cat. There also appears to be evidence that vaccinations may reduce the risk of developing an allergy. In contrast, there is no evidence supporting the opposite hypothesis that vaccinations may increase the risk of developing an allergy (Kopp et al., 2022).

1.7 SELF-MANAGEMENT

Despite available treatments for AR, including causal therapy approaches like AIT, a large proportion of AR patients opt for self-management of their allergic symptoms rather than seeking medical advice. Recent studies indicate that approximately 60% of AR sufferers favor self-management compared to 33.26% receiving treatment under medical supervision. However, with increasing symptom severity, patients are more likely to seek medical supervision (Muzalyova & Brunner, 2020), and higher severity of symptoms also correlates with undergoing an AIT (Muzalyova et al., 2019). One of the reasons was that especially patients with mild symptoms did not perceive their condition as a severe health issue, trivializing their disease and avoiding the effort to undergo treatment. Another contributing factor was a deficiency in specific knowledge and information. A correlation was also demonstrated between a higher level of knowledge and an increased likelihood of seeking medical supervision and opting for AIT, leading the authors to appeal for a better education about the disease and its treatment options (Muzalyova et al., 2019). Many patients appear to use over-the-counter medication and, in turn, consult pharmacists as their initial point of contact for addressing their AR (Bosnic-Anticevich et al., 2019; Bousquet et al., 2020; Lombardi et al., 2015; Muzalyova et al., 2019). In this context, especially the observed frequent use of nasal vasoconstrictors to

manage AR reflects an inadequate self-management (Lombardi et al., 2015). Moreover, there seems to be a common notion among patients that AR is a disease that should be self-managed, which may also be related to the accessibility of over-the-counter medications. Patients also describe a disillusionment with healthcare services due to delayed diagnosis and treatment fatigue in this context (Cvetkovski et al., 2018).

However, to effectively educate patients about their disease and treatment options, to improve self-management and to increase the likelihood of seeking medical supervision, mobile health applications (mHealth apps) may present a useful tool. They hold the potential of bridging the knowledge gaps and providing easily accessible and universally available, high-quality information. To provide further insight into the topic, mHealth apps will be discussed in detail in the following chapter.

1.8 MOBILE HEALTH APPLICATIONS

Due to the rapid advancements of digital health interventions and AI-applications in the medical field, the development of mHealth apps is widespread. They typically aim to alleviate the burden of specific health conditions and appear to experience a high demand from patients independent of the medical field. . Apart from their possible usefulness for the patient, mHealth apps also provide a basis for collecting large amount of real-world data for research that can address a wide range of scientific questions and thus can expand biomedical knowledge (B. Sousa-Pinto et al., 2022).

However, whether mHealth apps have a measurable positive impact on patients and provide real-life clinical use is still being investigated and depends largely on the app itself and the medical field. A systematic review from 2020 including 52 randomized controlled trials could not show compelling evidence that health-related apps improve health behaviors or health outcomes. In the systematic review, only a limited number of studies reported significant differences between app users and control groups (Milne-Ives et al., 2020). Despite this lack of clinical evidence, the development of mHealth apps is widespread, especially for chronic diseases such as AR. A review of 2022 identified more than 1500 apps specifically designed for AR and rhinosinusitis. However, solely 6 of the apps were scientifically evaluated in published literature, eventually leading the authors to appeal for “an urgent need to validate other apps” (B. Sousa-Pinto et al., 2022). As a result of the abundance of available mHealth apps, automatic

screening programs have been developed to assist healthcare professionals in identifying potentially relevant apps that may help their AR patients (Antó et al., 2022).

In the context of pollen allergies, mHealth apps typically contain advice to improve allergy management, provide knowledge and information about pollen allergy including possible treatments, and contain a diary to track the user's symptoms, behavior, and medication intake. Some allergy apps also offer a pollen forecast, which can be especially useful to patients as it serves as a guidance to avoid exposure to high pollen concentrations by adjusting the behavior accordingly. However, most of these applications provide forecasts with an accuracy rate of merely about 50%, which can be considered as insufficient (Bastl et al., 2017).

Commonly used apps for patients suffering from pollen-related AR in Germany are the "Husteblume", developed by the Techniker Krankenkasse and "Pollen", developed by the Stiftung Deutscher Polleninformationsdienst (PID). A study assessing the "Husteblume" app, however, did not show any significant changes in patient-reported health outcomes but only reported subjective improvements and benefits in the app users (Glattacker et al., 2020).

Globally the most widely recognized and scientifically evaluated mHealth app for AR appears to be MASK-air® (B. Sousa-Pinto et al., 2022), showing usefulness for patients and clinicians (Sastre et al., 2020). It also appears to be especially beneficial in providing data to better understand AR as a disease and to gain insights in behavioral patterns of patients and how patients manage their AR (Bousquet et al., 2023).

1.9 AIM OF THE DISSERTATION

In the context of the discussed potential benefits of mHealth, this thesis introduces a pilot study that implemented a randomized, controlled clinical trial addressing the utility of an mHealth app for patients suffering from grass pollen allergy in greater Augsburg. The "PollDi" app used in the presented study was purpose-built for the study and an analogous study, which was performed concurrently in spa town Bad Hindelang (Bavaria, Germany) and had not been utilized previously.

The following primary research questions were addressed in this thesis with the acquired data:

- Is there a correlation between symptom severity (reported and observed) and the rhinitis-related QOL (measured by the first mini-RQLQ survey)?

- Which exposure-related behaviors can be observed in the two study groups that used the app's diary, and how do relevant behaviors (e.g. avoiding outdoor pollen exposure, closing windows at night, washing hair after spending time outdoors) correlate with symptom severity according to the screening statement and according to the app's diary?

- Was it possible to reduce medication intake in group A, which had received the full app consisting of general information, diary and a pollen forecast, compared to the other two study groups?

- Was the use of the app perceived as positive or negative (stratification according to the screening data)?

Based on the research questions the following hypothesis were formulated and will be tested in this thesis:

1) There is a negative correlation between symptom severity (reported and measured by diary score) and rhinitis-related QOL (measured by the first mini-RQLQ survey)
2) Exposure-relevant, protective behaviors (e.g. avoiding outdoor exposure, closing windows at night, washing hair) correlate negatively with symptom severity according to the screening statement and the diary score.
3) In group A, which had received the full app, participants showed more frequently exposure-relevant, protective behaviors compared to the other two groups.
4) In group A, medication intake was reduced compared to the other two groups.

The following question should be analyzed in a hypothesis-free manner:

5) Was the use of the app perceived positively or negatively in the groups? (Stratification according to the screening data)

The secondary aim of this thesis was to evaluate whether it is possible to develop a personalized and / or generalized symptom forecast based on the obtained patient data and available environmental data.

2 MATERIAL AND METHODS

2.1 STUDY DESIGN

The present study was a controlled intervention study including 167 subjects suffering from grass pollen allergy and was carried out in Augsburg and surroundings (≤ 100 km radius) in Germany during local grass pollen season. During the intervention period, which took place from May 31st to August 31st, 2023 (93 days), each study participant used one of the versions of the pilot allergy app "PollDi". The app was purpose-built by TWT Digital Health together with a team of the Institute of Environmental Medicine (IEM) in Augsburg in three different versions for this study and an analogous study, which was performed concurrently in spa town Bad Hindelang (Bavaria, Germany) (the latter study was not subject of this thesis). All 167 participants, aged 18-72, were randomized into three groups (A, B and C) and received, according to their group, a different version of the app with the associated enabled functions. Group C served as a control group, with only the basic information function available. Group B had the information function and the diary function activated, and group A could use all three functions including the pollen and pollution forecast.

Main inclusion criteria were the presence of self-reported allergic rhinitis symptoms (+/- conjunctivitis, +/- asthma, +/- atopic dermatitis) during grass pollen season as well as tested sIgE antibodies against Timothy grass (Phadia ImmunoCAP g6 ≥ 0.35 kU_A/L). Due to personnel shortage in the study center and resulting difficulties in finding sufficient subjects few participants (n = 21) were included without sIgE blood test but with self-reported allergic symptoms during grass pollen season. Another small sub-sample (n = 9) was included with g6 <0.35 and reported symptoms during grass pollen season, which served as a negative control group. In this thesis the participants without a sIgE test and the negative control group with g6 <0.35 were excluded from the statistical analysis and only the participants with g6 > 0.35 were considered.

Originally planned to commence on May 1st, the start of the study had to be postponed to May 31st due to a delay in the app development. To gain more participants, the inclusion phase was therefore extended until July 14th, 2023. The majority of the subjects (n = 146) were randomized by the May 23rd, smaller subsets in June (n = 19) and in July (n = 2). Adherence of app usage throughout the intervention period was high as the participants completed their diary on a median of 87 days. Prior and subsequent to the intervention period a miniRQLQ™ questionnaire was obtained by each participant. Lastly, every subject had to answer a feedback questionnaire to assess the use of the app after finishing the intervention period. All

questionnaires were received by the participants via email and answered via survey tool Qualtrics™.

2.2 ETHIC APPROVAL

The study was conducted in accordance with the Declaration of Helsinki and its last revision in 2013. The protocol was approved by the Ethics Committee of the Faculty of Medicine of the Technical University Munich (2022-653-S-KH). A written informed consent was obtained from each participant prior to enrolment in the study. The subjects could discontinue their participation at any time without giving reasons by pressing a dedicated button in the app, which led to deletion of the gathered data.

2.3 INTERVENTION AND RANDOMIZATION

All participants who met the inclusion criteria were randomly assigned into the three groups, A, B and C. The groups were randomized by the self-reported average symptom severity of seasonal allergy symptoms during the grass pollen season (on a scale from 0-5), sex, and age. Every group received a different version of the app that had enabled specific app functions, depending on the respective group.

***Table 2**: Available app functions for each group. The figure is adapted from the study protocol of the study.*

Intervention	Group A	Group B	Group C
General information and questions about pollen allergy	X	X	X
Symptom diary	X	X	
Current grass pollen and air pollution forecast	X		

Accordingly, the subjects of all three groups (A, B, and C) used the general information function of the app during the intervention phase. This section included general information and questions about the topics pollen and allergy divided in the chapters “Information about pollen allergy”, “Allergy-Quiz”, “ChatGPT about allergies“, “Questions and answers” and “Fun facts”. The subjects of groups A and B additionally received a symptom diary and recorded their daily symptoms, well-being, exposure-related behavior, and medication intake of the previous day in the diary. The symptom diary was developed by PD Dr. Stefanie Gilles and team at the IEM Augsburg and was effectively used in prior studies (Mehmet Gökkaya et al., 2020). A Qualtrics™ version of the same diary is enclosed in the appendix (VII.B). The diary which was part of the PollDi app (groups A and B) represents a slightly modified version of the Qualtrics™ diary. As can be seen in *Table 2* only group A was provided with a short-term forecast (present-day and the following two days) of the grass pollen concentration and air pollution levels. The respective data acquisition and calculation algorithms for the values are illustrated separately in following chapters. The duration of the intervention period took place from May 31st to August 31st, 2023.

The randomization of the study participants was conducted by an employee of the study center at the IEM in Augsburg, who was not otherwise involved in the project. The employee created the randomization list with SAS V9.4 using the proc plan procedure. The block size was fifteen and overall, 360 (2*2*2*15*3=360) "randomization numbers" were generated. Participants were stratified by the reported average symptom severity of seasonal allergy symptoms (1-<=3, > 3-5), by gender (female, male), by age (<=35 years, > 35 years) and randomly assigned to groups A, B and C.

In order to log into the app and activate it, “App-IDs” (= 12-digit random code, using the pattern A-xxxxxxxxxxxx / B-xxxxxxxxxxxx / C-xxxxxxxxxxxx for the corresponding group) were automatically generated. The App-IDs were randomly assigned to the participant-IDs (= double-pseudonym) and sent via email to the correspondent subjects after enrolment combined with the download instruction for the app. The app could be downloaded directly via a link or via app distribution platforms (iOS: Appstore; Android: Google Play Store).

2.4 PARTICIPANTS

2.4.1 STUDIED AREA

The study area was Augsburg and its greater area located in Swabia, Bavaria, in the south of Germany. To be included, participants had to reside in Augsburg or within a radius up to 100 km around Augsburg to ensure comparable environmental conditions. If a participant was staying outside the 100 km mark for a day or a longer period during the intervention phase, they were instructed to not use the App during that period. There was also a button integrated in the app to indicate the stay outside the area of interest.

2.4.2 RECRUITING

The majority of subjects was recruited in the greater area of Augsburg via posters (e.g., university hospital of Augsburg), flyers (hospitals, doctors' offices, pharmacies) as well as websites (e.g., IEM Augsburg, Universities of Augsburg, German Allergy and Asthma Association, Allergy Information Service). The study was also mentioned on a television program (plan b, ZDF). Interested candidates contacted the IEM via the email address printed on the recruitment material to receive further information on the study and the inclusion process. In addition, former participants of previous studies conducted at the IEM who had indicated consent to be contacted for future research, were invited to participate in this study. As their allergy status, IgE profile and clinical background was already registered in the data base of the clinical study center, suitable subjects could be extracted directly from the database. These subjects also underwent a screening process to record any changes regarding their allergy or medical history.

Overall, 115 newly screened and recruited subjects and 51 subjects recruited among former participants of previous studies took part in the present study. Recruitment began in January 2023, inclusion and randomization took place from 23rd May to July 14th, 2023.

2.4.3 SCREENING

The screening was executed differently for new participants and former participants of previous studies.

Potential new participants initially contacted the study team via email as instructed on the recruitment material. They subsequently received an appointment for the first part of the screening, which was conducted via telephone. In the beginning of the screening interview, the aim, background, and procedure of the study were explained to the potential participant.
In the following, a specific anamnesis regarding the allergic symptoms was conducted to identify any possible exclusion criteria or confounders and to investigate the clinical background. The following items were obtained: Average symptom severity during grass pollen season on a scale from 0 to 5; presence of perennial allergies (e.g. house dust mites); relevant and severe comorbidities; permanent or long-term intake of immunosuppressing or immunomodulating medications; current or recent immunotherapy against grass pollen; travel plans during summer.
The Screening questionnaire for new participants is enclosed in the appendix (VII.A).
Potential participants who were eligible according to the screening interview were then given an appointment for a screening visit, where a blood sample was taken to determine serum sIgE (Phadia ImmunoCAP g6) levels. Before drawing the blood sample, the physician explained the study information, handed out the informed consent form (ICF) and pointed out possible risks to the potential participant. If agreed, the candidate gave written, informed consent to participate in the study and to have his/her study-related data processed. In some cases, candidates were also included based on sIgE results derived from blood samples taken at the "Betriebsärztlicher Dienst" of Helmholtz Munich or by proven sensitization in former, externally performed sIgE or skin prick tests (if the test report was no older than 10 years).
Due to difficulties in finding sufficient participants and personnel shortage in the study center, a minor subset of participants (N = 21) was included without an IgE test result, based on self-reported grass pollen allergy only. Nevertheless, they had to pass the screening interview without meeting any exclusion criteria.

Former participants of previous studies at the IEM who had given their consent to be contacted for future studies were contacted by email or telephone and invited to participate in this study. If interested, they underwent the same screening interview as the new participants, but with focus on any changes regarding their allergic symptoms and clinical background. Potential exclusion criteria and confounders were identified as well. The Screening questionnaire for former participants is also enclosed in the appendix (VII.A). Those eligible based on the telephone screening received the study information and ICF by email, together with the request to read the information carefully. The signed consent form had to be returned to the Clinical Study Center, and the inclusion was confirmed to the participants by email upon receiving the signed ICF.

Table 3 lists the inclusion and exclusion criteria of the study:

***Table 3**: Inclusion and exclusion criteria of the "KuHeMo Aux" study. Asterisks signal specifics which are explained at the bottom of the table.*

Inclusion criteria:	**Exclusion criteria:**

- Age ≥ 18
- Self-reported or physician-diagnosed grass pollen allergy
- Specific IgE against grass pollen (Phadia ImmunoCAP g6) ≥ 0.35 *1
- Seasonal symptoms on self-reported grass pollen
  o With or without coexisting allergic asthma
  o With or without allergy to other types of pollen
- Simultaneous sensitization (sIgE) to house dust mites or other perennial allergens is not a definite exclusion criterion, if the according symptoms are not masking the symptoms to grass pollen
- Written informed consent to participate in the study
	- Known or suspected idiopathic/chronic rhinitis
	- Known chronic sinusitis
	- Long-term systemic therapy with immunosuppressants and/or immunomodulators
	- Current and/or recent allergen-specific immunotherapy against grass pollen (since the current severity of symptoms cannot be assessed) *2
	- Perennial allergy, e.g., to house dust mites or animal hair with strong symptoms masking the symptoms during grass pollen season
	- Planned vacation during the study period that last longer than 4 weeks, especially if the destination is >100 km away
	- Severe disease (e.g., major depressive disorder, active cancer)

*1 9 participants with a g6 ≤ 0.35 and 21 participants without a sIgE test were included but not considered in the statistical analysis of this thesis.

*2 During the recruiting process 12 subjects with an ongoing hyposensitization were included and balanced equally in each group.

2.5 POLLEN FORECAST

The pollen forecast integrated in the app was based on a new prediction model for forecasting airborne grass pollen newly developed by Dr. Maria P. Plaza at the IEM Augsburg. During the intervention phase, the so-called “PollDi ensemble” generated every day at 4 am an expected pollen concentration for the present-day and the following two days. It updated itself every day, then also considering the real measurement of the day before.
Based on the generated values, the forecast in the app visually displayed the intensity of the expected pollen count and the corresponding label, ranging from “None / No pollen”, “low”, “medium”, “high” to “very high”.

The visual display of the pollen and air-pollutant forecast in the app is shown in the following figure:

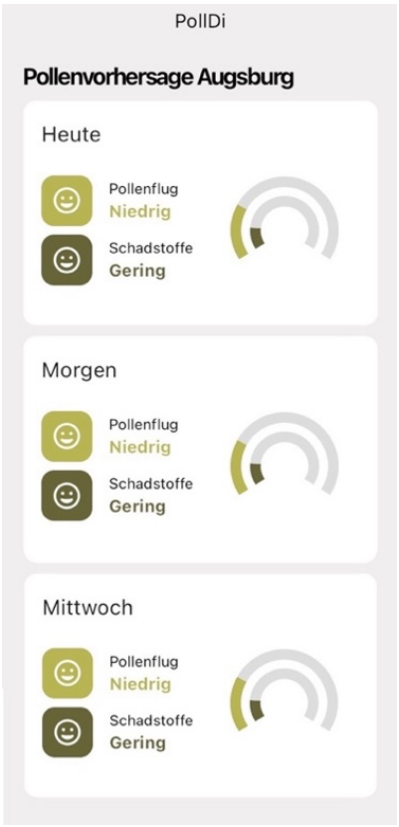


***Figure 1**: Visual display of the pollen and air pollution forecast in the PollDi app.*

The forecasted pollen concentration for each pollen label shown in the app can be derived from the following table:

***Table 4**: Forecasted pollen concentration calculated by the pollen forecast model "PollDi ensemble" and its corresponding label for the pollen forecast in the app. The predicted pollen concentration is indicated in pollen grains/m^3.*

Pollen forecast index	**Forecasted pollen concentration**	
	Lower limit	Upper limit
None / No pollen	0	< 3
Low	≥ 3	<10
Medium	≥ 10	< 30
High	≥ 30	< 60
Very High	≥ 60	∞

The classification of the labels with respect to the pollen concentration was determined by PD Dr. Stefanie Gilles, Caroline Holzmann, Dr. María P. Plaza and Prof. Athanasios Damialis based on current state of research (Plaza et al. unpublished, manuscript in preparation).

Technically speaking, the "PollDi ensemble" consisted of 7 sub-models (thus an "ensemble" of models), each weighted within the ensemble according to their performance in prior extensive testing and training. Each of the 7 sub-models was fed with data of the historical grass pollen concentrations measured in Augsburg, up to the day before the forecast, and historical meteorological data, but also forecasted, to integrate the influence of the weather conditions on the forecasted pollen concentration.

The grass pollen data used for the model had been collected at the IEM in the years of 2017-2022 via an Automatic Pollen Monitor (Hund BAA500 – "PoMo") located on the rooftop of the laboratory building of the IEM on the campus of the University Hospital in the northwest of Augsburg (48◦23′04.15″ N, 10◦50′35.95″ E) since 2017 (Plaza et al., 2022). It was integrated in the sub-models as the 3-day moving average. Meteorological data was obtained as a 3-day forecast provided by the German Weather Service / Deutscher Wetterdienst (DWD) and extracted from the DWD website with a dedicated Python script (kindly provided by Dr. Rajiv Karbhal, an employee of the IEM). The following metrological variables were considered: daily mean temperature, relative humidity and rainfall value / levels. The weighting of each variable included in the sub-models was approached differently, depending on the respective model.

As the “PollDi ensemble” is a state-of-the-art machine-learning based model, Dr. Plaza and the team will be publishing a dedicated sperate paper (Plaza et al., manuscript in preparation). This chapter only provides a simplified overview of its composition and an insight on how the pollen forecast for the app was generated.

2.6 AIR POLLUTION FORECAST

Alongside the short-term pollen forecast, the air pollution levels for the present-day and the next two days were displayed in the app. The pollution index consisted of the labels “low”, “medium” and “high” and was based on the values of NO_2, PM10, O_3 obtained by the Bavarian Environmental State Office / Bayerisches Landesamt für Umwelt (LfU). The values for the forecast were derived from calculating the weekly moving average of the daily mean values of the pollutants. The calculation algorithm was programmed by Dr. Rajiv Karbhal and automatically imported into the app every day at 4am along with the pollen data.
The pollution index represented the following composition of the pollutants:

Table 5*: Calculation algorithm of the pollution forecast. NO2, PM10 and O3 values are indicated by the LFU in µg/m³ every hour and integrated into the pollution index of the app as the 7-day moving average of the daily means.*

Pollution forecast index	**NO_2**	**PM10**	**O_3**
Low	< 30	< 30	< 90
Medium	< 30	≥ 30	≥ 90
Medium	≥ 30	< 30	≥ 90
Medium	≥ 30	≥ 30	< 90
High	≥ 30	≥ 30	≥ 90

The visual display of the pollution forecast in the app is also shown in *Figure 1*.

2.7 DATA ACQUISITION

2.7.1 APP DATA

The majority of the data acquisition was carried out through the symptom diary integrated into app. The raw data was gathered in an anonymized way, labeled only with the "APP-ID" (double-pseudonym) and date. The raw data of the diary was retrieved from the backend of the app and was subsequently arranged and processed with R Studio by the doctoral candidate to transform it to analyzable data.

The following data was used in the statistical analysis of this thesis and collected within the symptom diary:

- Date
- General well-being (scale from 0-10)
- Stress level (scale from 0-10)
- Exposure-related behavior (outdoor exposure, closing windows at night, washing hair)
- Organ-specific allergy-related symptom severity and relating qualitative symptoms (overall, nasal, ocular, bronchopulmonary)
- Allergy-related medication intake

In the app diary also dermal, pharyngeal, auricular, nerval and gastrointestinal symptoms were recorded. However, as this thesis focuses on overall and nasal symptoms these were not taken into account for the statistical analysis.

As shown in *Table 6* the organ-specific symptoms were reported in the diary on a scale from 0 to 3 according to the severity and the concomitant symptom qualities.

***Table 6**: Organ-specific symptom severity and symptom qualities that could be selected in the symptom diary.*

Organ	Symptom severity	Symptom qualities
Nasal symptoms	No symptoms = 0 Mild symptoms = 1 Moderate symptoms = 2 Severe symptoms = 3	Itching Sneezing Running Congestion

Ocular symptoms	No symptoms = 0 Mild symptoms = 1 Moderate symptoms = 2 Severe symptoms = 3	Itching Foreign body sensation Redness Tear flow Dryness Swelling
Bronchopulmonary symptoms	No symptoms = 0 Mild symptoms = 1 Moderate symptoms = 2 Severe symptoms = 3	Wheezing Dyspnea Cough Asthmatic reaction

Figure 2 provides a visual excerpt of the user interface of the "PollDi" app and illustrates how the symptoms were reported in the diary using nasal symptoms as an example:

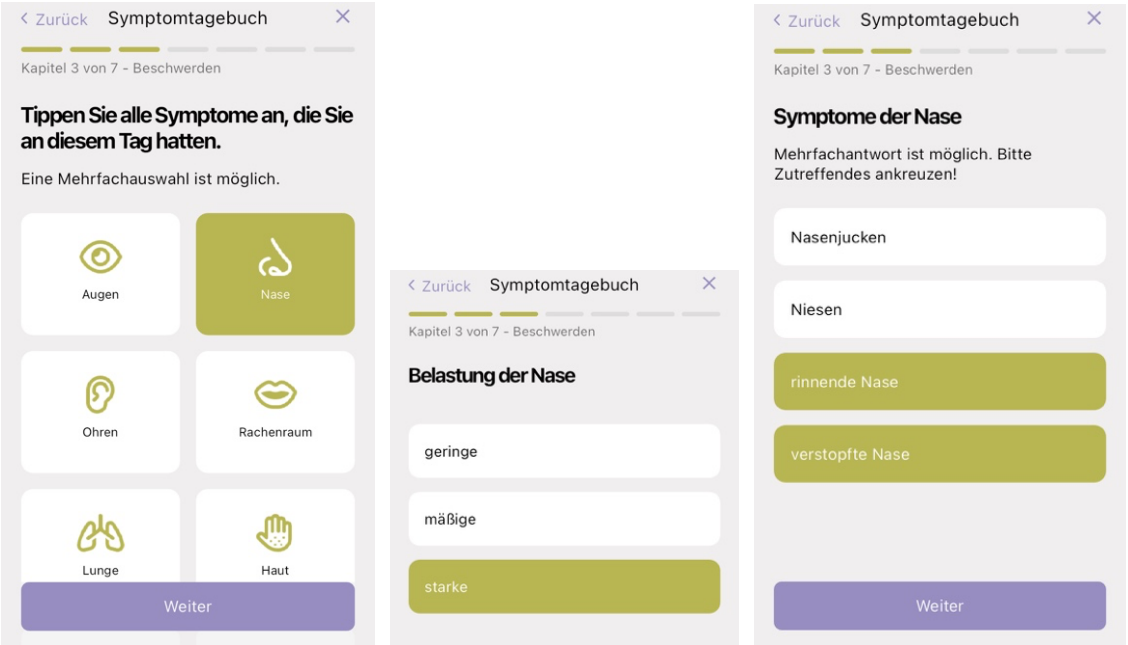


***Figure 2**: Visual display of the symptom diary in the PollDi app.*

Based on the collected data, a Total Symptom Score (TSS), Total Nasal Symptom Score (TNSS), Total Ocular Symptom Score (TOSS) and Bronchopulmonary Symptom Score (TBSS)

were calculated. However, only the TSS and TNSS were used in the statistical analysis of this thesis as it focused on overall and nasal symptoms. The approach of the calculation of the symptoms scores was based on previous literature (Bastl et al., 2014; Downie et al., 2004; Karatzas et al., 2014) and was conducted as follows:

TSS:

Total Symptom Score (TSS) was calculated as the sum of the nasal, ocular, and bronchopulmonary symptom severity (each range 0-3, so up to 9 overall) plus the inverse value of the overall well-being which was answered on a scale from 0-10. The organ-specific qualitative symptoms listed in *Table 6* were not considered in this score. This leads to a range for the TSS from 0 to 19 points.

Organ-specific symptom scores:

The TNSS, TOSS and TBSS consisted of the respective organ-specific symptom severity summed up with the quantity of qualitative symptoms reported as shown in *Table 6*. Each symptom quality was considered with 1 point. This resulted in a maximum score of 7 (TNSS, TBSS) or 9 (TOSS) respectively.

Medication score:

Also, a Medication score was calculated based on allergy-associated medication intake that could have been reported in the diary. The available options were:

- Nasal spray
- Eye drops
- Pills / Systemic medication
- Homeopathic medication
- Other

The Medication score was calculated with each category contributing 1 point to the total. This results in a maximum possible score of 5 points.

Total Symptom Medication Scores:

Additionally, for each symptom score, a symptom medication score (TSMS, TNSMS, TOSMS, TBSMS) was calculated. Depending on the score, each medication class was weighted according to their varying impact on the respective organs and symptoms. The weighting was

also based on previous studies (Bastl et al., 2014). The according weighting for each score is shown in *Table 7:*

***Table** 7: Description how the medication categories were weighted for each score.*

Medication	TSMS	TNSMS	TOSMS	TBSMS
Nasal drops	1.00 p	1.00 p	0.25 p	0.00 p
Eye drops	1.00 p	0.25 p	1.00 p	0.00 p
Pills	1.00 p	1.00 p	1.00 p	0.25 p
Homeopathic	1.00 p	0.30 p	0.30 p	0.25 p
Other	1.00 p	0.50 p	0.50 p	0.3 p

However, as this thesis focused on the TSS, TNSS and the medication score, the symptom medication scores were not used in the following statistical analysis.

2.7.2 SCREENING DATA

Data obtained during the screening process consisted of the screening interview as well as the sIgE tests. Screening data that was incorporated into the statistical analysis were: Sex, age, smoker (y/n), self-perceived average symptom severity (0-5), AR (y/n), AC (y/n), history of asthmatic symptoms (y/n), sIgE.

2.7.3 MINI RQLQ QUESTIONNAIRE

The Rhinoconjunctivitis Quality of Life Questionnaire is a validated questionnaire developed by Professor Elizabeth F. Juniper, MCSP, MSc (Elizabeth Juniper, 2024). It serves to measure the impairment of QOL during the last 7 days due to the pollen allergy. The short version of it, called “miniRQLQ”, was used in this study and consists of overall 14 questions which can be grouped in five sections:

- activity limitation
- practical problems

- nasal symptoms
- ocular symptoms
- non-nasal/ocular symptoms

For each question an impairment on a scale from 0 (no impairment) to 6 (high impairment) can be reported. The miniRQLQ score is then derived by calculating the average of all questions.
In this study of each participant prior and subsequent to the intervention period a miniRQLQ questionnaire was obtained. For the analysis of this thesis, only the first miniRQLQ questionnaire, that was obtained prior to the study, was considered.

2.7.4 FEEDBACK QUESTIONNAIRE

The feedback questionnaire used in this study was developed by the doctoral candidate and aimed to gain feedback from the subjects about the usability, usage behavior and above all the perceived clinical value of the app regarding their allergic management. The questions were designed to discover if the app usage had any subjective allergy-related effects on the participants, such as QOL, symptom control, exposure-related behavior, and medication intake. In addition to exploring potential positive outcomes, the intention was also to decipher any adverse effects, such as heightened anxiety or concern about allergic symptoms and overall health, which may stem from regular interaction with one's allergy symptoms.
To fulfill the desired requirements the questionnaire was grouped in three main categories which included:

- General questions about the usability and usage behavior
- General question about the clinical value of the app
- Specific question about the three features of the App
    - General information and questions about pollen allergy
    - Symptom diary
    - Pollen and air pollution forecast

As all three groups were using a different version of the app with the associated enabled functions, the participants of each group received a different version of the questionnaire tailored to their group. Overall, 53 question were designed for the questionnaire. The following table gives an overview over the received questions per group (following page):

***Table 8**: Overview of the received questions of the feedback questionnaire for each group.*

Question block	Group A	Group B	Group C
Usability and usage behavior	X	X	X
Clinical value of the app	X	X	X
General information and questions about pollen allergy	X	X	X
Symptom diary	X	X	
Pollen and air pollution forecast	X		

The entire feedback questionnaire is enclosed in the appendix (*VII.C*). It is also indicated which questions were received by each group.

2.7.5 POLLEN AND ENVIRONMENTAL DATA

In the statistical analysis of this thesis, also pollen data and environmental data were included. The pollen data was also derived from the Bio-Aerosol Analyzer BAA 500 (Pollen Monitor—PoMo) of the IEM located in the northwest of Augsburg city (Plaza et al., 2022). Weather data was obtained by the DWD (Deutscher Wetterdienst, 2024) and air pollution data by the LfU (Bayerisches Landesamt für Umwelt, 2024).

2.8 STATISTICAL ANALYSIS

The statistical analysis for this thesis was conducted in R, version 4.3.1 (R Core Team, 2023). It was performed by the doctoral candidate with consultation of PD Dr. Stefanie Gilles, the supervisor of this thesis, as well as Prof. Dr. Christine Meisinger and Dr. Dennis Freuer, who conducted the statistical consultation for doctoral candidates at the faculty of medicine at the University of Augsburg. The symptom forecasting model and the results of it were developed in collaboration with Dr. Maria Plaza, who is the group leader of “Human Exposure Science” at

the IEM in Augsburg. The plots presented in this thesis were created using the R packages "ggplot2", "ggstatsplot" and "statsExpressions".
The methods for the statistical analysis in this thesis for each subdomain are presented in the following. For all tests performed, the significance level was determined as $p < 0.05$. Significance levels in plots may be indicated by asterisks as follows:
NS: $p > 0.05$; *: $p \leq 0.05$; **: $p \leq 0.01$; ***: $p \leq 0.001$.

2.8.1 PARTICIPANT CHARACTERISTICS

Continuous variables were tested for normal distribution considering each variable's histogram and QQ-plot and using the Shapiro-Wilk test. If normally distributed, the continuous variables were reported as mean (SD), if not normally distributed or ordinal scaled as median (25.; 75. Percentile). Nominal data was presented as N (%). As the data was non-normally distributed differences between groups were tested using Kruskal-Wallis test for continuous and ordinal variables and Pearson-$\chi 2$-tests for nominal data.

2.8.2 CLUSTERING

To address the question if the app usage was perceived as positive or negative, the data was stratified by patient-specific variables from the screening questionnaire. The following variables were considered:
Reported average symptom severity, Allergic rhinitis (yes / no), Allergic conjunctivitis (yes / no), Allergic asthma (yes / no), Sex, sIgE g6, age.
Given the mixed datatype, containing numerical and categorical variables, Gower distance was employed. Further, partitioning around medoids (PAM) was used as a clustering algorithm and the silhouette width to identify the ideal number of clusters.
This led to building the clusters FA-, FA+, MA-, MA+. In the following these clusters will be referred to as "patient clusters" in this thesis. The complete analysis of the clusters and results are presented in the results. Kruskal-Wallis rank sum test was performed to evaluate the differences between the observed symptom severity across the clusters. Post-hoc pairwise comparison with a Dunn test was conducted using adjusted p-values (Bonferroni correction for multiple testing).
The clustering using Gower distance was applied as suggested by (Batool & Hennig, 2021; Botyarov & Miller, 2022; Martin, 2016).

2.8.3 CORRELATION OF MINI-RQLQ SCORES AND SYMPTOM SEVERITY

The first miniRQLQ, which was considered in this analysis, was originally intended to be completed by all participants prior to the intervention phase. However, due to a technical problem with the survey in Qualtrics, about 60% of the participants did not fully complete their questionnaire. After contacting the developer of the miniRQLQ, it was stated that incomplete questionnaires must not be included in the evaluation. Therefore, only participants (n=64) who filled the complete questionnaire were considered for this part of the analysis. Additionally, as a result to the extended inclusion period, some participants completed their first miniRQLQ later than the majority of participants. To ensure comparable results, two clusters were formed based on the dates the questionnaires were completed, thus controlling for the different pollen levels that the participants were exposed to before answering the first questionnaire.

The TSS was chosen instead of the TNSS for the correlation between mini-RQLQ score and observed symptom severity, because the miniRQLQ considers all symptoms and not only nasal-specific symptoms. In addition, the mini-RQLQ score was correlated to the average symptom severity, as reported in the screening questionnaire.

To examine the relationship between the mini-RQLQ score and the TSS, the median of the TSS for each participant over the entire intervention period was calculated. In the following, this metric will be referred to as “patient median TSS”. As the TSS was non-normally distributed, the median and not the mean was used.

The correlation analysis was then performed using scatter plots and Spearman's rank correlation coefficient, since the patient median TSS, average symptom severity and miniRQLQ scores were non-normally distributed.

2.8.4 CORRELATION OF EXPOSURE-RELATED BEHAVIOR AND SYMPTOM SEVERITY

To address the question how exposure-relevant behaviors (e.g. avoiding outdoor pollen exposure, closing windows at night, washing hair after spending time outdoors) correlate with the symptom severity according to the screening questionnaire and according to the symptom diary, the following strategy was applied:

For the correlation with the symptom severity according to the diary, both, the TSS and TNSS were considered. Therefore, the daily median score of the entire cohort was calculated. This metric will be referred to as the “daily median TSS” (or TNSS). The median was chosen instead

of the mean because the daily scores throughout the cohort were non-normally distributed. The daily median scores were then tested for correlation with the percentage of participants of the entire cohort who had engaged in the respective exposure-relevant behavior on the corresponding day or. Depending on the behavior, the symptoms of the next day were considered instead. The aim of this strategy was to investigate how an increasing ratio of e.g. closing windows at night vs. not closing the window within the cohort influenced the respective daily median symptom score.

To investigate in the relationship between the behavioral pattern and the symptom severity according to the screening statement a different approach had to be applied: For each participant the percentage was calculated on how many days he or she engaged in the respective behavior. This metric was then tested for correlation with the average symptom severity collected during the screening process. Within the context of these results also the relationship between the weather factors and pollen concentration was presented. Local weather data (Augsburg) was included as provided by the DWD.

The relationship of the discussed variables was visualized with scatter plots, and the degree of correlation indicated by the Spearman's rank correlation coefficient due to non-normal distribution of data.

2.8.5 EXPOSURE-RELATED BEHAVIOR BETWEEN GROUPS

2.8.5.1 DIARY USER GROUPS

The statistical comparison of the behavior variables between groups A and B as measured by the app diary was conducted using Pearson-χ2-test to investigate whether one group showed a certain behavior more frequently than the other group. When a significant difference was observed, a beta regression was employed to investigate whether the observed effect could be attributed to group differences. The response variable was defined as the percentage of days a participant engaged in the behavior throughout the study period. As predictor variables were considered: Group, Sex, median TSS, Asthma yes/no, sIgE, smoker yes/no and age. Effects were expressed as odds ratio (OR). Statistical significance of the model was evaluated with the p-value.

2.8.5.2 COMPARISON OF ALL GROUPS

The statistical comparison of all three groups (A, B and C) regarding the behavior was performed using the data from the feedback questionnaire, as group C did not have the diary function in the app available. The corresponding question in the feedback questionnaire that was analyzed in this context was “Did you pay more attention than usual to measures such as washing your hair, changing clothes, etc., due to the app usage?” (Q15n1 in the questionnaire). Descriptive statistics of the distribution of answers were calculated as % (n/N) and Pearson-$\chi 2$-test was used to detect significant differences between groups.
A logistic regression was applied to explore the relationships between behavior variables and symptom scores more thoroughly. Therefore, approving answers (partially, strong, very strong) and negating answers (hardly, not at all) were grouped to obtain a binary variable that can be used as a response variable in logistic regression. As predictors, the following variables were considered: Group, Sex, age, sIgE (ImmunoCAP g6), asthma (yes/no), smoker (yes/no), reported average symptom severity. Logistic regression was tested for significance using omnibus-test and to identify possible multicollinearity the Variance Inflation Factor (VIF) for each independent variable was calculated.

2.8.6 MEDICATION INTAKE BETWEEN GROUPS

2.8.6.1 DIARY USER GROUPS

To statistically compare the medication intake between group A and B based on the app diary the MS was considered. Mean (SD) and Median (25.; 75. Percentile) were calculated for both groups and differences between groups were tested using Mann-Whitney U test as the MS was non-normally distributed. The same strategy was also applied considering only days with “high or very high”, “medium” and “low” or “none” forecasted pollen levels to analyze whether the pollen forecast had an influence on medication intake.

To investigate further the relationship between medication intake and receiving pollen forecast information, the correlation between MS and pollen forecast level was compared between groups A and B. The hypothesis was that in group A, the correlation of the MS with the pollen level might be higher (or more significant) than in group B, since group A participants could base their decision to take medication or not on the pollen forecast level displayed to them, whereas group B participants did not have this option since they did not receive any pollen

forecast in their app version. To test this, the daily mean MS of the cohort was calculated. Even though the daily mean MS across all days were non-normally distributed, the mean was used instead of of the median. This decision was made because the median consistently equaled zero, due to the highly skewed distribution of the MS. In a similar approach, also the relationship between the daily mean MS and the daily mean TSS was analyzed. Spearman's rank correlation coefficient was applied as the respective variables were non-normally distributed.

It was also investigated if there are certain medication categories which were taken more often by any of the groups, A and B. As the data type was nominal, the N (%) of the medication for each category was calculated and Pearson-χ^2-tests were performed to detect significant differences. The analysis was also performed regarding the clusters (FA-, FA+, MA-, FA+) to identify patterns within the patient characteristics that may influence medication intake behavior.

2.8.6.2 COMPARISON OF ALL GROUPS

The statistical comparison of all three groups (A, B and C) regarding the medication intake was performed identically to the comparison regarding the behavior. However, the corresponding question in the feedback questionnaire in this context was whether less allergy medication than usual was taken while using the app in the study period (Q16n1 in the feedback questionnaire). Descriptive statistics of the distribution of the answers were calculated as % (n/N), and Pearson-χ2-test was used to detect significant differences between groups.
Secondly, a logistic regression was applied to explore the relationships between the variables more thoroughly. Again, the approving answers (partially, strong, very strong) and negating answers (hardly, not at all) were grouped to obtain a binary variable that can be used as a response variable within logistic regression. As predictors the following variables were considered: Group, Sex, age, sIgE g6, asthma (yes/no), smoker (yes/no) and reported average symptom severity. Logistic regression was tested for significance using omnibus-test and to identify possible multicollinearity the Variance Inflation Factor (VIF) for each independent variable was calculated.

2.8.7 EVALUATION OF THE FEEDBACK QUESTIONNAIRE STRATIFIED BY SCREENING DATA

To address the question whether the use of the app was perceived as positive or negative by the participants (stratification according to the screening data), the descriptive statistics regarding the entire cohort were reported as percentages (n/N) for the relevant questions. Statistical comparison between the clusters was then performed using Pearson-χ2-test. For significant findings, a logistic regression was performed to identify potential significant factors within the clusters. To obtain a binary variable, the answers “very strong” and “strong“ were grouped, and “partly”, “hardly” and “not at all” were grouped. The decision to categorize “partly” within the grouping of “hardly” and “not at all” in this context was based on the aim to identify the predictors for responding at least “strong” and not “partly”.

Furthermore, logistic regression was performed regarding the questions whether the participants would use the app again in following pollen seasons (Q43n1) and if they enjoyed using the app daily (Q8). The answers were again grouped to obtain a binary variable and to identify possible predictors for at least responding “most likely yes” (Q43n1) or “I enjoyed using the app” (Q8). For this analysis, besides patient characteristics, also the answers to certain questions from the questionnaire were considered as predictor variables. The aim was to determine which factors were the most relevant in influencing the decision to answer “Yes, I would use the app again” and “I enjoyed using the app”. Logistic regression was tested for significance using omnibus-test and to identify possible multicollinearity the Variance Inflation Factor (VIF) for each independent variable was calculated.

2.8.8 SYMPTOM FORECAST MODEL

To address the question of whether it is possible to develop a symptom forecasting model using the data obtained in this study, a NNAR model (Neural network auto regression) was considered. It is a machine learning based model, more specifically a neural network, that includes autoregression and may be used for forecasting. As it’s a neural network it has the power to model complex non-linear relationships without any prior assumption about the nature of these relationships (Sena & Nagwani, 2015). The choice of model was based on the prior work of Dr. Maria Plaza on the pollen forecasting model which was integrated into the PollDi app and on previous promising results of machine-learning based methods regarding predictions in the medical literature (Dong et al., 2021; Heo et al., 2019; Silva et al., 2022). Also, including autoregression was important, as grass pollen were shown to have a lag effect on the symptoms

of up to 5 days (Kiotseridis et al., 2013). Also, the complex nature of the data of this study, consisting of a time series with binary, discrete and continuous variables, many of which may be autocorrelated, supported the decision.

For the development of the model the packages "forecast" and "modeltime" in R were used. Of each variable included in the formula 5 lagged values were included, which represents the number of input nodes in the NNAR. The decisions to include 5 lags was based on a previous study evaluating a symptom forecasting model for AR patients (Voukantsis et al., 2015) and also on the discussed findings of Kiotseridis et al. showing lag effects of up to five 5 days of pollen grass pollen on symptoms (Kiotseridis et al., 2013).

Further, the model consists of one single hidden layer, in this case with 10 nodes. The fitted model is presented as NNAR (p, k) with p showing the number of input nodes or lags respectively and k indicating the number of hidden nodes.

Three parallel approaches were pursued to train and evaluate the models: Firstly, two "personalized" models were developed: In the "1_NNAR" 70% of data was randomly selected and used as training data, whereas the remaining 30% of the data served test data. Therefore, the model was already able to learn from existing data of each participant and predicted randomly selected datapoints in the time series of each patient. In the "2_NNAR" approximately 70% of days of the study period were used as training data and the remaining 30% served as test data. This resulted in using the data from May 31st until August 3rd as training data and August 4th until August 30th as test data. This approach should present more realistic conditions as the model was already able to learn from existing data and predicted the remaining study period or pollen season respectively. Further, a "generalized" model was developed using data from approximately 70% of the participants as training data and the data from the remaining 30% of the participants as test data. Within this approach, the model had to create a symptom prediction for completely unknown "users". To evaluate and compare the quality of the models, standard metrics to assess machine-learning models (MAE, MAPE, MASE, SMAPE, RMSE, R-Square) were considered (Chicco et al., 2021). Further, the prediction of the symptom time series of five random patients was observed and the accuracy of predicting symptom levels on the test data.

Data that went into the models for training were (i) daily-scale environmental data (mean temperature; relative humidity; precipitation; pollen concentration; NO2 concentration; O3 concentration; PM10 concentration); (ii) demographic data (age, sex, smoker status); (iii) patient-derived baseline information (sIgE level as measured by Phadia g6; quality of symptoms); and (iv) symptom scores and behavior as entered in the app diary.

To provide realistic forecasting conditions, the testing and results of the model were performed integrating the forecasted pollen concentration and not the real values.

3 RESULTS

3.1 PARTICIPANT CHARACTERISTICS

3.1.1 DESCRIPTION OF THE STUDY POPULATION

Overall, 167 participants, aged 18-73, were included in the present study with 55 participants randomized to group A, 55 participants to group B and 57 participants to group C. A total of 55 participants were male and 112 participants were female. The median age was 32 (27; 46.5) years.

Statistical comparison of the groups showed 65.5% of participants of group A, 69.1% of group B, and 66.7% of group C were female. Accordingly, the sex ratio showed no significant differences between the groups (Pearson's χ^2-test: X-squared = 0.17088, df = 2, p-value = 0.9181). The median age was 35 (28; 50) years in group A, 32 (25.5; 45) years in group B and 31 (26; 44) in group C. There was also no significant difference regarding the age (Kruskal-Wallis rank sum test: chi-squared = 2.2281, p-value = 0.3282) and the smoker status between the groups (Pearson's χ^2-test: X-squared = 0.072363, df = 2, p-value = 0.9645). Overall, 10 participants considered themselves as former smokers. (p = 0.07322) and 53 participants indicated to consume alcohol (p = 0.8275)

The median of the reported average symptom severity in group A was 3 (2.5; 4), in group B 3 (2.5; 3.5), and in group C 3 (2.5; 4). No significant difference was found between the groups regarding the reported average symptom severity. (Kruskal-Wallis rank sum test: chi-squared = 0.38434, df = 2, p-value = 0.8252).

A total of 12 participants were included undergoing a current AIT, balanced equally between groups (p = 0.4848). Overall, 73 participants indicated that they were undergoing an AIT in the past. (p = 0.5867). Thereof 52.78% described an improvement of symptoms, 30.56% no change in symptoms, 4.17% an aggravation of symptoms and 1.39% indicated to have had no symptoms anymore. 11.11% reported having discontinued the AIT for various reasons. Participants without an sIgE test (n=21) regarding timothy grass (g6) were also balanced equally between the groups (p = 0.8823).

Table 9 summarizes the descriptive statistics including the clinical background of the study population with the according statistical comparison:

***Table 9**: Descriptive statistics of the study population. For numeric variables the median (25.; 75. Percentile) and for categorical data absolute frequencies (relative frequencies) were calculated. Kruskal-Wallis-Test (for metric variables) and χ^2-test (for categorical variables) were computed for statistical comparison.*

	A (n = 55)	**B (n=55)**	**C (n = 57)**	**Statistical comparison**
Demographics				
Age (years)	35 (28; 50)	32 (25.5; 45)	31 (26; 44)	*p = 0.3282*
Sex (female)	36 (65.5 %)	38 (69.1%)	38 (66.7 %)	*p = 0.9181*
Smoker (y)	9 (16.36%)	8 (14.55%)	9 (15,79%)	*p = 0.9645*
Alcohol (y)	19 (34.55%)	16 (29.09%)	18 (31.58%)	*p = 0.8275*
Clinical Background				
Average symptom severity	3 (2.5; 4)	3 (2.5; 3.5)	3 (2.5; 4)	*p = 0.8252*
Allergic rhinitis (y)	54 (98.18%)	55 (100%)	55 (96.49%)	*p = 0.3765*
Allergic conjunctivitis (y)	52 (94.55%)	53 (96.36%)	54 (94.74%)	*p = 0.8862*
Asthmatic symptoms (y)	20 (36.36%)	22 (40%)	29 (50.88%)	*p = 0.2692*
Autoimmune disease (y)	3 (5.45%)	5 (9.09%)	7 (12.28%)	*p = 0.4501*
Systemic disease (y)	1 (1.82%)	2 (3.64%)	1 (1.75%)	*p = 0.7630*
Current hyposensitization (y)	3 (5.45%)	3 (5.45%)	6 (10.53%)	*p = 0.4848*
Former hyposensitization (y)	23 (41.82%)	22 (40%)	28 (49.12%)	*p = 0.5867*
No sIgE test (y)	6 (10.91%)	7 (12.73%)	8 (14.04%)	*p = 0.8823*

In the following also the distribution of the age (*Figure 3, A*) and average symptom severity (*Figure 3, B*) across the cohort is presented, as these will be addressed in the discussion of the study population.

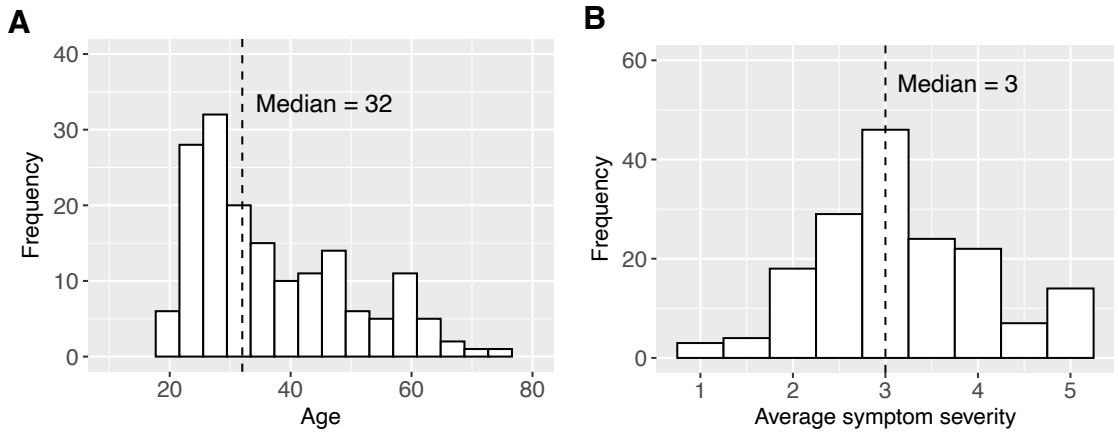


***Figure 3**: Distribution of the age (A) and average symptom severity (B) across the cohort.*

3.1.2 PARTICIPANT FLOW

Overall, 225 candidates were screened for eligibility. 58 were excluded. Major reasons for exclusion were (i) not fulfilling the inclusion criteria (n=18); (ii) declined participation during the process; (iii) loss of contact; or (iv) other reasons (n=30).

Accordingly, 167 subjects were assigned to the randomization process and 55 participants were assigned to group A, 55 to group B and 57 to group C. Two more participants were randomized normally along with the others (so originally 169 participants) and then retrospectively excluded because an error in the inclusion criteria was noticed.

During the intervention phase overall 12 participants discontinued the study and thus were registered as a drop-out. Major reasons described by these subjects were a shortage of time and forgetting to use the app.

The data of the remaining 155 participants entered the analysis. 9 participants were included with an sIgE < 0,35 kU/l and were originally intended to serve as negative controls. However, due to the low number of negative controls, these participants were retrospectively excluded from the statistical analysis. A subset of participants (n=21) had reported a grass pollen allergy but did not undergo sIgE testing. They were distributed equally between the groups but were ultimately also excluded from the statistical analysis because the variable of sIgE level (g6) was part of the data required for the analysis. 3 of the 21 participants without sIgE test discontinued the intervention. One participant of group B did not fully complete the feedback questionnaire and was therefore, depending on the question, excluded from some of the analyses. In this case, the count for group B is n = 37, instead of n = 38.

Figure 4 displays the flow chart of the participants included in the study.

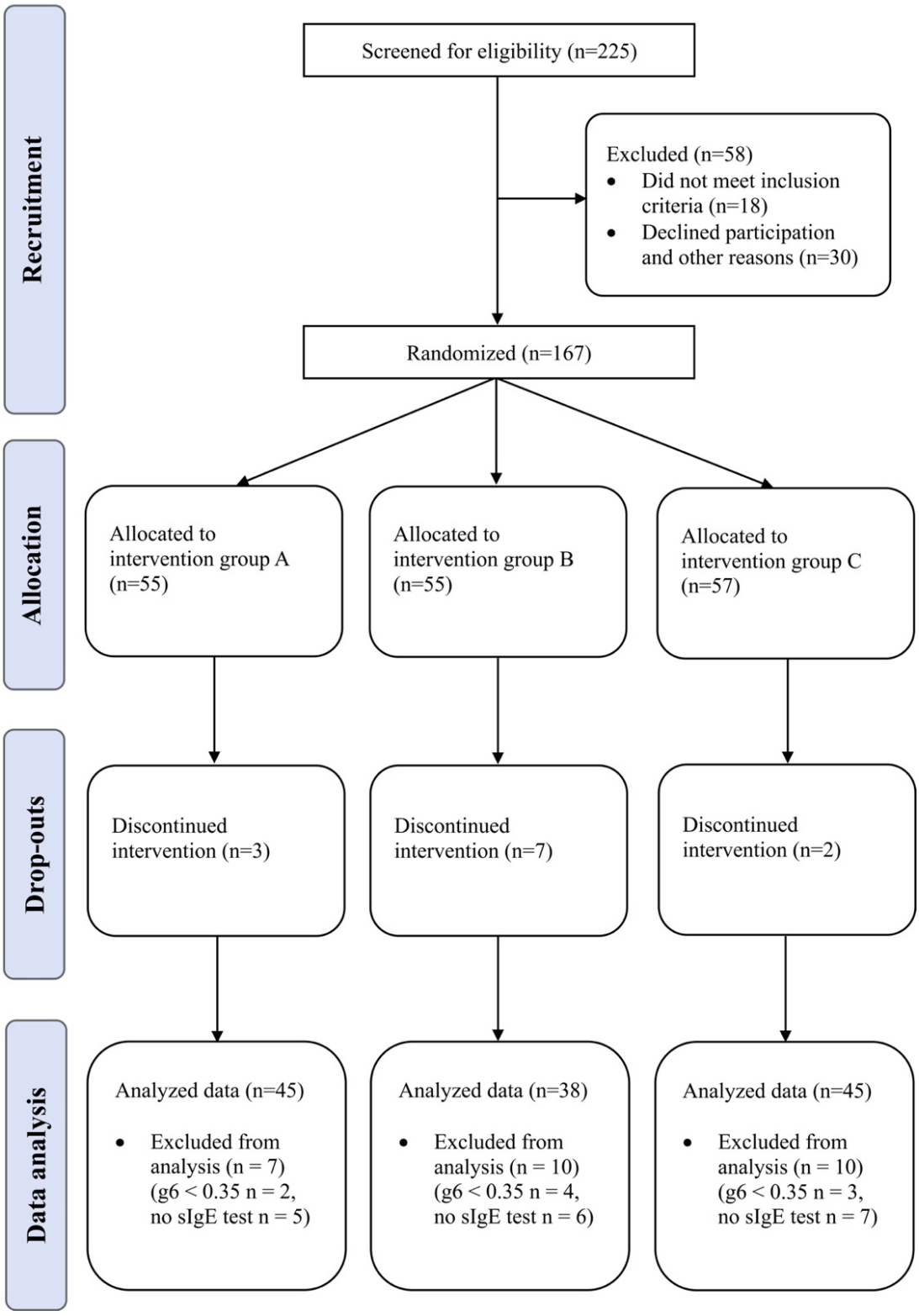


***Figure 4**: Participant flow chart.*

3.2 CLUSTERING OF THE POPULATION

To identify potential patterns of the patient characteristics regarding the feedback questionnaire and further specific questions a clustering of the study population was performed based on the variables obtained during the screening process. The results for identifying the most reasonable number of clusters (k) using the silhouette width is shown in *Figure 5:*

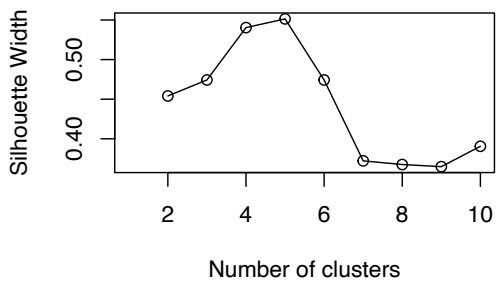


***Figure 5**: Silhouette width for the number of clusters (k).*

As can be derived k = 5 and k = 4 showed the highest silhouette width. Even though the silhouette width for k = 5 was slightly higher than for k = 4 it was decided to choose four clusters as the optimal number as the sample size was relatively small (n = 128). As a result, a higher sample size per cluster was ensured. *Figure 6* shows the patient clusters visually. Each data point reflects one participant, colored according to the corresponding cluster.

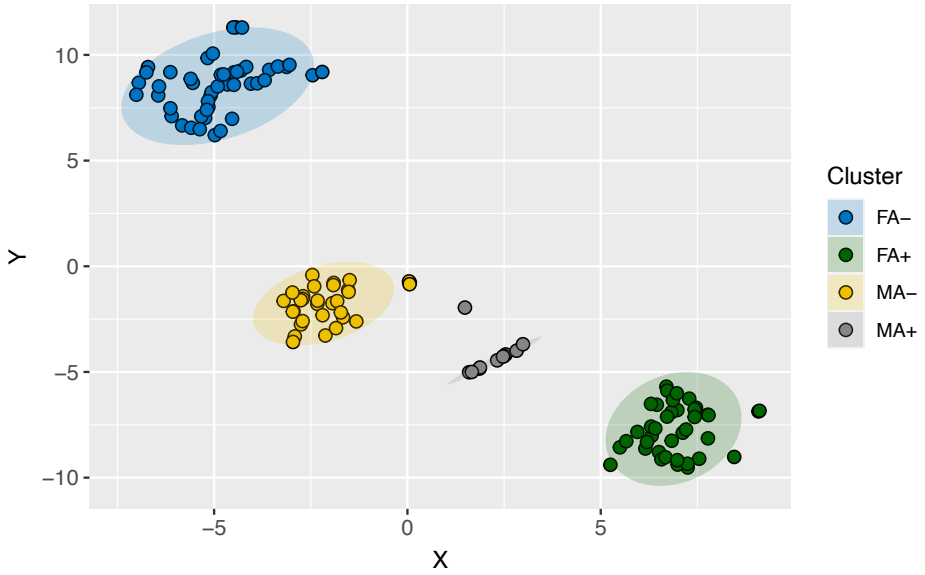
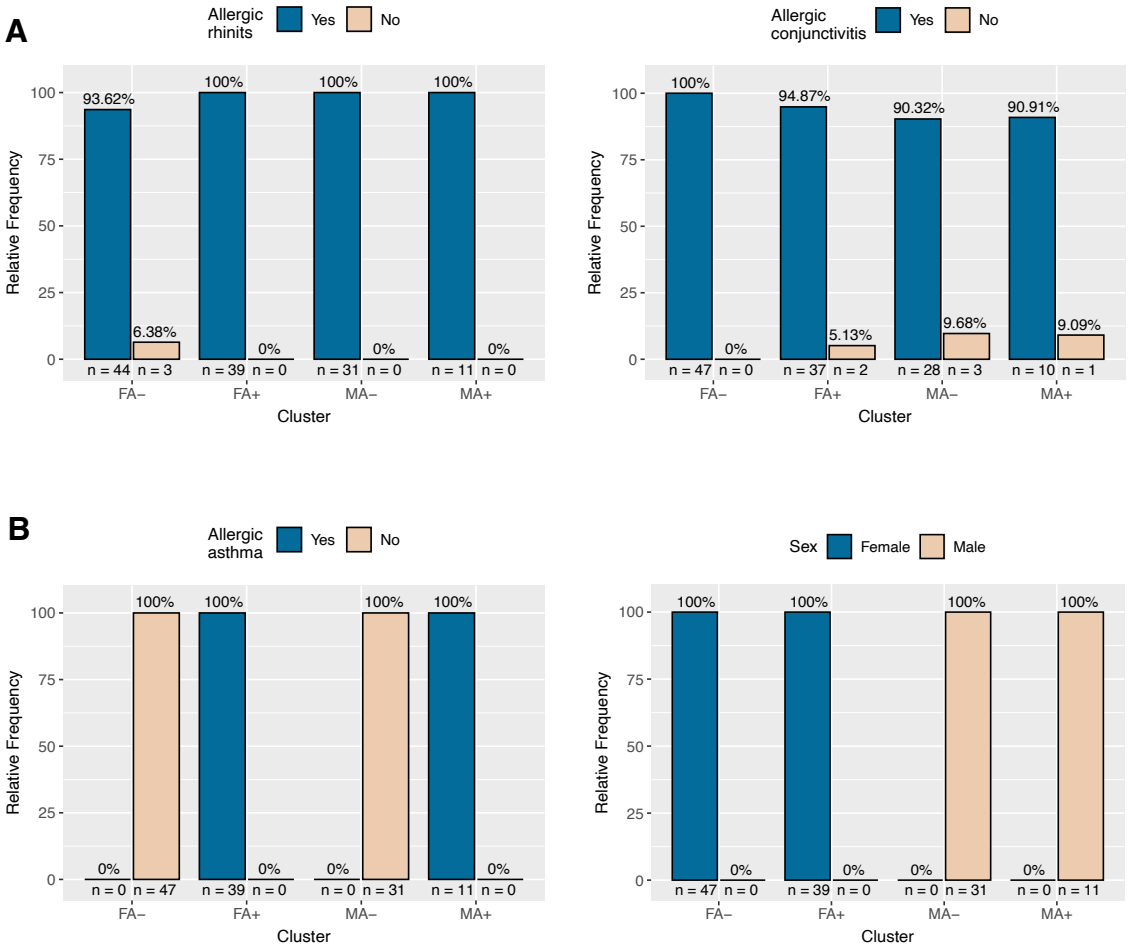


***Figure 6**: Visual display of the identified clusters using Gower distance and PAM.*

To gain further understanding of the generated clusters, descriptive statistics were performed of each cluster for categorical variables (*Figure 7*, A-B) and for continuous variables (*Figure 7*, C-D). Taken together, the key characteristics of FA- were female sex and no history of allergic asthma. FA+ were female participants with history of allergic asthma. Key characteristics of MA- were male sex and no history of allergic asthma, whereas MA+ were male participants with a history of allergic asthma.

Compared to cluster FA-, cluster FA+ showed higher medians for average symptom severity, g6, and age. MA+ had higher medians for average symptom severity, g6 and age compared to MA.



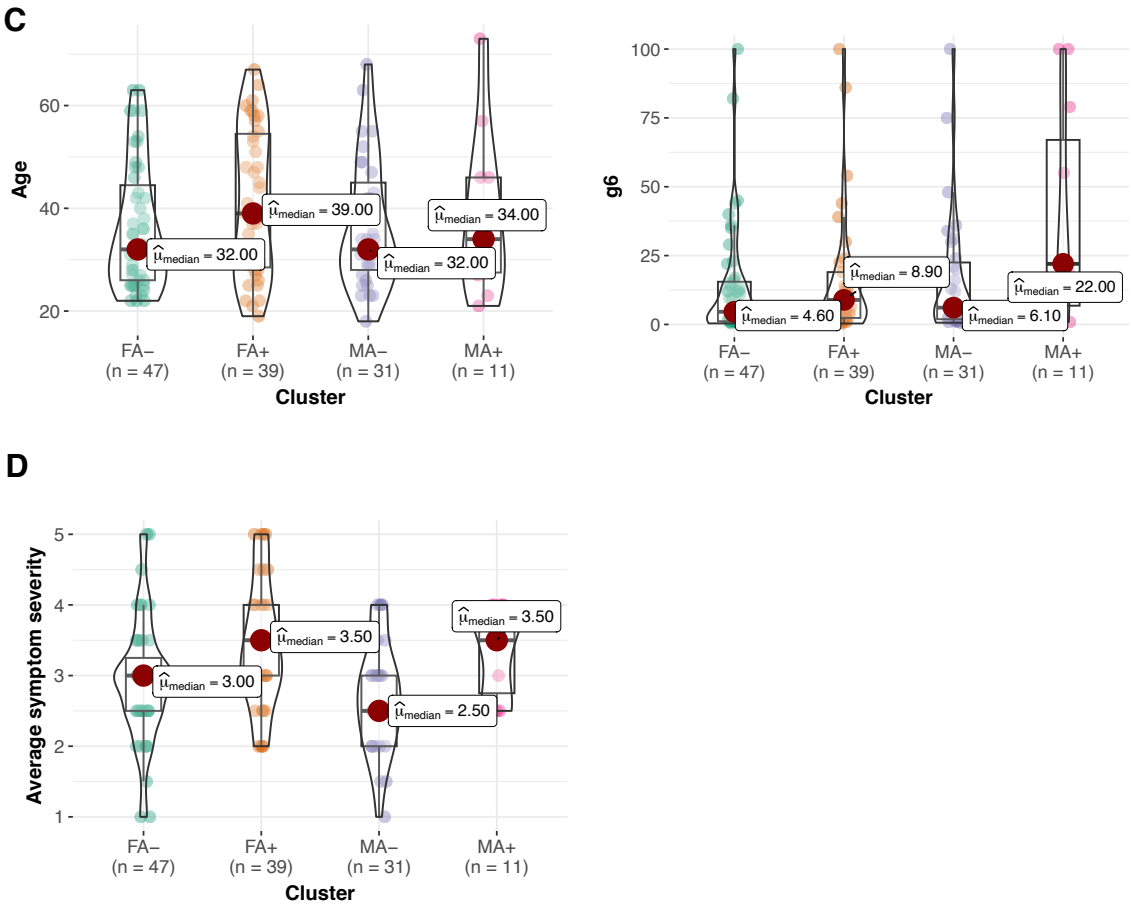


***Figure** 7: Descriptive statistics of the patient clusters. Rows A-B show categorical variables, C-D continuous variables.*

It is also important to highlight the symptom severity (as recorded in the symptom diary) of each cluster. Because group C did not have the symptom diary function in their app, this analysis could only be done with participants of the groups A and B. *Figure 8* shows the boxplots of the TSS across the clusters with the according statistical comparison.

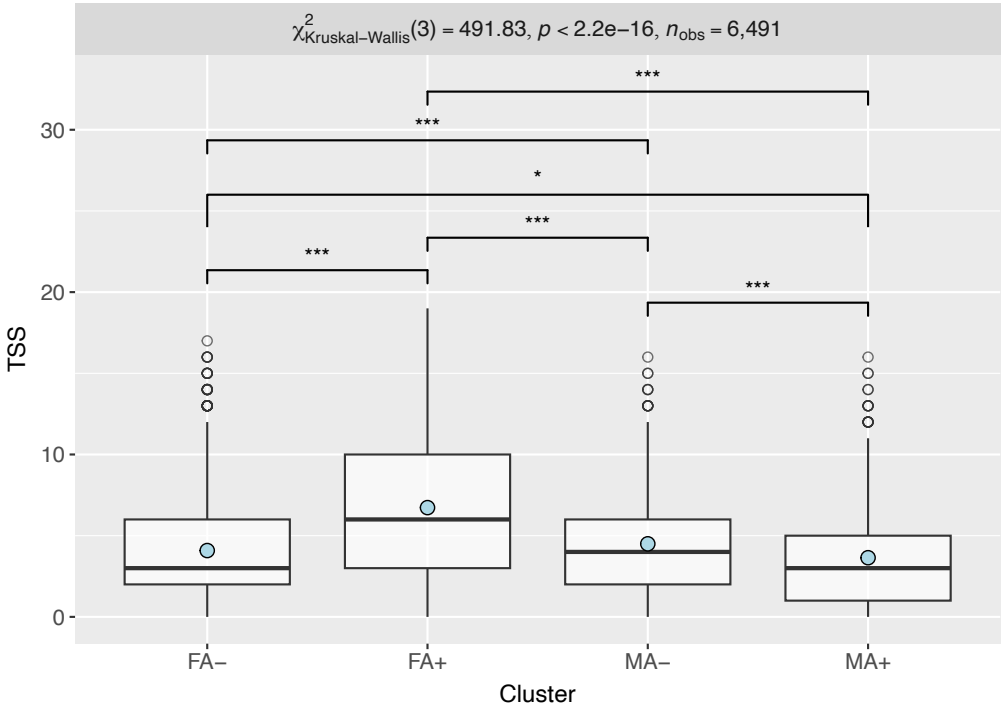


Figure 8*: Boxplot showing the distribution of the TSS across clusters. The light-blue dots represent the according mean. Kruskal-Wallis rank sum test was performed showing significance. Post-hoc a Dunn-test was conducted for pairwise comparison using Bonferroni adjusted p-values.*

The results indicated the highest TSS during the intervention period for participants within cluster FA+ (Mean: 6.73, Median: 6) followed in descending order by MA- (Mean: 4.5, Median: 5), FA- (Mean: 4.08, Median: 3) and MA+ (Mean: 3.64, Median: 3) with Kruskal Wallis test showing significancy. Additionally, post-hoc pairwise comparison with a Dunn test was conducted revealing significant differences between all groups. Adjusted p-values were applied with the Bonferroni method.

3.3 DESCRIPTIVE STATISTICS OF THE SYMPTOM SCORES

As the calculated symptom scores represent a key variable in the analysis and results of this thesis, the distribution of the TSS (*Figure 9, A*) and TNSS (*Figure 9, B*) throughout the intervention period is presented in the following.

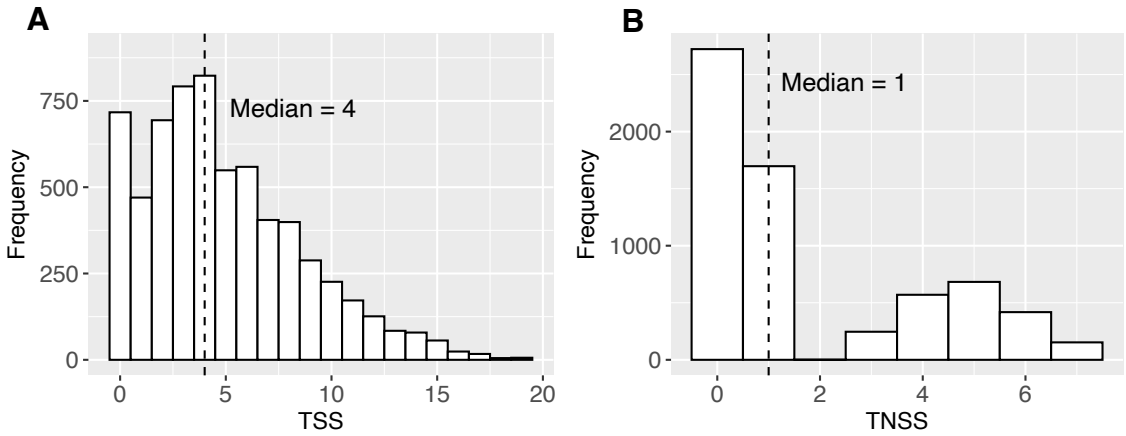


***Figure 9**: Distribution of the symptom scores TSS (A) and TNSS (B) including all data points (n = 6491) of the intervention period.*

Given that the symptoms follow a seasonality driven by the seasonal presence of grass pollen, also the time series of the symptom scores during the intervention period is presented. The time series is shown in *Figure 10A*. The individual data points represent the median of the symptom score across the entire cohort, per day (daily median scores). *Figure 10B* shows the according time series of the pollen concentration during the intervention period, as measured by the BAA-500 ("PoMo").

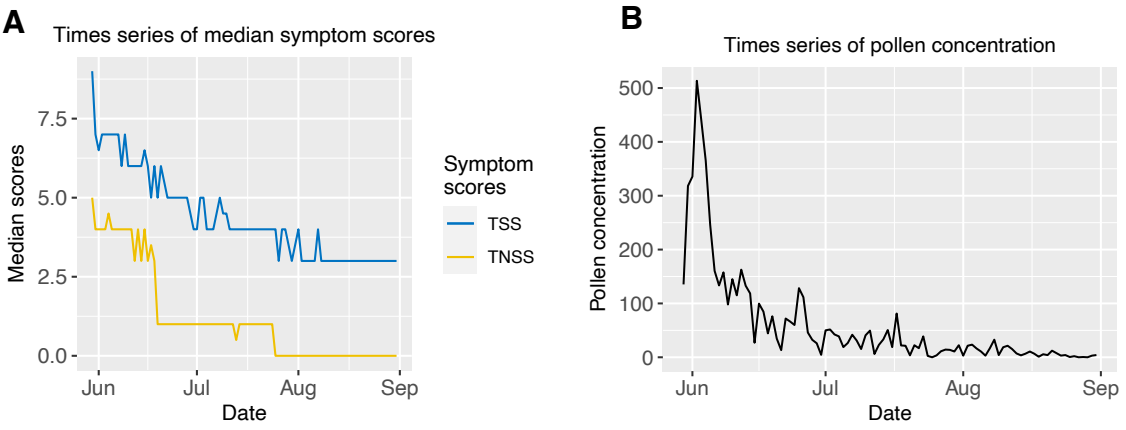


***Figure 10**: Time series of the symptom scores, TSS and TNSS. Each datapoint reflects the score as the median of the entire cohort for the according day. B: Time series of the airborne pollen concentrations indicated as pollen grains/m3.*

As can be derived the symptoms followed the time series of the pollen concentration. Towards the end of the study period, the TSS remained above zero, despite low to zero pollen counts. To further assess the relationship between symptoms and the pollen concentrations, the correlation between both variables was depicted. Both, TSS (*Figure 11, A*) and TNSS (*Figure 11, B*) were significantly and positively correlated (0.82) with the pollen concentration during the intervention period.

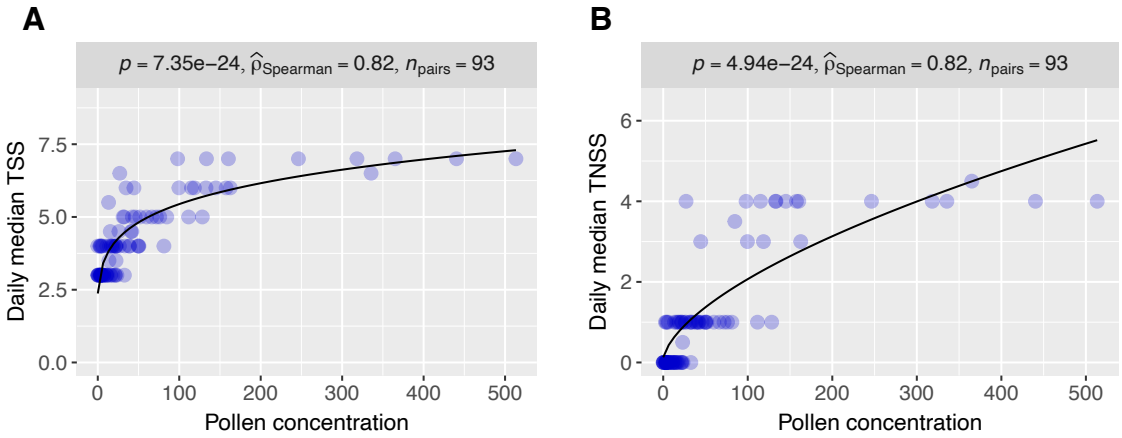


***Figure 11**: Scatter plots of the pollen concentration and the daily median symptom scores. The y axis shows the aggregated symptom scores (A: TSS; B: TNSS) as the median of all participants per day. The x axis shows the pollen concentration of the according day in pollen grains/m3. The black lines represent the best fit. Spearman's rank correlation coefficient was applied to analyze the relationship.*

3.4 PRIMARY OUTCOMES

3.4.1 CORRELATION OF MINI-RQLQ SCORES AND SYMPTOM SEVERITY

As stated in the chapter "Statistical Analysis", for this analysis, the participants who fully completed their first miniRQLQ were clustered with respect to the date the questionnaire was completed.

Figure 12 shows the two clusters with the corresponding median pollen concentration of the previous 7 days before the questionnaire was completed:

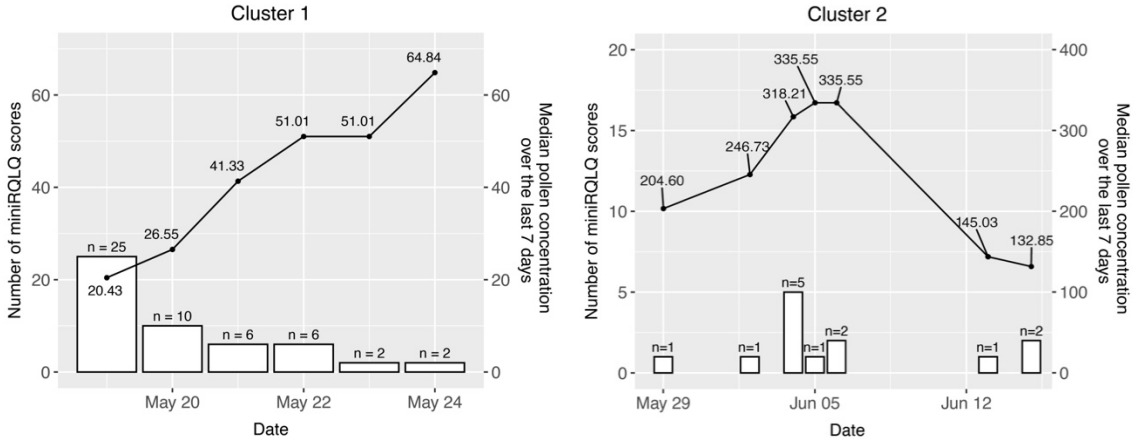


Figure 12*: The left y-axis presents the count of completed miniRQLQ questionnaires. The right y-axis presents the median pollen concentration in grains/m³ of the previous 7 days, as the miniRQLQ refers to this period. The x-axis shows the date. Pollen concentrations are rounded to two decimals.*

As the pollen concentrations varied rather significantly, further clusters were built based on the magnitude of the median pollen concentration of the previous 7 days prior to completing the questionnaire. To define clusters of patients with similar pollen exposure levels, the same pollen level classification was used as in the pollen forecast. This resulted in the patient clusters "medium exposure" (pollen concentration = 10 – 30, n = 35), "high exposure" (pollen concentration = 30 – 60, n = 14) and "very high exposure" (pollen concentration > 60, n = 15). As apparent from *Figure 12*, only participants of the cluster "medium exposure" formed a group with a fair sample size ($n \geq 30$). Due to the low sample size ($n < 30$) in the other clusters, these were excluded from the correlation analysis.

Figure 13 shows the relationship between the reported average symptom severity and the miniRQLQ score in the subcluster "medium exposure". No significant ($p = 0.25$) correlation could be derived regarding these variables.

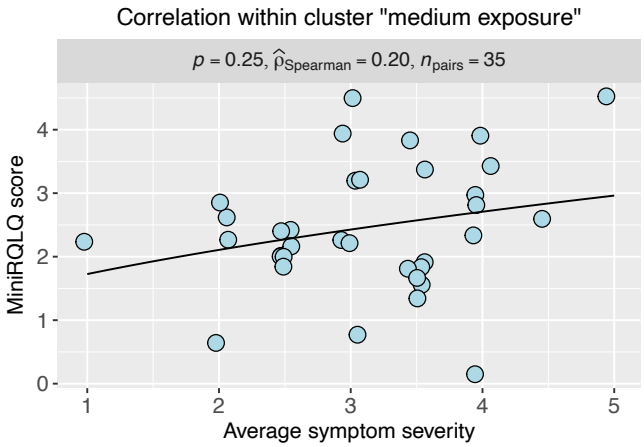


***Figure 13**: Scatter plot of the miniRQLQ score and reported average symptom severity within the cluster who were exposed to a medium pollen load in the previous 7 days. Spearman's rank correlation coefficient was applied. A line of best fit is presented in the plot. To increase clarity and reduce visual clutter a slight jitter was applied.*

Considering the relationship between the miniRQLQ score and the observed symptom severity, a positive correlation was observed, which did not reach statistical significance (p = 0.07). The number of datapoints was only n = 20 because only group A and B participants had used the app with the diary function and thus, the participants of group C could not be regarded in this analysis. *Figure 14* shows the according scatter plot:

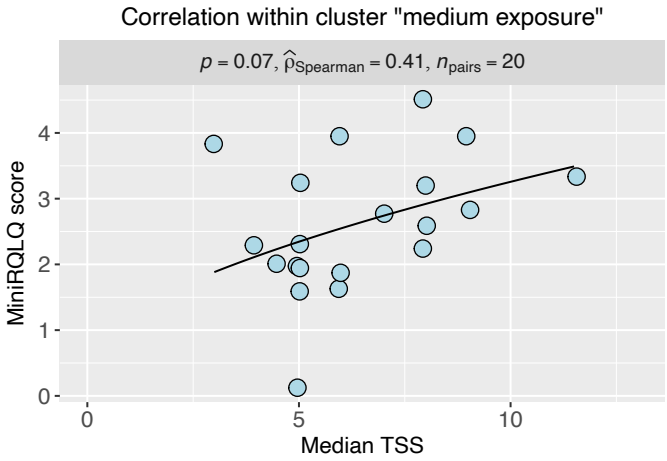


***Figure 14**: Scatter plot of the miniRQLQ score and the median TSS for each participant within the cluster who had been exposed to a medium pollen load in the previous 7 days. Spearman's rank correlation coefficient was applied. The positive correlation did not reach statistical significance. The black line represents the best fit. To increase clarity and reduce visual clutter slight jitter was applied.*

Regarding both relationships (*Figure 13 and 14*), also one outlier was detectable who had a miniRQLQ score of 0 despite indicating a relatively high average symptom severity (4) and

showing a median TSS of 5. However, as Spearman ranks coefficient is robust to outliers, it was not excluded.

3.4.2 CORRELATION OF EXPOSURE-RELATED BEHAVIOR AND OBSERVED SYMPTOM SEVERITY

3.4.2.1 AVOIDING OUTDOOR POLLEN EXPOSURE

Figure 15 shows the correlation analysis of the daily median scores of the cohort and the percentage of subjects who were not outside and thus potentially avoiding pollen exposure.

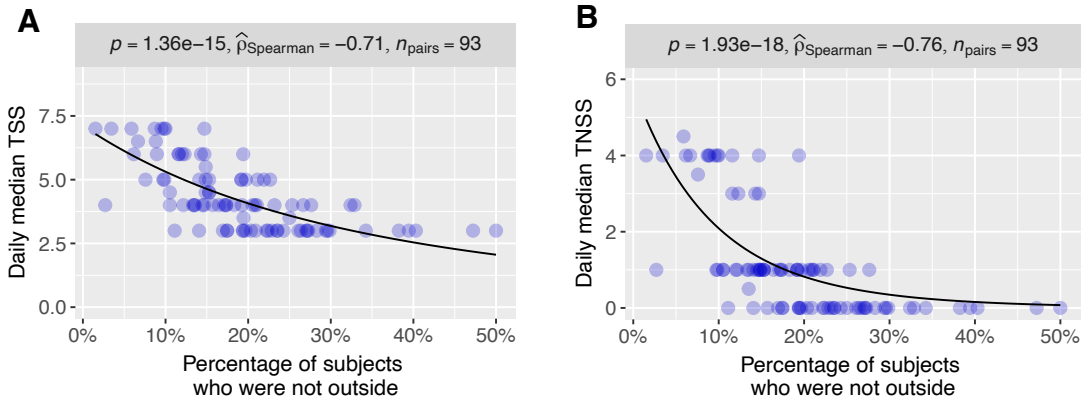


***Figure 15**: Scatter plots of the percentage of subjects who were not outside and the daily median TSS (A) and TNSS (B) of the study population for the corresponding day. As the data was non normally distributed Spearman's rank correlation coefficient was applied. The variables show a strong negative (-0.65) and negative very strong negative (-0.72) correlation. Also, a line of best fit is presented in the plot.*

Both, the TSS (A) and TNSS (B) showed a significant negative correlation with a decreasing percentage of participants per day who had not spent time outdoors. The correlation can be interpreted as very strong for both, TSS (r = - 0.71) and TNSS (r = - 0.76).
However, there are various variables which might influence if a person is going outside or not. Among these are weather factors (e. g. rainfall, temperature), which also affect the pollen concentration and may thus indirectly have an impact on the symptoms.

Therefore, the relationship between weather factors and the percentage of participants staying indoors was analyzed, which is presented in *Figure 16*:

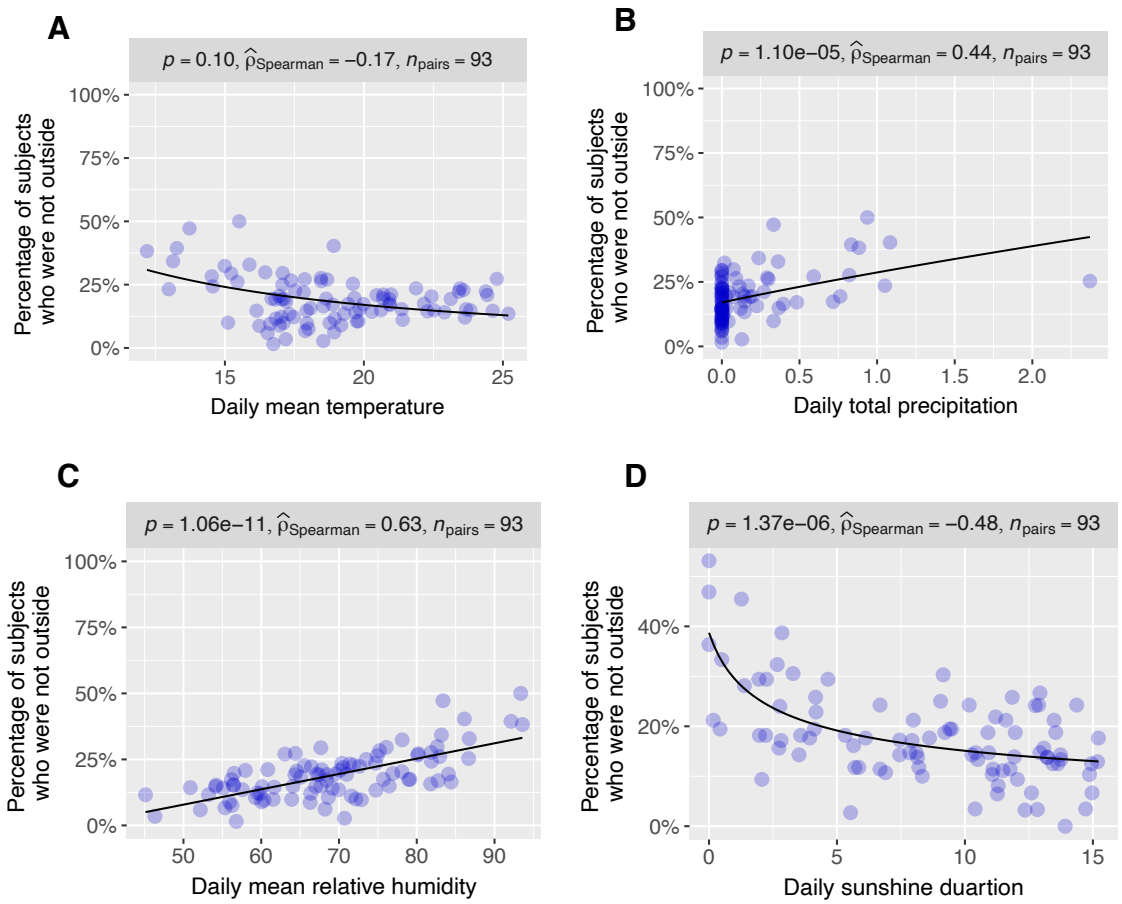


***Figure 16**: Scatter plots of the percentage of participants who were not outside and the daily mean temperature (A), the daily total of precipitation (B), the daily mean relative humidity (C) and daily sunshine duration (B). As provided by the DWD the mean daily temperature is indicated in degrees Celsius and the precipitation in mm. The daily mean relative humidity is indicated in percentages. Daily sunshine duration in hours. Spearman's rank correlation coefficient was applied. A line of best fit is presented in the plots.*

The daily temperature showed a negative correlation with the percentage of participants not going outside, which missed statistical significance ($p = 0.10$). However, there was a significant moderate and positive correlation with the precipitation ($r = 0.44$, $p < 0.001$). As can be seen, with increasing precipitation the percentage of the cohort not going outside appeared to increase as well. The same accounts for the relative humidity, showing a strong positive correlation ($r = 0.63$, $p < 0.001$). Increasing daily sunshine hours per day appeared to show a moderate negative correlation ($r = -0.48$, $p < 0.001$) with the percentage of participants staying inside.

Within this context it is important to note that the pollen concentration also showed a significant and strong correlation with humidity ($r = -0.74$), a significant and moderate correlation with precipitation ($r = 0.43$) and a significant strong correlation with daily sunshine hours, as illustrated in *Figure 17* (following page):

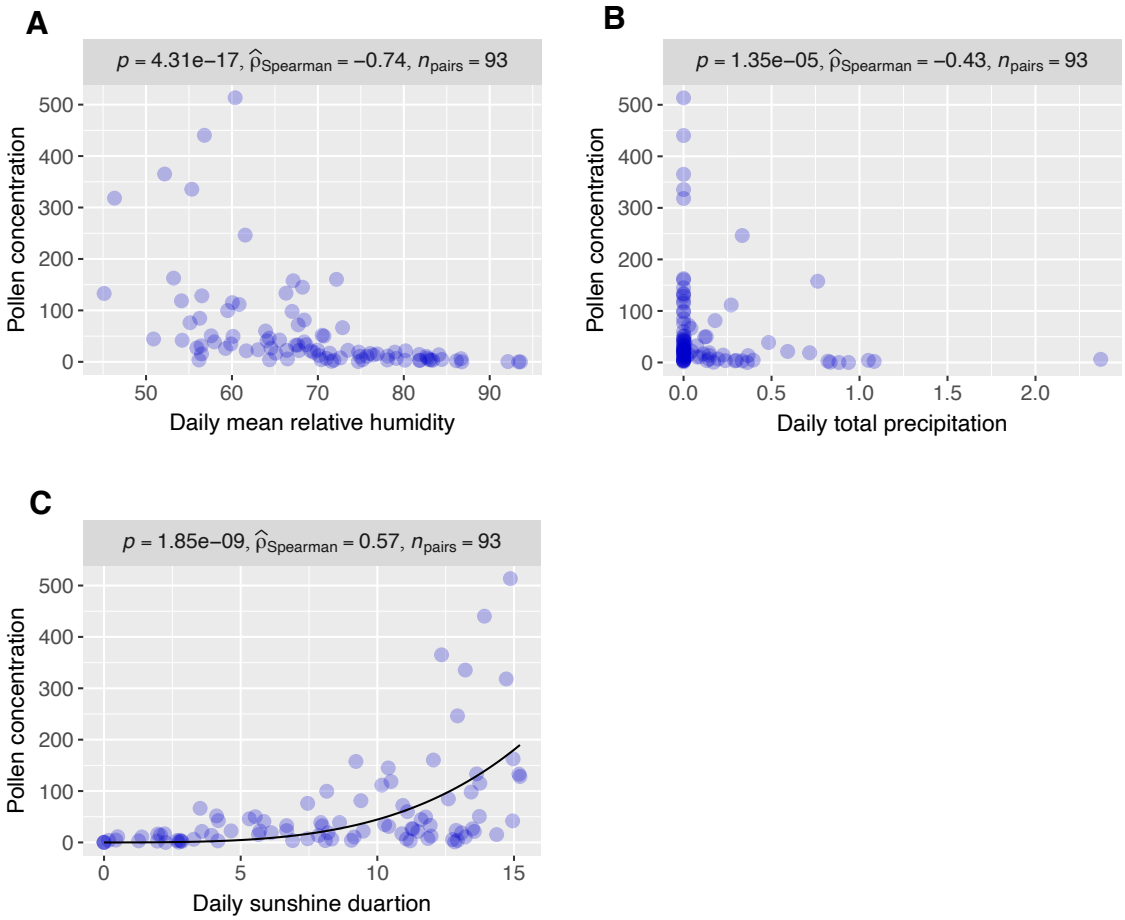


***Figure 17**: Scatter plots and Spearman's rank correlation between the daily pollen concentration in grains/m3 and the daily mean relative humidity in percentages (A) precipitation in mm (B) and daily sunshine duration in hours (C). If applicable, a line of best fit is provided.*

3.4.2.2 WASHING HAIR

In the symptom diary, participants could select if she or he washed her/his hair on the respective day and, if yes, at what time during the day. Options that could be selected within "yes" were "in the morning", "right after coming home", "in the evening" and "at another time". *Table 10* shows the correlation between these variables and the daily median symptom scores of the cohort.

***Table 10**: Correlation matrix of the daily median symptom scores and the time of washing hair or not washing it respectively. It shows Spearman's roh and the corresponding p-value in brackets below. Greyed numbers signal that the correlation was not significant.*

Time of washing hair	TSS	TNSS
In the morning	- 0.25 *(0.0171)*	- 0.26 *(0.0110)*
After coming home	0.13 *(0.2022)*	0.14 *(0.1664)*
In the evening	0.44 *(8.345e-06)*	0.47 *(1.653e-06)*
At another time	- 0.50 *(4.302e-07)*	- 0.43 *(1.35e-05)*
Hair was not washed	0.04 *(0.7089)*	- 0.02 *(0.8349)*

As can be derived from *Table 10* washing hair "at another time" showed the highest negative correlation throughout all symptom scores (TSS: r = -0.50; TNSS = - 0.43). Washing hair "in the morning" also correlated negatively with the symptom scores. Washing hair "In the evening", however, showed a positive correlation with the symptoms scores. Possible reasons for that are addressed in the discussion. There was no significant correlation observed between not washing hair and the symptom scores.

Due to the seasonality of pollen, it was further investigated if the indicated effects would differ for days with higher or lower pollen concentrations, respectively. The data was divided into two subsets, the first representing days with "low" and "medium" pollen concentration, the second representing days "high" and "very high" pollen concentration". Grouping together "low" and "medium" as well as "high" and "very high" pollen concentration days was decided to avoid too small sample sizes for the correlation analysis (n > 30).

***Table 11**: Correlation matrix of the daily median symptom scores and the time of washing hair or not washing it respectively, categorized into two groups: days with measured low to medium pollen concentrations and days with measured high to very high pollen concentrations. It shows Spearman's roh as well as the corresponding p-value in brackets below. Greyed numbers signal that the correlation was not significant.*

Time of washing hair	**Low and medium pollen concentration (n=45)**		**High and very high pollen concentration (n=40)**	
	TSS	**TNSS**	**TSS**	**TNSS**
In the morning	0.07 *(0.633)*	0.00 *(0.9921)*	- 0.35 *(0.0250)*	- 0.37 *(0.0172)*
After coming home	0.09 *(0.5708)*	0.11 *(0.4526)*	0.06 *(0.7147)*	0.13 *(0.4149)*
In the evening	0.11 *(0.4915)*	0.23 *(0.1311)*	0.32 *(0.0432)*	0.31 *(0.0515)*
At another time	- 0.20 *(0.1837)*	- 0.05 *(0.7328)*	- 0.61 *(2.832e-05)*	- 0.54 *(0.0003)*
Hair was not washed	0.00 *(0.9956)*	- 0.20 *(0.1841)*	0.25 *(0.113)*	0.26 *(0.1082)*

The relationship of the symptom scores with washing hair "in the morning" and "at another time" were only significant for days with "high" and "very high" pollen concentrations, and the correlation coefficients were higher than when taking all days into account. The percentage of washing hair in the morning showed a weak and negative correlation with the TSS (r = -0.35) and TNSS (r = -0.37), whereas "at another time" showed a strong and negative correlation regarding the TSS (r = -0.61) and a moderate, negative relationship regarding the TNSS (r =-0.54). Also, when focusing on days with high and very high pollen concentrations, a significant positive correlation between washing hair in the evening and the TSS could be observed (r = 0.32).

3.4.2.3 CLOSING WINDOWS WHILE SLEEPING

Regarding the question if participants slept with windows opened or closed, three options were provided to select within the diary: slept with windows "completely closed", "partly opened and partly closed", or "opened". The relationship is presented in *Table 12*:

***Table 12**: Correlation matrix showing the relationship between the relative percentage of how many participants slept with either windows "closed", "partly opened, partly closed", or "opened windows" and the median symptom scores of the cohort of the following day. Spearman's roh is shown as well as the corresponding p-value in brackets below. Greyed numbers signal that the correlation was not significant.*

Windows while sleeping	**TSS**	**TNSS**
Closed	- 0.19 *(0.0701)*	- 0.14 *(0.1849)*
Partly opened, partly closed	- 0.50 *(5.07e-07)*	- 0.52 *(7.776e-08)*
Opened	0.44 *(1.171e-05)*	0.39 *(0.0002)*

Sleeping with windows "opened" showed a positive, moderate correlation with the symptom severity. No significant relationship was observed between sleeping with windows "closed" for the TNSS (p = 0.1849) and the TSS (p = 0.0701). Sleeping with windows "party opened and partly closed" showed a negative, moderate correlation regarding both symptom scores. It was further investigated if the observed correlations would differ for higher or lower pollen concentrations, respectively, and the same strategy was followed as described above.

***Table 13**: Correlation matrix showing the relationship between the relative percentage of how many participants slept with either windows "closed", "partly opened, partly closed", or "opened windows" and the median symptom scores of the cohort of the following day. Spearman's roh is shown as well as the corresponding p-value in brackets below. Greyed numbers signal that the correlation was not significant. Compared to washing hair only 44 days could be considered for "low and medium pollen concentration" as the symptoms of the following day were taken into account for this analysis.*

Windows while sleeping	**Low and medium pollen concentration (n=44)**		**High and very high pollen concentration (n=40)**	
	TSS	**TNSS**	**TSS**	**TNSS**
Closed	0.30 *(0.0465)*	0.45 *(0.0023)*	- 0.69 *(7.837e-07)*	- 0.72 *(1.525e-07)*
Partly opened, partly closed	- 0.52 *(0.0003)*	- 0.59 *(2.856e-05)*	0.05 *(0.771)*	0.11 *(0.4863)*
Opened	- 0.10 *(0.5276)*	- 0.25 *(0.1013)*	0.76 *(1.44e-08)*	0.79 *(1.435e-09)*

3.4.3 CORRELATION OF EXPOSURE-RELATED BEHAVIOR AND REPORTED SYMPTOM SEVERITY

The correlation of the exposure-related behavior and the average symptom severity according to the screening statement, is shown in *Figure 18*:

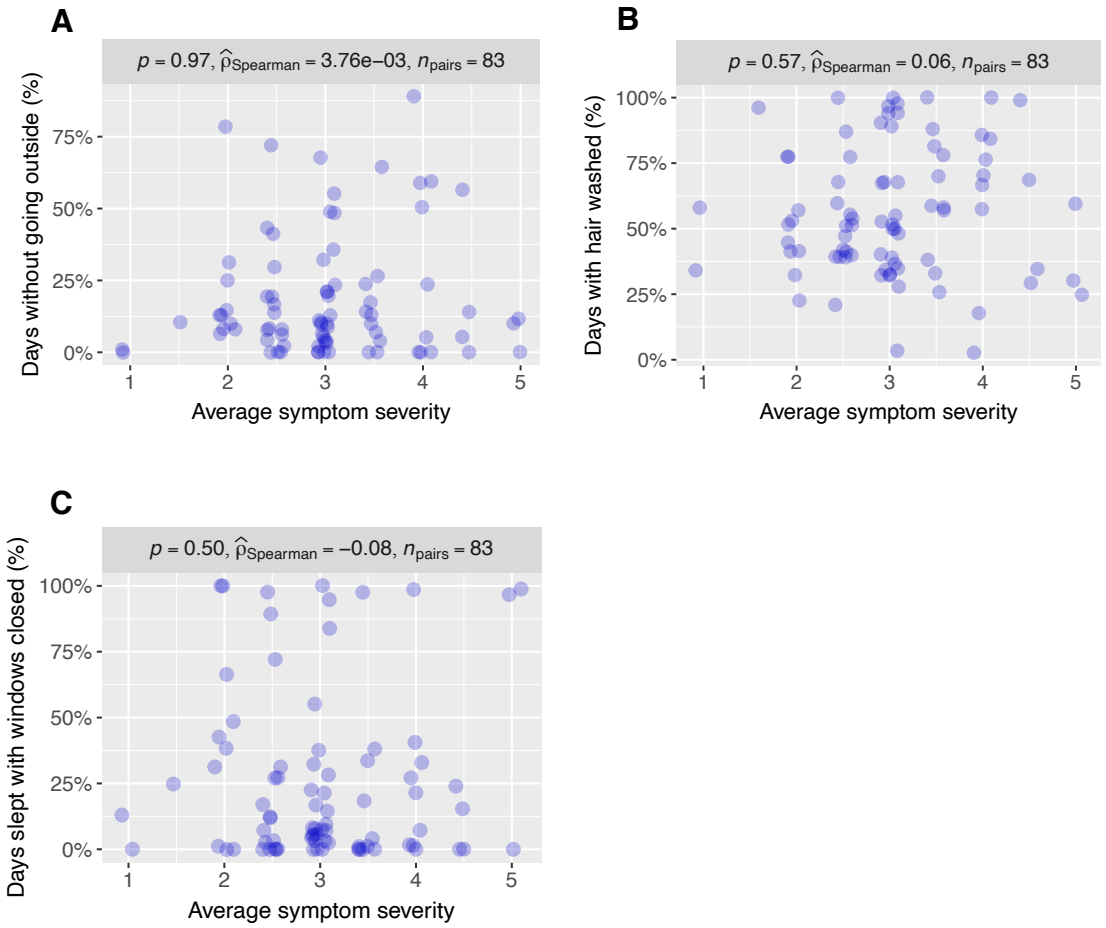


***Figure 18**: Scatter plots of the patient-reported average symptom severity during the screening process (x-axis) and the percentage in % without going outside (A), days with hair washed (B), and days slept with windows closed (C). Spearman's rank correlation coefficient was applied to evaluate the relationship. To increase clarity and reduce visual clutter a slight jitter was applied.*

The analysis showed no signs of a relationship between the average symptom severity of the participants before the study as reported in the screening questionnaire and the frequency of not going outside (p = 0.97), hair washing (p = 0.57) and sleeping with windows closed (p = 0.5)

The same analysis was conducted only regarding group A and days with a “high” or “very high” pollen forecast, and in this case as well, no significant relationships were observed (*Figure 19*).

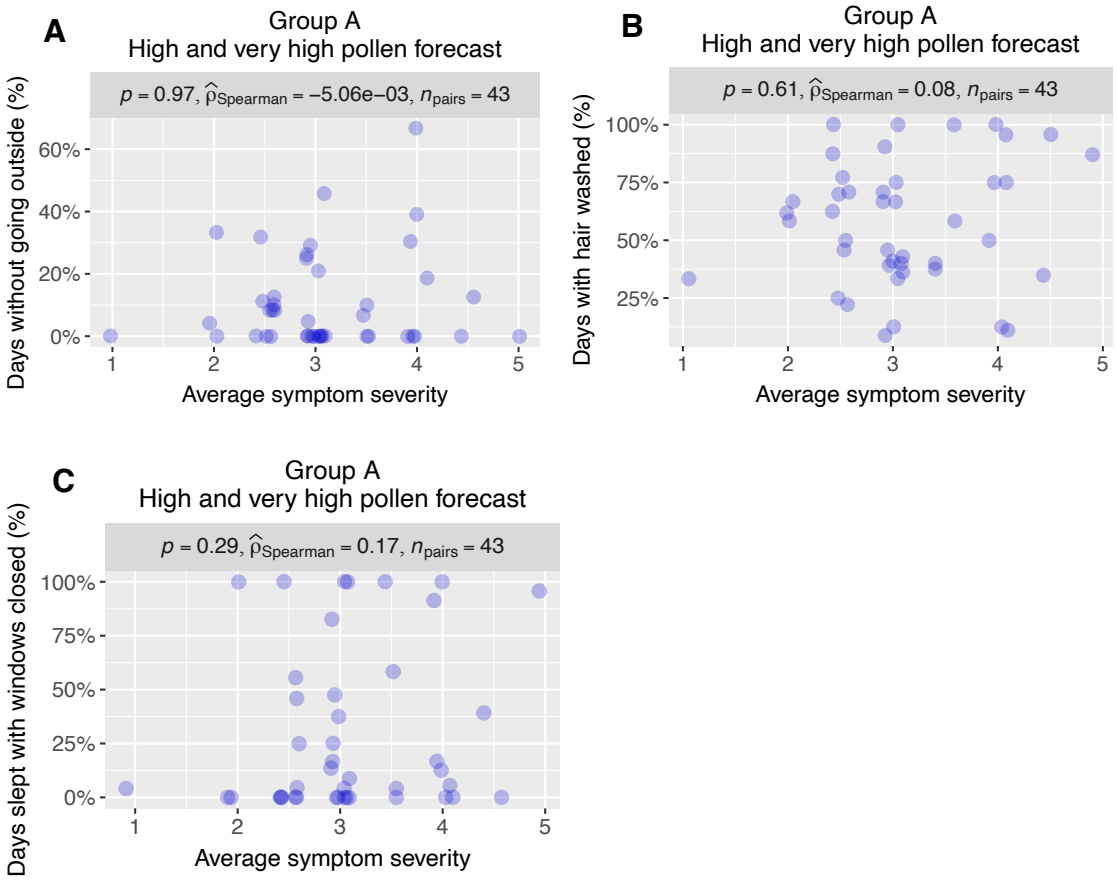


***Figure 19**: Scatter plots of the patient-reported average symptom severity during the screening process (x-axis) and the percentage in % without going outside (A), days with hair washed (B), and days slept with windows closed (C). This figure only encompasses participants of group A and days with a high or very high pollen forecast. Spearman's rank correlation coefficient was applied to evaluate the relationship. To increase clarity and reduce visual clutter a slight jitter was applied.*

3.4.4 EXPOSURE-RELATED BEHAVIOR BETWEEN GROUPS

3.4.4.1 DIARY USER GROUPS

To test whether there was a difference in exposure-related, potentially protective behavior between the groups A and B, firstly Pearson-χ2-tests were applied. In addition to considering the data from all days, it was also investigated if there were differences regarding only days with a high or very high pollen forecast. Since this information was only available for group A participants, only these participants were able to base their behavior on the forecast, which led to the assumption that more protective behaviors might be observed in group A than in group B. In this analysis again, time spent outside (*Figure 20, A*), washing hair (*Figure 20, B*) and sleeping with windows closed (*Figure 20, C*) were considered.

Figure 20 shows the according bar plots with the results of the Pearson χ2 test for all days (overall) and regarding only days with a high or very high pollen forecast:

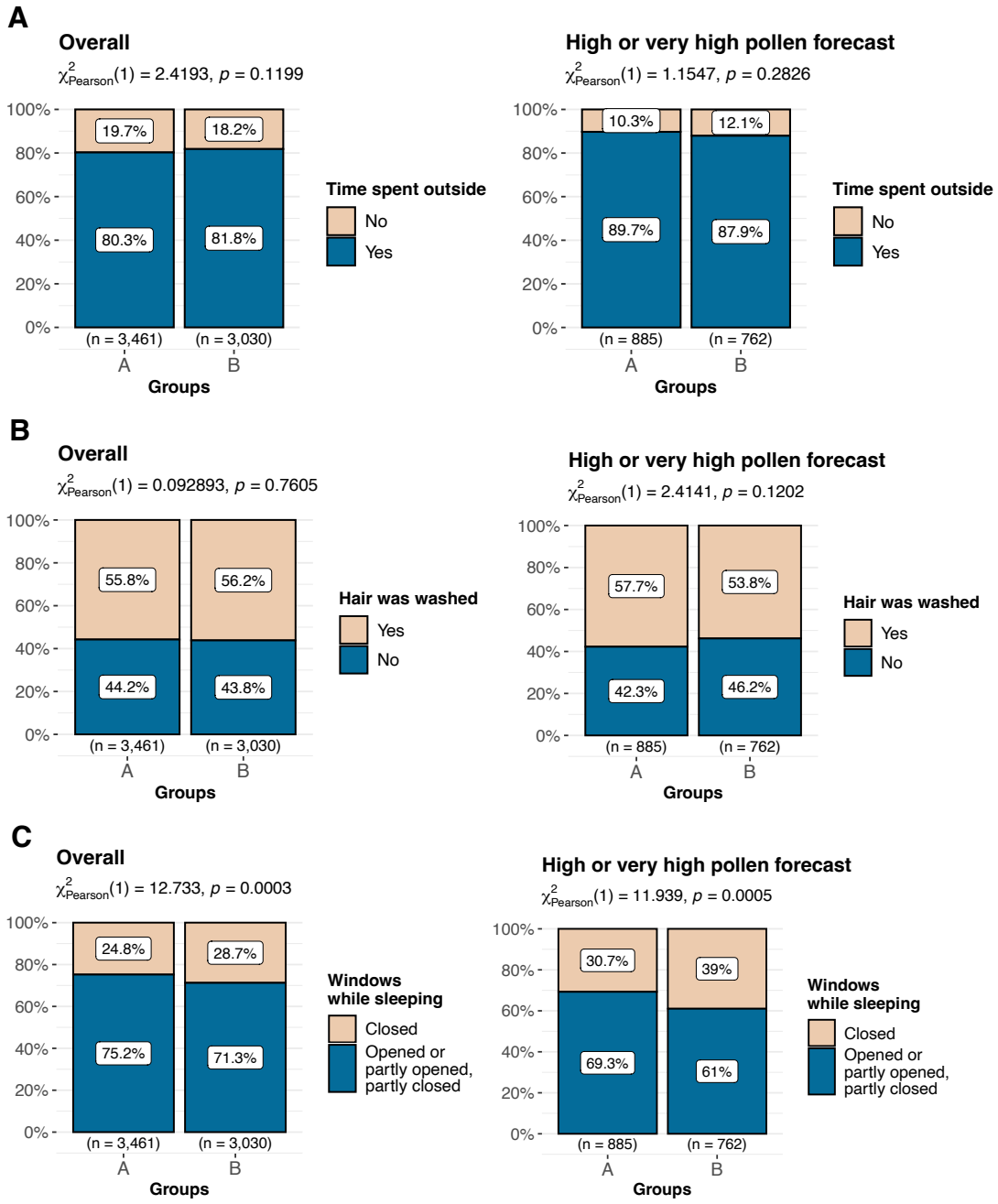


Figure 20: *Bar plots showing the relative frequency how often the participants of group A and B spent time outside (A), washed their hair (B) and slept with windows closed (C). Each row shows the frequencies for all days of the intervention period on the left whereas the plots on the right show only days with high or very high pollen forecast presented in the app. Differences between groups were tested with Pearson χ2 test.*

Regarding all days (overall) the frequency how often the participants spent time outside no significant difference between both groups (p = 0.1199). Also considering only days with high or very high pollen forecast, no significant difference between the groups could be observed (p = 0.2826).

Regarding the frequency of washing hair, also no significant difference could be observed, neither for all days (p = 7605) nor for days with high or very high pollen forecast (p = 0.1202). However, group B showed a significant higher frequency regarding sleeping with windows closed overall (p = 0.0003) and for days with high and very high pollen forecasts (p = 0.0005).

Whether someone is sleeping with windows opened or closed, respectively, may have various interfering variables. Therefore, a beta regression was applied to identify confounders. Besides the respective group, the following variables were included as possible confounders: sex, median TSS, Asthma yes/no, sIgE (g6), smoker yes/no and age. Applying the beta regression, belonging to group A or B showed no significance (p = 0.8221). The only significant variable was the smoker status (p = 0.0339). According to the model, in smokers the expected percentage of sleeping with windows closed at night can be seen as 55% lower ($e^{ß} = 0.45$). The overall model was significant (p = 6.85e-14) with a Pseudo R-squared of 0.1044. The results are presented in *Table 14*:

***Table 14**: Results of a beta regression identifying significant predictors for a higher percentage of sleeping with windows "closed". Greyed numbers signal insignificance.*

Predictor variable	**Estimate / ß**	**Std. Error**	**p-value**
Group B	0.05847	0.2824	*0.8360*
Smoker (y)	- 0.8074	0.3824	*0.0347*
Sex (m)	0.4196	0.3087	*0.1741*
Median TSS	- 0.02613	0.05094	*0.6081*
Allergic asthma (y)	- 0.09774	0.3206	*0.7605*
sIgE g6	- 0.00008	0.0061	*0.9901*
Age	- 0.00545	0.01104	*0.6210*

3.4.4.2 COMPARISON OF ALL GROUPS

The statistical comparison of all three groups (A, B and C) was performed analyzing the data obtained from the question Q15n1 of the feedback questionnaire: “Did you pay more attention than usual to measures such as washing your hair, changing clothes, etc. due to the app usage?”. Independent of group, 3.1% (4/127) of participants indicated “very strongly”, 10.2% (13/127) “strongly”, 37% (47/127) “partially”, 25.2% (32/127) “hardly”, and 24.2% (31/127) “not at all”. The possible response options as well as the distribution across groups is shown in *Figure 21*. Performing a Pearson-χ2-test no difference between the groups could be observed (p = 0.7024).

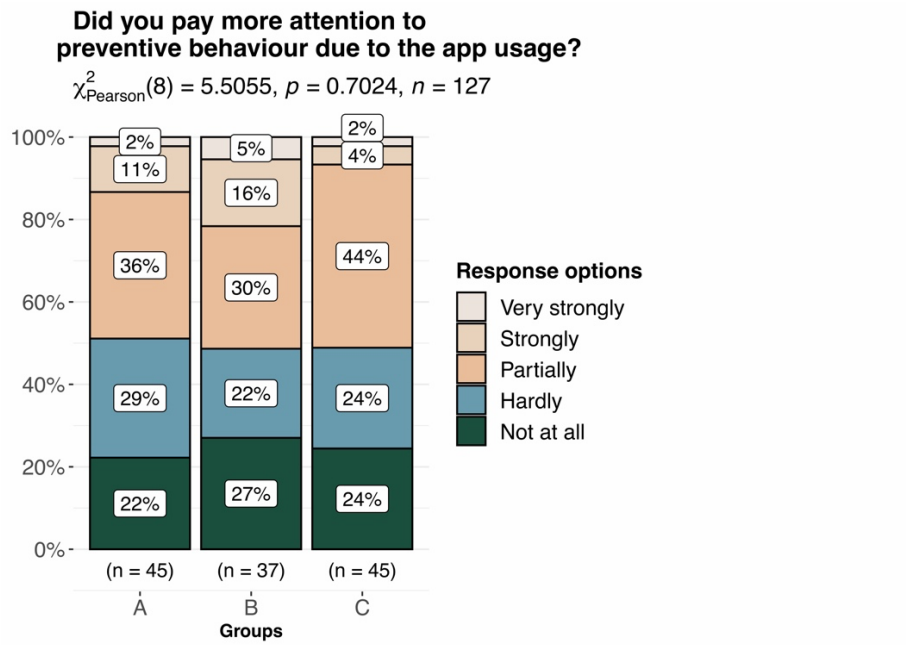


***Figure 21**: Bar plots showing the relative frequency of the response options regarding preventive behavior across groups. Differences between groups were tested with Pearson χ2 test. The percentages may not sum up to 100% as they were rounded to ensure readability and avoid visual clutter.*

Overall, 50,4% (64/127) of participants indicated to have at least partially paid more attention to preventive behavior due to the app usage. The percentages ranged from 48.9% (22/45; group A) over 51.4% (19/37; group B) and 51.1% (23/35; group C). When grouping the approving (partially, strongly, very strongly) and negating (hardly, not at all) responses, no significant difference between approving and negating was observed (Pearson's χ^2-test: X-squared = 0.063601, df = 2, p-value = 0.9687). The same held true for a comparison of approving and negating answers between the patient clusters. (X-squared = 0.2633, df = 3, p-value = 0.9668).

As the analysis did not reveal a significant effect, a logistic regression was performed to explore the relationships between the variables more thoroughly and to assess whether the absence of an effect might be attributed to confounding factors. The following predictor variables were considered in the model: Group, sex, age, sIgE g6, asthma (yes/no), smoker (yes/no), reported average symptom severity. Also, the logistic regression analysis revealed no statistically significant impact of any of the included predictors on the outcome variable (approving or negating answer on Q14n1) (data not shown).

3.4.5 MEDICATION INTAKE BETWEEN GROUPS

3.4.5.1 DIARY USER GROUPS

Table 15 shows the results of the descriptive statistics and statistical comparison of the Medication score between group A and B. Additionally, a stratification of the results was conducted based on the forecasted pollen level. Statistical comparison was performed using Mann-Whitney U test.

***Table 15**: Descriptive statistics of the medication score showing the mean (SD) and median (25.; 75. Percentile) for each group. Mann-Whitney U tests were performed to identify differences between groups. Greyed numbers signal that the p-value did not show significance.*

	Medication score Group A		**Medication score Group B**		**Statistical Comparison**
Forecast	Mean	Median	Mean	Median	p-value
Overall (n=6491)	0.28 ± 0.67	0 (0; 0)	0.17 ± 0.47	0 (0;0)	*4.095e-11*
High or very high (n=1647)	0.52 ± 0.94	0 (0; 1)	0.33 ± 0.66	0 (0; 0)	*0.0012*
Medium (n=728)	0.28 ± 0.64	0 (0; 0)	0.20 ± 0.50	0 (0; 0)	*0.1122*
None or low (n=3891)	0.18 ± 0.51	0 (0; 0)	0.09 ± 0.34	0 (0; 0)	*1.096e-08*

The results indicated a significant difference between the medication scores of group A and group B regarding all days (overall). (W = 5561965, p-value = 4.095e-11). The same was observed for days with a pollen forecast of “high or very high” (W = 361752, p-value = 0.001207) and for “low” and” no pollen” (W = 1992262, p-value = 1.096e-08). However, no significant difference was observed for days with a forecasted “medium” pollen level (W = 68956, p-value = 0.1122).

To address the question further whether the participants of group A based their decision to take medication on the pollen forecast, a Spearman's correlation analysis was conducted. As illustrated in *Figure 22* there was a significant and strong relationship between the medication score and the pollen forecast level for both, groups A (*Figure 22, A*) and B (*Figure 22*, B), and no difference in the coefficients could be observed.

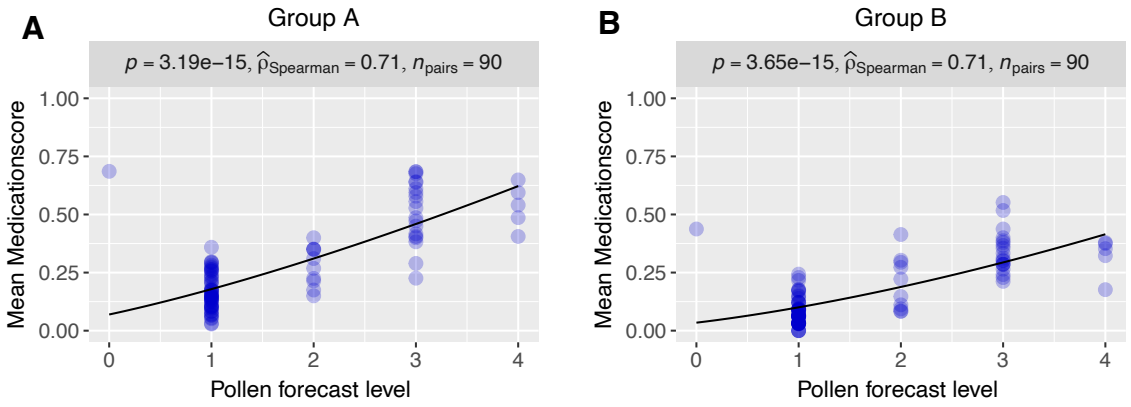


***Figure 22**: Scatter plots showing the relationship between the daily mean Medication score of group A (A) and group (B) and the pollen forecast level shown in the app. To test the relationship Spearman's rank correlation coefficient was applied.*

Under the alternative assumption that patients rather took their medication based on their symptoms, a correlation analysis of the symptom severity and medication scores was performed, revealing a strongly significant and positive correlation between both variables (p <0.001, r = 0.91).

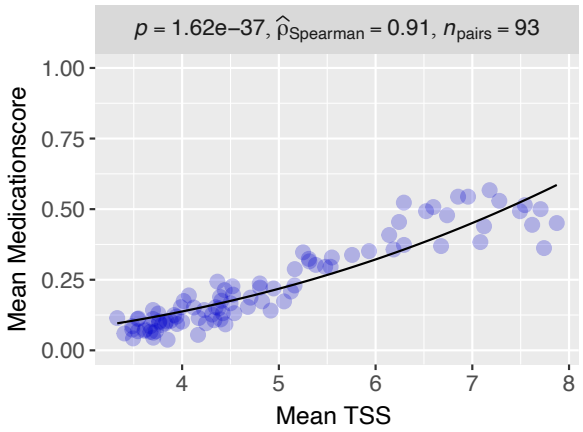


***Figure 23**: Scatter plots showing the relationship between the daily mean Medication score of the cohort and the mean TSS for the corresponding day. Spearman's rank correlation coefficient was applied.*

To further investigate if there are certain medication categories which were taken more often by either of the groups, a comparison to focus on the medication type was conducted as well. *Table 16* illustrates the results of *Pearson-*χ^2-tests, revealing a statistically significant more frequent medication intake in group A across all categories, except for homeopathic remedies.

***Table 16**: Absolute frequencies (relative frequencies) of the medication intake stratified by medication category across groups. Pearson-*χ^2*-tests were used for statistical comparison between groups A and B. Greyed numbers signal that the p-value shows no significance.*

Medication		**Group A** (n=3461)	**Group B** (n=3030)	**Statistical Comparison**
Systemic medication	Yes	434 (12.54%)	271 (8.94%)	*p = 4.123e-06*
	No	3027 (87.46%)	2759 (91.06%)	
Nose drops	Yes	147 (4.25%)	65 (2.15%)	*p = 2.819e-06*
	No	3314 (95.75%)	2965 (97.85%)	
Eye drops	Yes	116 (3.35%)	41 (1.35%)	*p = 2.637e-07*
	No	3345 (96.65%)	3075 (98.65%)	
Homeopathic medication	Yes	16 (0.46%)	5 (0.17%)	*p = 0.05942*
	No	3345 (99.54%)	3025 (99.83%)	
Other medication	Yes	225 (6.50%)	119 (3.93%)	*p = 5.066e-06*
	No	3236 (93.50%)	2911 (96.07%)	

Table 16 also illustrates that the most frequent medication during the intervention period was systemic medication, compared to homeopathic medication being the least common.

To identify further patterns within the medication intake, the frequency was also analyzed applying the clustering of patients. Due to the very low frequency of homeopathic medication, it was not considered in this analysis. Applying a χ^2-test, it showed significant results throughout all medication groups. Depending on the medication type, either cluster FA+ or MA- appeared to take the most medication. *Figure 24* shows the results regarding systemic medication (A), nasal spray (B), eye drops (C), and other medication (D):

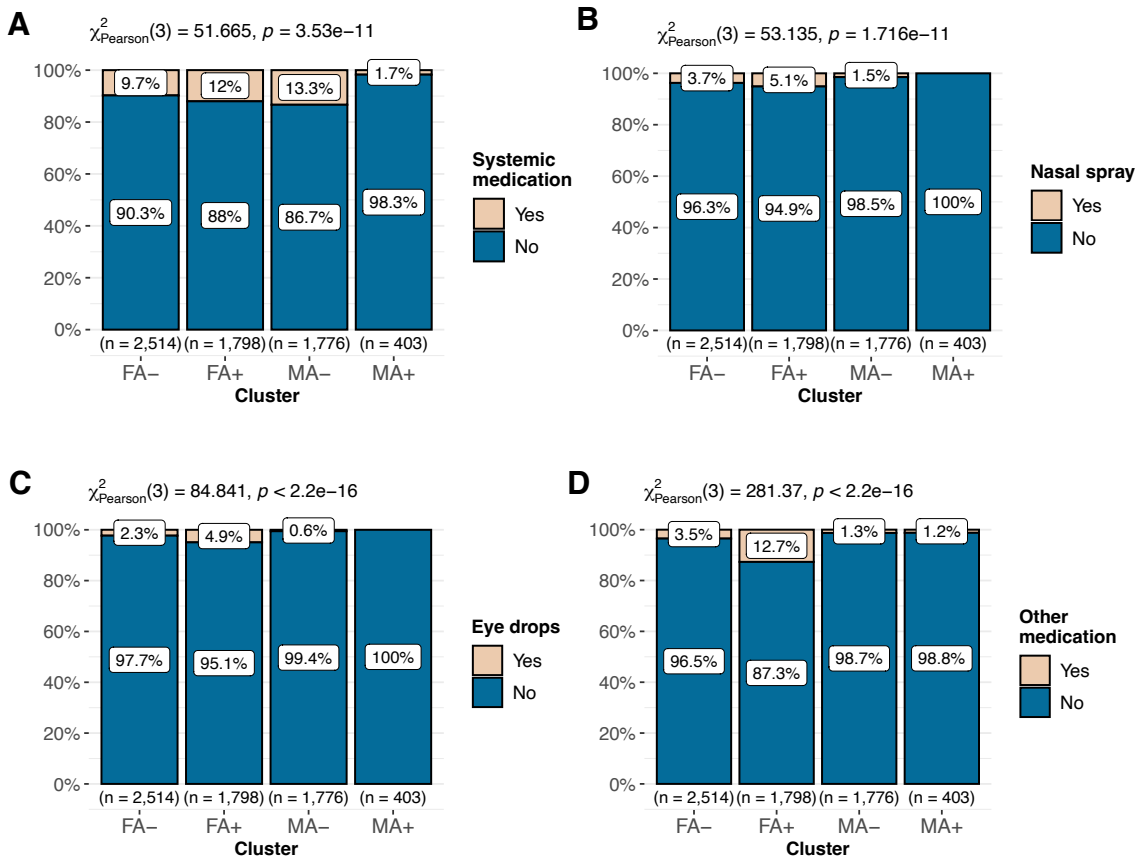


***Figure 24**: Bar plots showing the relative frequency how often the participants in the respective cluster took systemic medication (A), nasal spray (B), eye drops (C), and other medication (D). Significance testing for differences between clusters was conducted using the Pearson's χ2 test.*

3.4.5.2 COMPARISON OF ALL GROUPS

The comparison of all groups (A, B, C) regarding the medication intake was performed analyzing the question Q16n1 in the feedback questionnaire: “Did you take less allergy

medication than usual while using the app during the allergy season?" Independent of the group, 15.0% (19/127) of participants reported they needed partially less medication, 10.2% (13/127) needed less medication and 5.5% (7/127) needed considerably less medication. 66.9% (85/127) of participants reported no difference in medication intake, and 2.3% (3/127) reported more medication use. Figure 25 shows the distribution between groups:

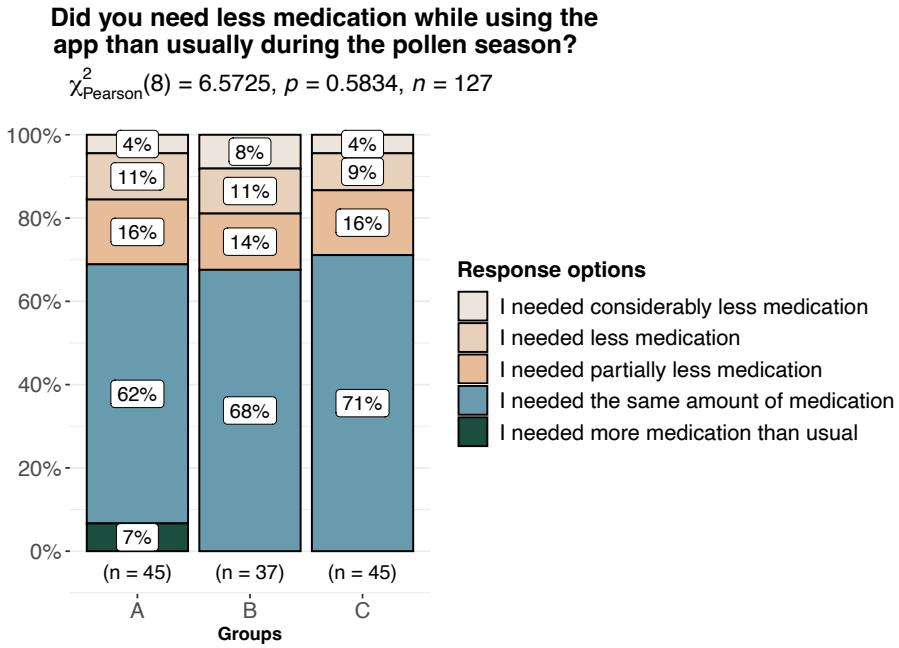


***Figure 25**: Bar plot illustrating the distribution of response frequencies regarding medication intake across groups. Differences between groups were tested with Pearson χ2 test. The percentages may not sum up to 100% as they were rounded to ensure readability and avoid visual clutter.*

Pearson-χ^2-test showed no significant differences between the groups (p = 0.5834).

However, it can be noted that 30.7% (39/127) in group A, 32.4% (12/37) in group B and 29% (13/45) in group C reported to have achieved at least a partial reduction in medication intake during the intervention period in comparison to previous pollen seasons. Overall, these were 30.7% (39/127) participants who stated needing at least partially less medication.

Of these, 71.8% (28/39) reported needing less systemic Antihistamines, 28.2% (11/39) needing lees nasal spray, 2.6 % (1/39) needing less nose drops, 2.6 % (1/39) needing less painkiller, 2.6 % (1/39) needing less cortisone, and 7.7% (4/39) needing no medication at all.

When grouping the approving (partially, less, considerably less) and negating (same amount, more) responses, also no significant difference between groups was observed (Pearson-χ^2-test: χ^2 = 0.12513, df = 2, p-value = 0.9394). Also, when applying the clustering of patients, no significant differences regarding the responses between the clusters were observed (Pearson-χ^2-test: χ^2= 0.42849, df = 3, p-value = 0.9343).

An additional logistic regression was performed with approving vs. negating answers as response variable, but none of the predictor variables significantly impacted the outcome. As predictor variables were considered: group, sex, age, sIgE (g6), asthma (yes/no), smoker (yes/no), reported average symptom severity.

In context of medication intake, the daily duration of the app usage per group was also observed. The differences however did not reach statistical significance (X-squared = 7.9828, df = 4, p-value = 0.0922) The distribution is shown in *Figure 26*:

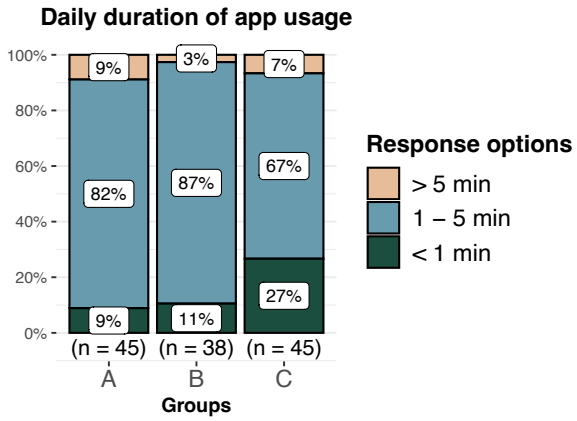


***Figure 26**: Bar plot illustrating the distribution of response frequencies regarding the daily duration of the app usage across groups. Differences between groups were tested with Pearson χ2 test. The percentages may not sum up to 100% as they were rounded to ensure readability and avoid visual clutter.*

3.4.6 PERCEIVED VALUE OF THE APP USAGE

Independent of group and clusters, a total of 46 % (59/128) participants stated that they liked (34.4%; 44/128) or very much liked (11.7%; 15/128) using the app daily. 43.0% (55/128) reported neither liking nor not liking using the app, and 10.9% (14/128) stated that they disliked (10.2%; 13/128) or strongly disliked (0.8%; 1/128) using the app. Grouping positive (liked, very much liked) and negative responses (disliked, strongly disliked) and performing a Pearson-χ^2-test no significant difference was observed neither between groups ($\chi^2 = 2.0476$, df = 2, p-value = 0.3592) nor patient clusters ($\chi^2 = 3.912$, df = 3, p-value = 0.2711). Furthermore, 75.8% (97/128) indicated that it was “easy” or “very easy” to integrate the app into the daily routine as compared to 19.5% (25/128) stating it was “neither easy nor difficult” and 4.7% (6/128) reported it was “difficult”. Regarding the patient clusters no statistical difference using Pearson-χ^2-test was found ($\chi^2 = 10.439$, df = 9, p-value = 0.3161). Considering the usability, the usage of the app was generally perceived as simple with 98.4% (126/128) of participants rating it as

"very simple" or "simple". In this case also, no differences between patient clusters were observed (χ^2 = 6.9896, df = 6, p-value = 0.3218). 79.7% (102/128) rated the user interface design as "very good" (31.2%; 40/128) or "good" (48.4%; 62/128), showing no differences between patient clusters (X-squared = 11.113, df = 12, p-value = 0.5193).

The following table gives an overview of the descriptive statistics of questions regarding the impact of the app usage and the perceived clinical value of the app functionalities. To identify patterns according to patient characteristics the statistical comparison between the clusters is also shown.

***Table 17**: Descriptive statistics of selected questions of the feedback questionnaire independent of group. To ensure visibility the questions are shortened but labeled with the according number. The response options "very strongly" and "strongly" and also "hardly" and "not at all" are summed up. Pearson-χ^2-test were performed to identify differences between the clusters. The according p-value is shown in the table. Greyed numbers signal that the p-value shows no significance.*

Questions	Very strongly or strongly	Partly	Hardly or not at all	Statistical comparison between clusters
Clinical impact				
Q9n1: Helpful regarding QOL?	25.0% (32/128)	49.2% (63/128)	25.8% (33/128)	*p = 0.0085*
Q18n1 Helpful regarding everyday school/study/work life?	5.5% (7/127)	19.7% (25/127)	74.8% (95/127)	*p = 0.5256*
Q35 Did the pollen forecast help to avoid exacerbation of your allergy?	15.9% (7/44)	27.3% (12/44)	56.8% (25/44)	*p = 0.6129*
Q37 Did you avoid going outside on days with a high pollen forecast?	11.4% (5/44)	22.7% (10/44)	65.9% (29/44)	*p = 0.511*
Q39 Did you take medication preventive on days with a high pollen forecast?	4.5% (2/44)	20.4% (9/44)	75.0% (33/44)	*p = 0.5624*
Q12 Did the usage lead to increased anxiety regarding allergies and health status?	3.9% (5/128)	13.3% (17/128)	82.8% (106/128)	*p = 0.38*

App functionalities				
Q14 Was the app helpful in providing recommendations for coping with high pollen counts?	38.6% (49/127)	43.3% (55/127)	18.1% (23/127)	*p = 0.4031*
Q20 Was the "knowledge / information" section helpful to better understand your allergy?	18.9% (24/127)	52.8% (67/127)	28.3% (36/127)	*p = 0.5583*
Q29n1 Was the symptom diary helpful for the management of your allergy?	48.8% (40/82)	37.8% (31/82)	13.4% (11/82)	*p = 0.2798*
Q31 Was the pollen forecast helpful for the management of your allergy?	59.1% (26/44)	25.0% (11/44)	15.9% (7/44)	*p = 0.219*

The results indicate a significant difference between clusters regarding the benefit in terms QOL (p = 0.0085). The strongest benefit regarding QOL for participants was observed for patient cluster FA+ (*Figure 27*).

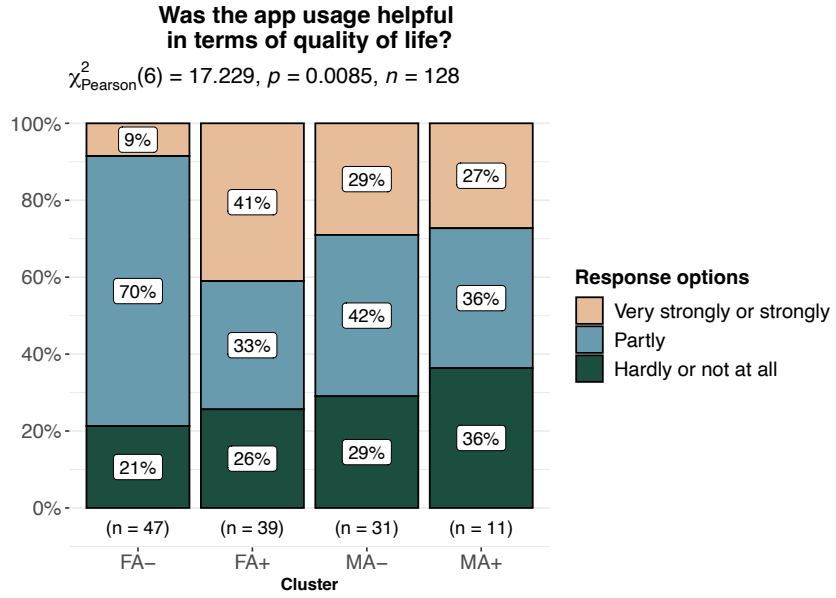


Figure 27*: Bar plot illustrating the distribution of response frequencies regarding quality of life across cluster. Differences between cluster were tested with Pearson χ2 test. The percentages may not sum up to 100% as they were rounded to ensure readability and avoid visual clutter.*

To determine which variable was associated with an increased likelihood of responding "very strongly" or "strongly" a logistic regression was performed by also grouping the remaining answer options "partly" and "hardly" and "not at all". The results indicated significant increased odds of 3.42 for suffering from an asthmatic condition and responding, "very strong" or "strong" (p = 0.0104). The remaining variables which were considered showed no significancy, including the group. The model showed significance (p= 0.0358) and no collinearity between variables was observed. *Figure 28* illustrates the odds ratio based on the logistic regression.

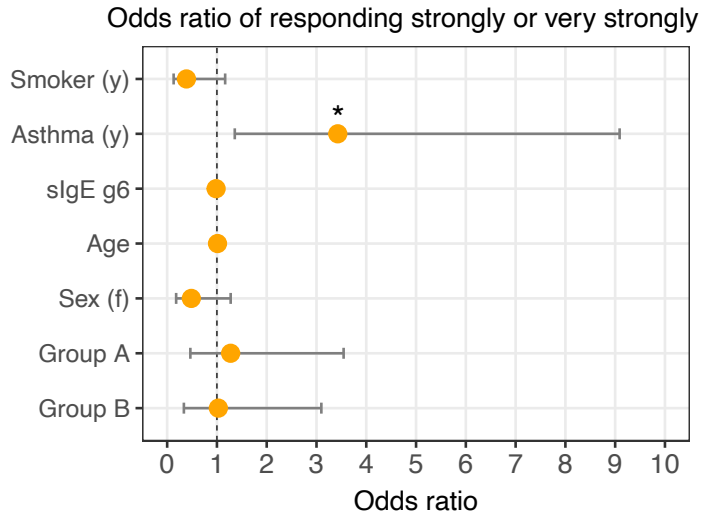


***Figure 28**: Odds ratio of responding "very strongly" or "strongly" to the question whether the app usage was useful in terms of quality of life. The performed logistic regression showed significance ((p= 0.0358) using an omnibus-test. Asterisks signal significant odds ratio.*

To broaden the picture of the helpfulness of the app for cluster FA+, also the distribution of the question regarding the helpfulness of avoiding exacerbation of allergic symptoms is shown in *Figure 29,* despite not reaching statistical significance:

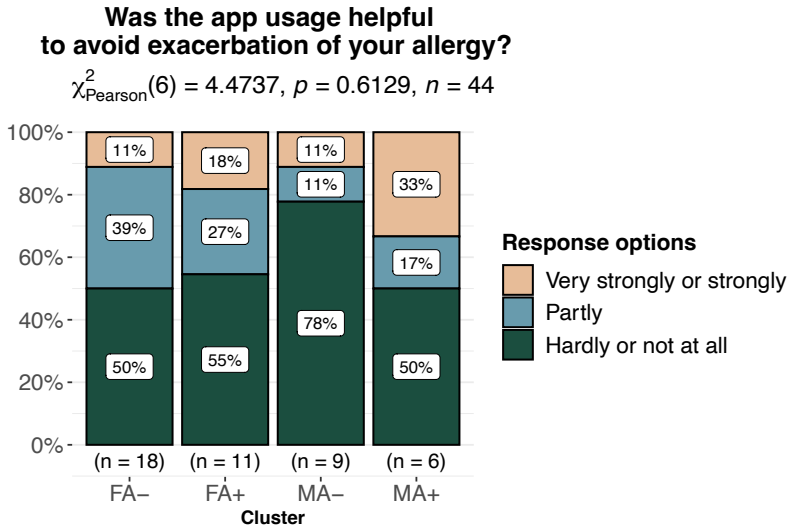


***Figure 29**: Bar plot illustrating the distribution of response frequencies regarding exacerbation of allergic symptoms across cluster. Differences between cluster were tested with Pearson χ2 test. The percentages may not sum up to 100% as they were rounded to ensure readability and avoid visual clutter.*

Further analyzing the question whether the participants would use the app again in following pollen seasons, 55.9% (71/127) of participants answered, “definitely yes” (18.1%; 23/127) or “most likely yes” (37.8%; 48/127). 22% (28/127) answered with “neither yes nor no”, 22.0% (28/127) with “most likely no” (17.3%; 22/127), and 4.7% with “definitively no” (6/127). Regarding the patient clusters, no difference was observed applying Pearson-χ^2-test (χ^2 = 7.2019, df = 12, p-value = 0.844). Further, predominant reasons cited for reluctance to reuse the app included: not having all functions available (being in group C), experiencing no benefit from the app usage, refusing to allow the allergy impose limitations upon oneself, a too repetitive knowledge section and too much time effort for too little outcome.

To identify possible factors being associated with the likelihood of responding “definitely yes” or “most likely yes”, a logistic regression was performed. Besides patient characteristics also responses of the questionnaire were included as predictor variables. This was done to determine which factors were the most relevant in influencing the decision to use the app again. Performing an omnibus-test the model showed significance (p= 1.904e-06) and no collinearity between variables could be observed. The results are presented as odds ratio in *Figure 30*:

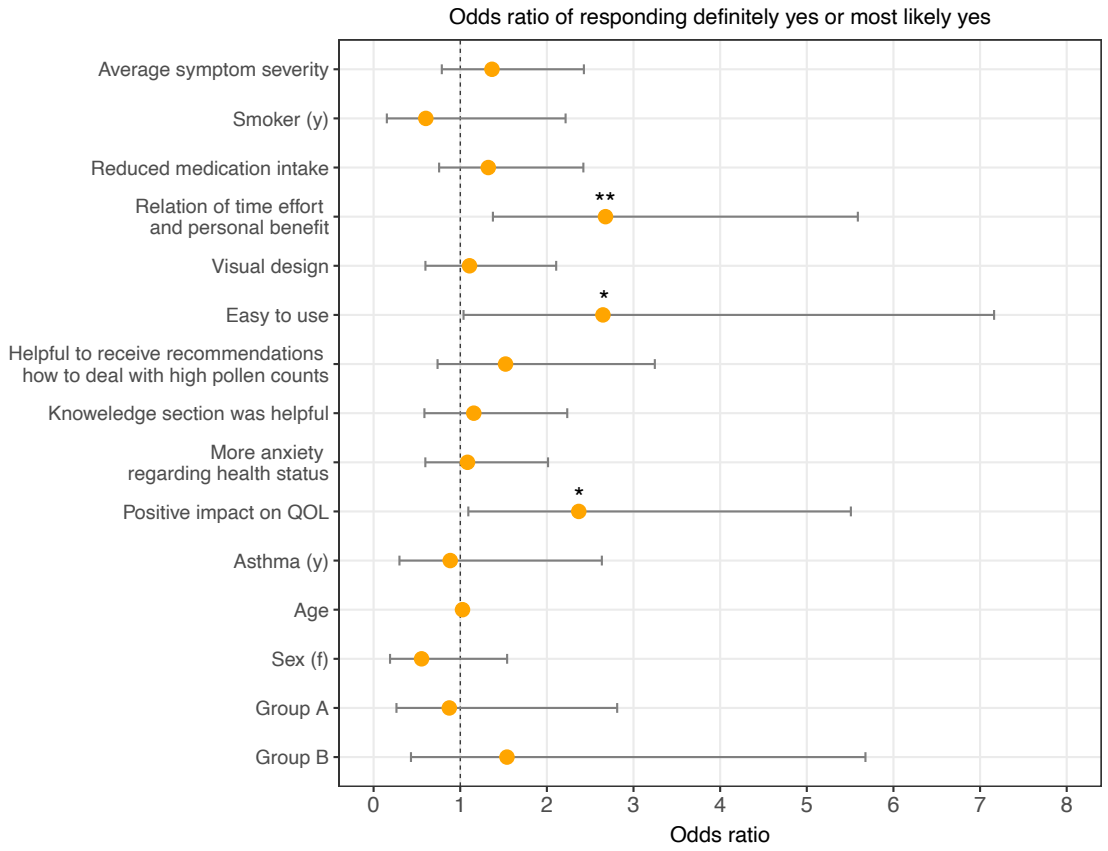


***Figure 30**: Odds ratio of responding "definitely yes" or "most likely yes" to the question whether the participant would use the app again in following pollen seasons. The performed logistic regression showed significance (p= 1.904e-06) using an omnibus-test. Asterisks signal significant odds ratio.*

Giving a higher rating regarding the relation of time effort and personal benefit (Q10) (p= 0.0054; OR: 2.68 (1.37; 5.58)), the simplicity of using the app (Q2n1) (p = 0.0461; OR: 2.65 (1.04; 7.16)), and a positive impact on QOL (Q9n1) (p = 0.0347; OR: 2.37 (1.09; 5.51)) showed significant associations with the response variable.

Regarding the question if participants liked using the app daily (feedback questionnaire Q8), the outcome of the response variable ("liked it" or "very much liked it") was significantly associated with age (p = 0.02795) and higher ratings on the visual design of the app (Q4) (p = 0.0052). The results indicated an odds ratio of 1.04 (1.01; 1.08) for increasing age and an OR of 2.55 (1.37;5.15) for higher ratings regarding visual design. No multicollinearity was given, and the model showed significancy (p = 0.0003). The same predictor variables were considered as in the model shown in *Figure 30.*

3.5 SECONDARY OUTCOMES

3.5.1 SYMPTOM FORECASTING MODEL

The following represents the results regarding the question whether it is possible to develop a symptom forecast model based on the data obtained within this study. To evaluate this question as described in the statistical analysis, a NNAR model was considered to predict the TSS.

The metrics of the "personalized models" (1_NNAR and 2_NNAR) and "generalized model" (3_NNAR) regarding the performance on the test data are presented in *Table 18.*

***Table 18**: Metrics of the NNAR tested for the prediction of symptoms. MAE: Mean absolute error, MAPE: Mean absolute percentage error, MASE: Mean absolute scaled error, SMAPE: Symmetric mean absolute percentage error, RMSE: Root mean squared error, RSQ: R-squared.*

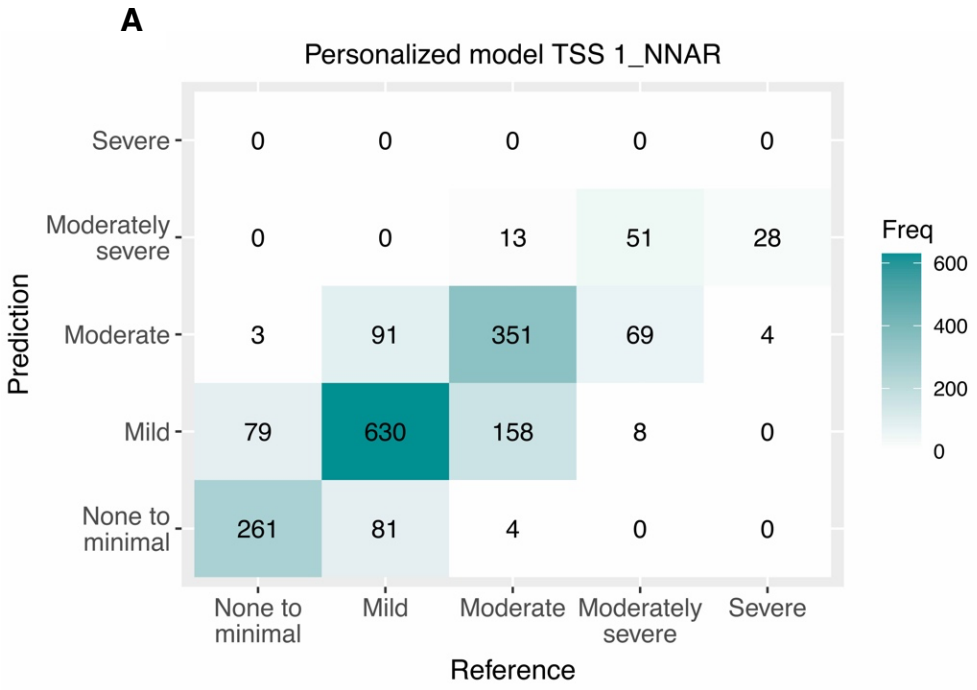
	MAE	MAPE	MASE	SMAPE	RMSE	RSQ
Personalized Model						
1_NNAR(5,10)	1.31	Infinity	0.34	49.59	1.85	0.75
2_NNAR(5,10)	1.24	Infinity	0.36	61.44	1.71	0.70
Generalized Model						
3_NNAR(5,10)	1.97	Infinity	0.78	49.61	2.45	0.52

The performance of the two approaches on the respective test data is further illustrated in confusion matrices. For the visualization the predictions and the actual scores were grouped into levels according to the severity of the symptoms. This was decided because providing levels may be more descriptive and helpful for patients than numbers, analogous to a Visual Analogue Scale. The classification was determined as follows:

***Table 19**: Values of the TSS and the according symptom level.*

Overall symptom level	**TSS**	
	Lower limit	Upper limit
None to minimal	0	< 2
Mild	≥ 2	< 6
Moderate	≥ 6	< 11
Moderately severe	≥ 11	< 15
Severe	≥ 15	≤ 19

The following figure shows the confusion matrices illustrating the predictions of the 1_NNAR model (*Figure 31, A*), 2_NNAR model (*Figure 31, B*) and the 3_NNAR model (*Figure 31, C*) versus the according real values of the TSS.



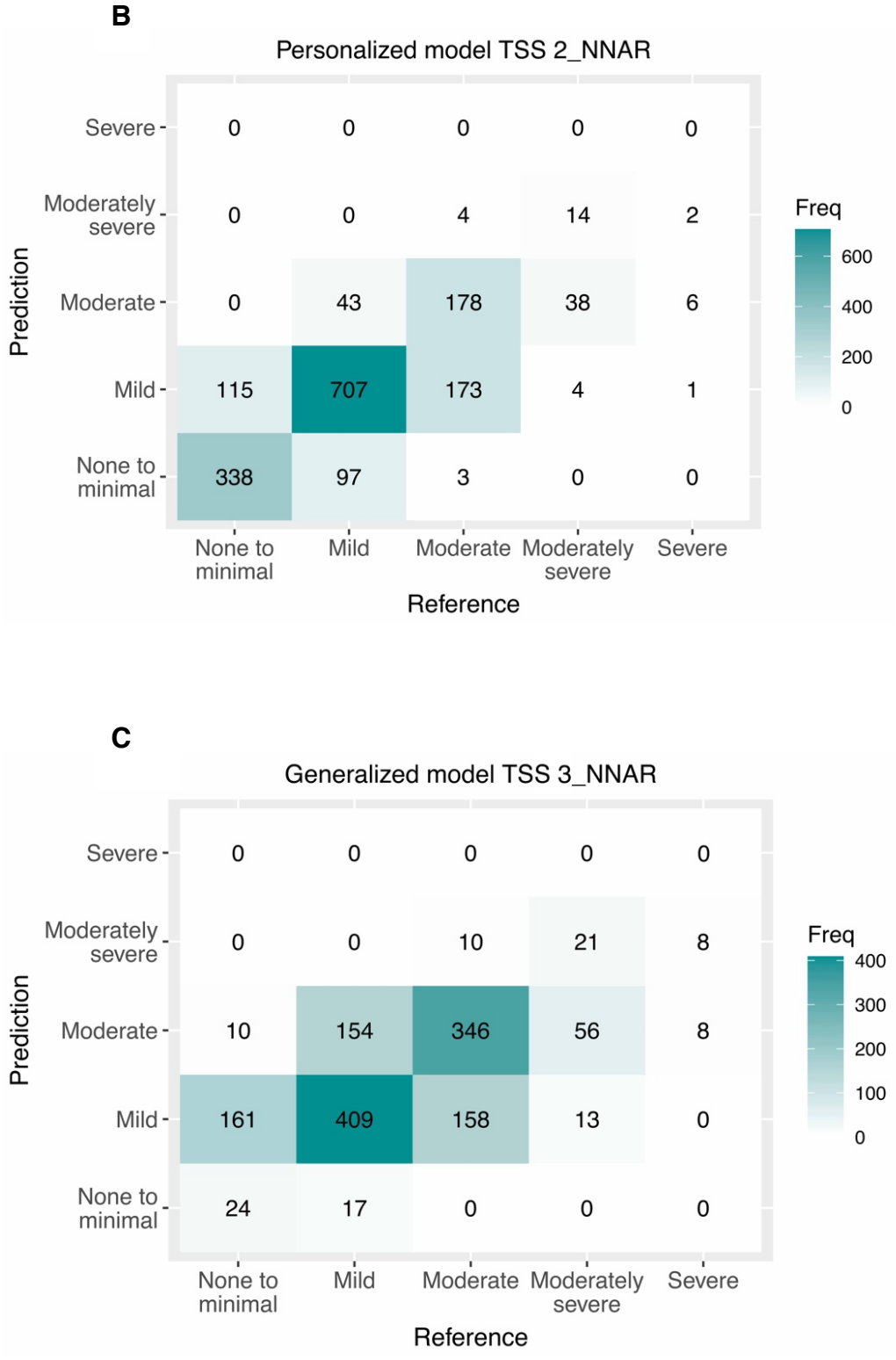
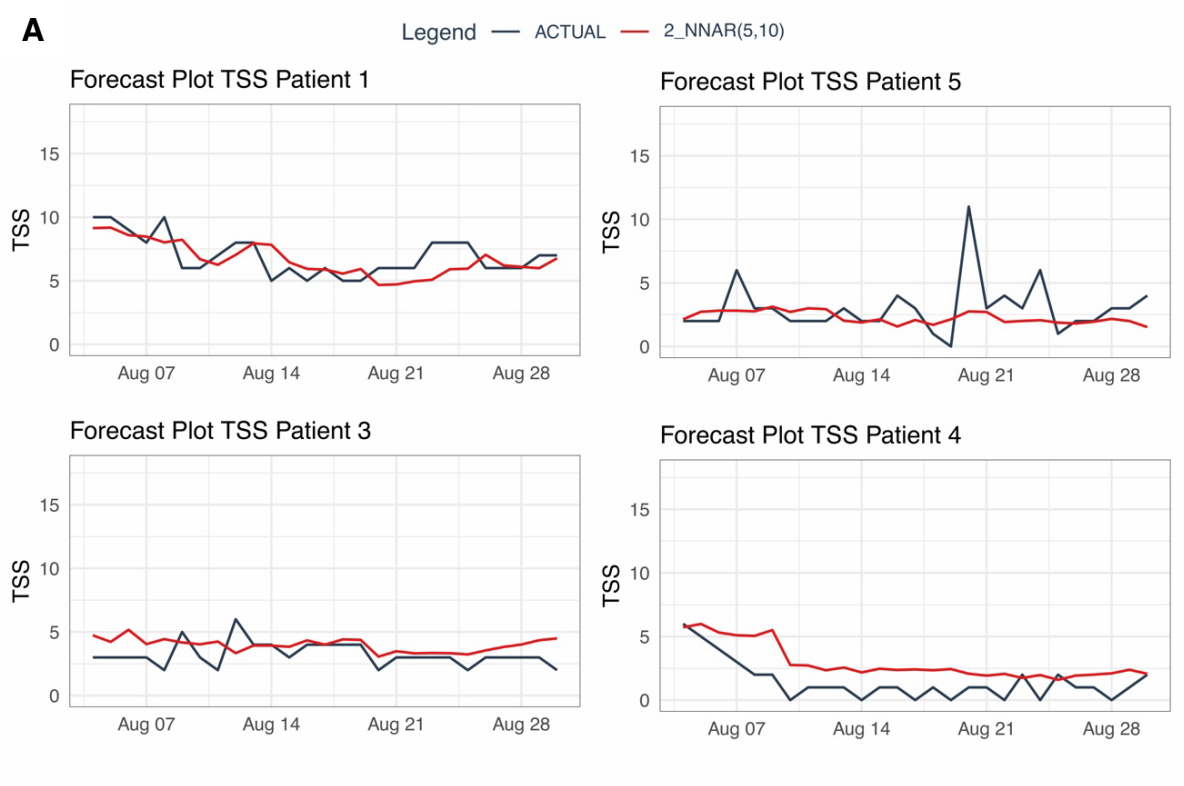


***Figure 31**: Confusion matrices of the personalized models 1_NNAR (A) and 2_NNAR (B) and the generalized model 3_NNAR (C) showing the distribution of real vs the predicted values of the TSS.*

Accordingly, the 1_NNAR predicted the correct symptom level with an accuracy of 70.62%, the 2_NNAR with an accuracy of 71.79% and the 3_NNAR with an accuracy of 57.35%.

The performance of the models was further evaluated by showing the predicted time series of the models compared to the actual symptoms of four four patients of the cohort. Regarding the 2_NNAR "patient 5" was considered instead of "patient 2" as the TSS of this patient showed more fluctuations in August and thus the limitations of the model can be better illustrated. Regarding the 1_NNAR no time series is presented as this would be of limited use: It was already trained on approximately 70% of the data of each patient and therefore only about 30% of a time series would be predicted and also in a random manner.

Figure 32 shows the time series of the 2_NNAR from August 4th until 30th August (*Figure 32, A*) and of the 3_NNAR over the entire study period (*Figure 32, B*).



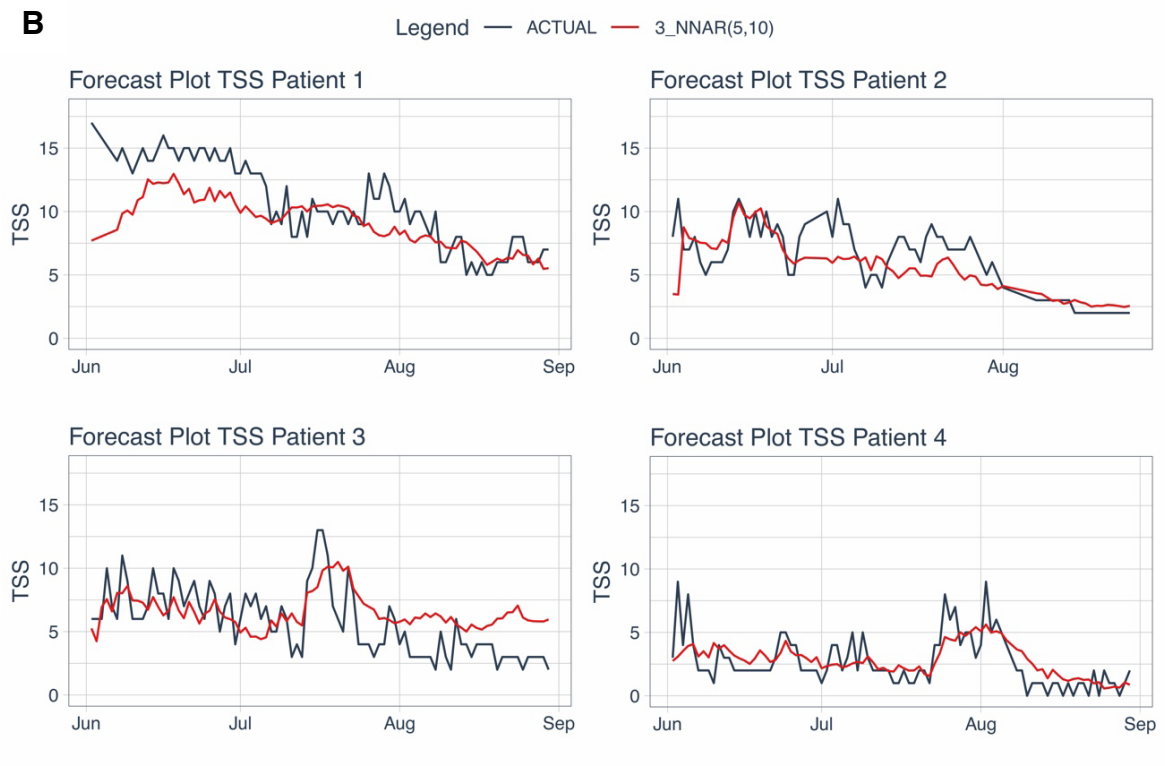


***Figure 32**: Time series of predicted values by the personalized (2_NNAR) and generalized model 3_NNAR) vs the real values of the respective patient.*

4 DISCUSSION

4.1 SUMMARY OF RESULTS

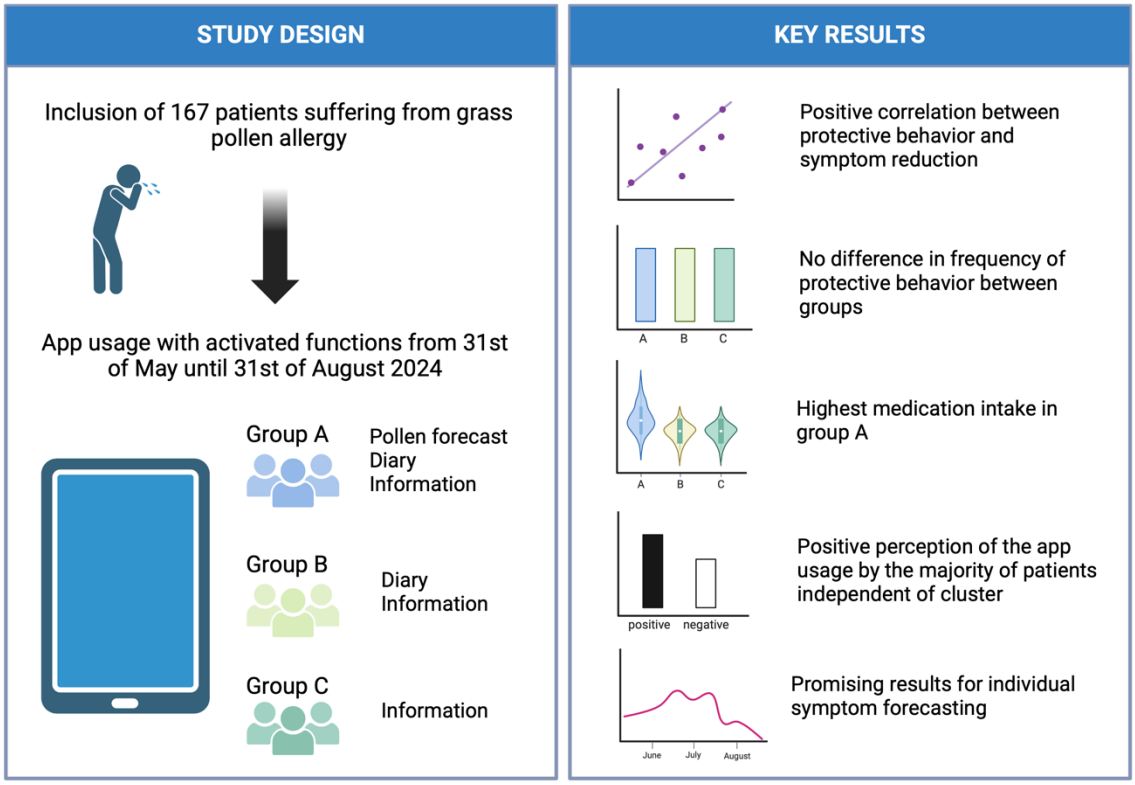


***Figure 33**: Graphical Abstract*

Taken together, the results showed a positive correlation between increasing frequency of protective behavior and reduction of symptom severity across the cohort. No difference between the groups was observed regarding the frequency of the addressed behavioral strategies. Group A showed the highest medication intake throughout the study period; however, no signs were observed that group A based their medication intake or behavior on the pollen forecast. Generally, the app usage was perceived as positive by the majority of participants without showing differences across the patient clusters. However, in terms of QOL, asthmatic patients, and among these especially female patients, appeared to benefit most of the app usage. The evaluation of the pollen forecasting model showed reasonable results for the personalized approach and yet insufficient results for the generalized approach. In the future accurate symptom forecasts appear possible, having high-quality data available.

The major results are summarized in the following:

Regarding the analysis of the first miniRQLQ questionnaire, no significant correlation was observed between the miniRQLQ score and the observed ($p = 0.07$) and reported average symptom severity ($p = 0.25$).

Significant correlation was shown between the observed symptom severity and the measured pollen concentration (TSS: $\rho = 0.82$, $p < 0.001$; TNSS: $\rho = 0.82$, $p < 0.001$).

Regarding exposure-relevant behavior, significant correlations were shown between the observed symptom severity and avoiding outdoor pollen exposure (TSS: $\rho = -0.71$, $p < 0.001$; TNSS: $\rho = -0.76$, $p < 0.001$) and for days with high and very high pollen concentrations between the symptom severity and sleeping with windows closed (TSS: $\rho = -0.69$, $p < 0.001$; TNSS: $\rho = -0.72$, $p < 0.001$), sleeping with windows opened (TSS: $\rho = 0.76$, $p < 0.001$; TNSS: $\rho = 0.79$, $p < 0.001$) and, depending on the time of day, with washing hair ("In the morning" TSS: $\rho = -0.35$, $p = 0.025$; TNSS: $\rho = -0.37$, $p = 0.017$; "At another time": " TSS: $\rho = -0.61$, $p < 0.001$; TNSS: $\rho = -0.54$, $p < 0.001$; "In the evening": TSS: $\rho = 0.32$, $p = 0.043$). Interfering effects and limitations of this analysis will be addressed in the discussion.

Considering the frequency of exposure-relevant behaviors, no significant difference was observed between groups A and B based on the responses given in the app, neither for all days nor for days with a high or very high pollen forecast. Also, no significant difference was found between groups A, B and C based on the data of the feedback questionnaire ($p = 0.702$). However, overall, 50,4% of participants indicated to have at least partially paid more attention to preventive behavior due to the app usage.

Moreover, no significant relationship was observed between the reported average symptom severity of the patients during the screening process and the frequency of exposure-related behavior.

Regarding the medication intake throughout the study period, group A showed a significant higher medication score compared to group B ($p < 0.001$). The same applies when only considering days with a "high" and "very high" forecast ($p = 0.001$) and days with "none" or "low" forecasted pollen concentration ($p < 0.001$). No significant difference was observed for days with a "medium" pollen forecast ($p = 0.112$).

Further, there was no clear evidence to support the hypothesis that group A based their medication intake on the pollen forecast. Instead, a very strong positive and significant correlation was found between medication intake and the observed symptom severity across the cohorts (TSS: $\rho = 0.91$, $p < 0.001$).

Considering the specific medication categories, the results also indicated a significant, more frequent medication intake regarding systemic medication, nasal spray, eye drops and other medication in group A compared to group B (for all medication categories $p < 0.001$). The most

frequently taken medication type throughout the study period was systemic medication (Group A: 12.54%, Group B: 8.94%).

Comparing groups, A, B, and C based on the subjective assessment in the feedback questionnaire, no significant differences were observed regarding the medication intake. However, overall, 30.7% of participants indicated to have at least achieved a partial reduction medication intake due to the app usage. Thereof, the most frequent omitted medication were systemic Antihistamines, indicated by 71.8%.

Evaluating the feedback questionnaire a total of 46 % stated they “liked” or “very much liked” using the app daily. 75.8% indicated it was “very easy” or “easy” to integrate the app into their daily life. Also, 98.4% of participants rated the app as “very simple” or “simple” to use. 59.1% agreed “very strongly” or “strongly” on the question whether the pollen forecast is helpful for their allergy management. 48.8% stated the same regarding the symptom diary, and 18.9% regarding the “knowledge / information” section. Stratified by the patient characteristics, the only significant difference for the analyzed questions was found regarding how the participants rated the app in terms of QOL. The patient cluster FA+ appeared to profit most from the app usage, with 41% agreeing “very strongly” or strongly” to the question if they found the app helpful in terms of QOL. Investigating further, logistic regression revealed having a history of allergic asthma to be the significant predictor in responding “very strongly” or “strong” (OR 3.42).

55.9% of all participants answered “definitely yes” or “most likely yes” when asked if they would use the app again in following pollen seasons. Logistic regression revealed higher ratings for “easy to use”, “relation of time effort and personal benefit”, and “positive impact on QOL”, to be significant predictor variables to answer more likely with “definitely yes” or “most likely yes”. No significant predictors within the patient characteristics were identified.

Evaluating the development of the symptom forecasting model, the “personalized” approaches showed good-quality results (1_NNAR: R^2 = 0.75, 2_NNAR; 2_NNAR: R^2 = 0.70) and predicted the correct symptom level with an accuracy of 70.62%. (1_NNAR) and 71.79% (2_NNAR), respectively. The “generalized” approach (R^2 = 0.52) appeared to be limited with an accuracy of solely 57.35%.

In the following, the scientific questions and hypotheses will be discussed in the context of the findings, their limitations and in consideration of current state of research. Due to the innovative nature of the study, current research was limited. Regarding the evaluation of the efficacy of the app usage, two similar studies on mHealth for pollen allergy sufferers performed in Germany

were found. These studies evaluated the “Husteblume” app (Glattacker et al., 2020) and the “APOLLO” app (Landesberger et al., 2023).

To begin with, the study population, the symptom scores and the data acquisition with the app will be briefly discussed.

4.2 STUDY POPULATION

One of the limitations regarding the study population is the relatively small sample size (n = 167) with only 127 of participants considered in the data analysis of this thesis. In the data analysis that considered only the groups A and B (the two diary user groups), the sample size was even further limited (n = 83). On the other hand, due to the longitudinal data structure, there were overall 6491 observations, providing an extensive dataset. As a result, depending on the approach of the statistical analysis, the small sample size may have had more of an impact on outcome x than outcome y. The limitation due to the sample size is therefore addressed specifically when discussing the respective research questions. Especially regarding the feedback questionnaire, the small sample size may have concealed significant results.

One strength is that the participants were successfully randomized, i.e. equally distributed between groups with respect to demographic characteristics and clinical background, therefore avoiding selection bias. However, a selection bias or volunteer bias respectively may still be present to some extent. As many of the participants were recruited from an existing database and / or were employees in a health institution, this may have led to an enhanced knowledge and interest regarding their allergic disease in this subsample compared to the general population. Volunteer bias may have also influenced the sample to be more receptive regarding the use of mHealth technologies. If or in which direction this may have influenced the results cannot be determined. A bias towards patients with severe symptoms seems unlikely as the average symptom severity was relatively evenly distributed throughout the cohort. But as can be seen in *Figure 3B* a discrete cluster reporting very high symptoms (5) can be observed.

Moreover, it should be noted that the majority of participants were female (67.07%) compared to male (32.93%), which is a rather typical gender distribution for studies on AR at the IEM (S. Gilles, personal communication). The gender-bias may have caused the results being biased towards female in cases where the analysis was not stratified by sex. Also, the median age (32) of the study population was relatively young compared to the German general population (Female: 44.3; Male: 47.5, as of 2024) (Bundesinstitut für Bevölkerungsforschung 2024).

However, the overall age distribution of the sample (*Figure 3A*) is appropriate regarding the prevalence of grass pollen allergy in Germany presented in the Introduction (Haftenberger et al., 2013). Further studies evaluating apps for pollen allergy reported female sex in 59% (Husteblume study) and 60.9% (APOLLO study) of participants and a mean age of 39 years (Husteblume study) and 34 years (APOLLO study) (Glattacker et al., 2020; Landesberger et al., 2023). As suggested in previous studies, to which extent demographic characteristics influence mHealth use remains to be investigated (Glattacker et al., 2020; Wildenbos et al., 2016).

A strength that can be emphasized - also in comparison to other studies using allergy apps - is that all participants included in the statistical analysis had a positive sIgE test, proving a IgE-mediated grass pollen allergy. It must, however, be noted that a significant proportion of participants were most likely polysensitized. As the majority of participants were only tested for sIgE g6 during the screening process it is not possible to include other sensitizations or sensitization patterns as a factor in the analysis.

Another factor to consider is the possibility that participants in group B and C may have used publicly available pollen forecast information during the study period, which could have influenced their behavior. Data from a previous study suggests that the proportion of allergy sufferers that uses available pollen information services can be considered as low (Muzalyova et al., 2019).

4.3 SYMPTOM SCORES AND APP DATA

Prior research showed that the specific method used for calculating symptom scores regarding grass pollen allergy did not appear to be critical (Bastl et al., 2020). As the TSS and the TNSS calculated in this analysis showed a strong positive correlation with the pollen concentration, it can be assumed that the symptom scores and their calculation algorithm served as an effective tool to measure the symptom severity. Positive, strong correlations between different scores were also found in previous literature (Bastl et al., 2020; de Weger et al., 2021; Feo Brito et al., 2010). One aspect of the TSS which must be discussed is that it also incorporates the general well-being. Therefore, this metric may be more susceptible to other aspects that influence well-being, such as unrelated diseases, psychological stress, or other individual daily-life circumstances. This can be also seen in *Figure 10A*, where median TSS is still quite high despite the low pollen concentration towards the end of the pollen season in August. However, due to the very high positive correlation with the pollen concentration, it was still an effective metric for the statistical analysis.

Regarding the data acquisition via the app, self-report bias may have impacted the results. Especially a recall bias should be considered, as the participants filled their diary retrospectively for the previous day. However, as the recall period was relatively short (mostly 1 day), the effects on the results may be considered as minor. A specific strength - also in contrast to other app studies - is that the participants used the app on a regular basis (mostly daily) and for a relatively long period. The median duration of the app use across the cohort was 87 days out of a total of 93 days.

4.4 RELATIONSHIP BETWEEN SYMPTOM SEVERITY AND RHINITIS-RELATED QUALITY OF LIFE

According to the statistical analysis, the findings do not support the hypothesis that there is a negative correlation between symptom severity (observed and reported) and rhinitis-related QOL (evaluation of the first mini-RQLQ survey).
However, these findings should be interpreted with caution: The sample size for this analysis was already very low (n=64) because of the abovementioned technical issues with the data acquisition of the questionnaire. Due to the different time points the participants completed the questionnaire, the participants were further stratified by the exposed pollen count to adjust for the different pollen exposure prior to the questionnaire completion. This served as good measure to provide a comparable analysis. However, as a result, the number of participants that were included in each "exposure cluster" was very low. The overall low sample size might have led to a non-significant outcome even though there is an association between the variables (Weiß, 2019).

Further factors contributing to the absence of an effect in this analysis may be the applied methods: The miniRQLQ is only an excerpt of one week of symptoms, whereas the other two metrics that were considered for the symptom severity were assessed over a longer period. The median TSS was obtained over the entire study period and the average symptom severity indicated how severe the patients generally perceive their symptoms on a scale from 0 to 5. Due do the shorter time period the magnitude of the miniRQLQ score may be more susceptible for extremes compared to an entire season or generally. For instance, as a polysensitization was no exclusion criterion, some of the patients may have been exposed to more potential allergens than others during the observed week (e.g. fungal spores). Also, a patient who had been spending less time outside than usual during the observed week might have had a better

miniRQLQ score than usual. This may also be a reason for the outlier that was observed in *Figure 13 and Figure 14*. However, as the outlier showed a miniRQLQ score of 0, reasons such as not completing the miniRQLQ thoughtfully or technical problems appear more likely.
A more effective measure to answer this research question may have been to obtain the miniRQLQ questionnaire weekly during the study period and investigate the relationship with the median observed symptom severity of the diary of the same week. The same applies to the average symptom severity, but then by observing the relationship with an average of the miniRQLQ scores of the entire pollen season.
The use of the miniRQLQ rather than the full RQLQ appears to be an unlikely factor biasing the results. It was shown to be representative and yield similar results as the full RQLQ (Juniper et al., 2000).

Observed symptom Severity (TSS)

In the scatter plot showing the relationship of the miniRQLQ score with the TSS (*Figure 14*), the distribution of the datapoints also suggest a correlation, which did not reach significance due to the low sample size. Putting the results in the context of current research supports the assumption that the absence of significance was caused by the low sample size and discussed limitations of the applied methods. In previous literature, higher symptom severity was associated with an increasing negative impact on QOL (Bousquet et al., 2007; Bousquet et al., 2012; del Cuvillo et al., 2010). It was also reported that the longer patients suffer from AR, the lesser the negative impact on QOL. Whether this effect was merely caused by an adaption to the symptoms was uncertain (Li et al., 2021). Independent of the reason for this effect, this may also have biased the results, as the duration of the allergy was not considered in the analysis of this thesis.

Reported average symptom severity

The relationship of the miniRQLQ score with the average symptom severity as reported in the screening (*Figure 13*) appeared more diffuse and an absence of an effect appears more likely due to the discussed limitation of the applied methods rather than the low sample size. No similar research was found that addresses the question to what extend a self-perceived average

symptom severity correlates with QOL. Therefore, it was not possible to put these results into context of current research.

4.5 RELATIONSHIP BETWEEN SYMPTOM SEVERITY AND EXPOSURE-RELATED BEHVIOR

4.5.1 DIARY SCORES

As discussed in the Introduction, according to recent studies the clinical efficacy of protective behavior to reduce and prevent symptoms remains still unclear. The recommendations appear to be mostly based on common sense and expert opinions (Wise et al., 2023; Wise et al., 2018). Therefore, discussing the results in context of current research is limited.
The findings of this thesis are consistent with the hypothesis that there is a negative correlation between avoiding outdoor pollen exposure, closing windows at night, washing hair and the observed symptom severity (TSS, TNSS) of the dairy user groups.

Avoiding outdoor pollen exposure

The data analysis indicated a strong negative correlation with the symptom severity and staying inside the entire day. Similar effects were also shown in a study during the Covid-19 pandemic concluding that spending less time outside had caused a reduction in symptoms compared to prior pollen seasons (Sözener et al., 2021).
The results of this thesis may be biased by weather factors that may influence both, the airborne pollen concentration, and the behavior of the participants. Considering the influence of weather factors on measured pollen counts, previous studies have shown a positive association between higher temperatures and increasing sunshine hours with increasing pollen concentrations. In contrast, a lower pollen concentration was described to be associated with higher precipitation and increased relative humidity (Crimi et al., 2004; Kizilpinar et al., 2011). This inverse association is suggested to be partly caused by rainfall or relative humidity, respectively, increasing the weight of the pollen grains and decreasing its airborne dispersion (Crimi et al., 2004). The findings of this thesis were consistent with the results of the cited research, showing the same significant relationships between pollen concentration and temperature, sunshine hours, precipitation, and humidity. These relationships are important, as the data also showed that these weather factors influence the likelihood of participants staying inside all day:

Participants were more likely staying inside with increasing relative humidity and precipitation and decreasing daily sunshine duration. As these factors are also associated with a decreasing pollen concentration it supports the assumption that the results are at least partly biased by the weather factors.

A further limitation of the results is that it was not assessed whether the participants aired the room if they indicated staying inside the entire day. As current research showed evidence for pollen concentrations being higher in rooms with frequently opened windows and doors (Jochner-Oette et al., 2022; Menzel et al., 2017), this may have also biased the pollen count indoors and thus the symptoms of the respective patient.

It is also important to consider that less pollen does not equal less symptoms and it must be regarded in the context of meteorological factors: It has been shown that if the relative humidity rises above a threshold of 60%, only half the grass pollen concertation is required to cause the same symptom severity. (Damialis et al., 2019) Also the indoor pollen concentration may be influenced by meteorological factors. It was found that on rainy days the pollen concentration was higher indoors, compared to outdoors in relative terms (Jochner-Oette et al., 2022).

The discussed effects influencing the relationship between pollen concentrations and symptom severity make it difficult to determine the extent of the positive effect that can be attributed to the behavioral strategies. Further research on these topics is required to develop a solid basis for the analysis of allergen avoidance.

Sleeping with windows closed

For days with high or very high pollen counts the results showed a strong negative correlation between sleeping with windows closed and the TSS and TNSS of the following day. Concordantly, sleeping with windows opened showed a strong positive correlation with TSS and TNSS on the next day. Based on the evidence for pollen concentrations being higher in rooms with frequently opened windows and doors (Jochner-Oette et al., 2022) the results seem reasonable and support the findings.

One unexpected finding in this analysis was that for days with only low and medium pollen concentrations, sleeping with windows partly opened / partly closed showed a medium negative correlation with the symptom severity and sleeping with windows closed showed a positive correlation. An explanation for the observation may be the discussed findings of Jochner-Oette et al. showing that on rainy days the indoor pollen concentration is higher than outside in relative terms (Jochner-Oette et al., 2022). As rainy days are also associated with a lower pollen

concentration, on such days, airing the room to a certain extent may be beneficial to reduce the indoor pollen concentration. As these results are also subject to the complex interrelationships of meteorological factors, pollen concentration and symptom further research focusing on this topic is required to either confirm or negate the hypothesis.

Washing hair

On days with high and very high pollen concentration, the data showed a significant negative correlation for washing hair "in the morning" and "at another time" and the symptom severity. No effect of hair washing on the symptom severity was observed for days with low and medium pollen concentration. Also, a positive but weak correlation was observed for washing hair "in the evening" for days with high and very high pollen concentration. This unexpected finding may be caused by participants washing their hair in the evening if they had strong symptoms throughout the day to get relief from their symptoms.
A limitation regarding this analysis is that "at another time" was unspecific and no certain point in time can be inferred from this information. Moreover, participants did not indicate if they washed their hair more than once. No research was found addressing the benefits of washing hair on allergic symptoms to compare the results.

4.5.2 SCREENING STATEMENT

The findings were not consistent with the hypothesis that the average symptom severity (as reported in the screening) correlates negatively with the exposure-related, protective behavior. There was no evidence found that patients who indicated a low average symptom severity would pay more attention to such behavior. Also, no evidence was observed that patients who indicated a high average symptom severity would more likely pay attention to the discussed behaviors.
Therefore, a further analysis considering only group A was conducted. It served to analyze more in-depth if an effect would be observable under the circumstances of a high pollen forecast. The rationale for this analysis was that patients who indicated to have strong or low symptoms, respectively, might have adjusted their behavior on days with a high pollen forecast. (Only group A participants were included since they were the only group that had access to the pollen forecast). Here also, no signs were observed that patients who had indicated a high or low

average symptom severity in the screening would pay more attention to preventive behavior, respectively, on days with a high pollen forecast.

These findings are contrary to previous studies which suggested that the self-perceived symptom severity, which can be compared to the average symptom severity of the results of this thesis, was associated with an increased likelihood performing measures to avoid allergen exposure (Muzalyova & Brunner, 2020). Other than that, no further research investigating this topic was found.

Besides the low sample size, no further limitations regarding this analysis can be indicated. Also, the average symptom severity appeared to severe as a good measure and no ceiling effect could be observed throughout the cohort (*Figure 3B*).

4.6 EXPOSURE-RELATED BEHAVIOR BETWEEN GROUPS

The findings were not consistent with the hypothesis that participants in group A showed more frequently protective, exposure-related behavior compared to groups B and C. The results showed neither a difference regarding the diary user groups (A and B) based on the app data nor between all groups based on the feedback questionnaire. Focusing only on days with a high or very high pollen forecast, a significant difference was observed showing that group B more frequently slept with windows closed. This effect was negated by performing a beta regression, indicating the smoker status to be the significant predictor and not the group. Also, no statistical evidence was observed which would suggest that group A based their behavior on the pollen forecast. This finding is also in accordance with the feedback questionnaire with only 11.4% of participants in group A stating they avoided going outside on days with a high pollen forecast.

Putting the findings in context of current research, the assessment on mHealth apps in terms of improving health behavior is inconsistent. Both, a systematic review not finding compelling evidence (Milne-Ives et al., 2020) and a review showing positive effects (Lee et al., 2018) were found.

Push notifications

Considering the app utilized in this study, the absence of an effect may also be attributed to the lack of push notifications. To provide an example: There was no notification integrated in the app that would show recommendations to group A on days with high or very high pollen

forecast to engage, if possible, in protective behaviors. The usefulness of notifications appears important according to current research on mHealth apps. It was shown that such reminders are strongly associated with the engagement in the app itself and also in change of behavior due to the app usage (Alkhaldi et al., 2016; Bell et al., 2020; Bidargaddi et al., 2018). A positive effect of daily reminders was also found in the "APOLLO" study, with 97.14% of participants stating that push notifications helped them to fill the app (Landesberger et al., 2023). A notification could have further reduced the dropouts of the study presented in this thesis as "forgetting to use the app" was cited as one of the major reasons for dropping out.

Individual factors

A further contributing factor to the absence of an effect may be that patients may generally not perceive protective behavior as valuable. This assumption is supported by prior research which showed that there is a general awareness of the strategies but only half of the known strategies are applied by patients (Muzalyova et al., 2019). Also, the willingness to use protective strategies may be very individualized and, as mentioned previously, was shown to depend on the individually perceived symptom severity of a patient (Muzalyova & Brunner, 2020; Muzalyova et al., 2019).

Moreover, the feasibility of strategies to avoid allergens may vary significantly depending on the individual circumstances of the patient. For instance, occupation or leisure activities may have more of an influence on the behavior compared to the symptoms or future symptoms caused by the allergy.

To provide recommendations in an app for e.g. avoiding outdoor pollen exposure it appears also reasonable to explore the relationship between the duration of staying outside and the symptom severity. This may show if it is already beneficial to reduce the time spent outside to a certain extent. This analysis was also intended to be performed in this thesis. However, the question in the diary asking how much time the participants spent outside could not be included in the analysis due to a technical issue with the data acquisition in the app for this specific question. Generally, it is also important to note that allergen avoidance strategies "should never isolate individuals from social interactions" (Bousquet et al., 2020).

4.7 MEDICATION INTAKE BETWEEN GROUPS

Regarding the effect of the different app versions on the medication intake the findings do not support the hypothesis that the medication intake in group A was reduced compared to group B and C. Instead, the app data showed a significantly higher medication score in group A compared to group B. These results are consistent with the results of the feedback questionnaire, revealing that only participants in group A reported taking more medication than usual (7% of participants in group A versus 0% in group B and C). The participants did not indicate any reasons for taking more medication.

On-demand medication intake

The results of the comparison of the medication intake suggest that group A could have taken more medication due to high pollen forecasts. As group A also showed a higher medication score for days with “none” or “low” pollen forecast, this assumption is challenged and suggests other reasons for the observation. Also, when considering the equal correlation coefficient between the medication score and the pollen forecast in groups A and group B it can be assumed that patients in group A did not take their medication according to the pollen forecast levels. This is also reflected in the results of the feedback questionnaire with only 4.5% of participants of group A stating they took medication preventively on days with a high forecast.
Putting these findings in context with the very strong positive relationship between medication intake and symptom severity it suggests that the participants generally took their medication on-demand because of experiencing symptoms, rather than preventively or continuously. This finding is also consistent with previous real-life data showing that patients tend to treat themselves based on their symptoms and favor on-demand / symptomatic treatment compared to continuous therapy (Bousquet et al., 2020; Bernardo Sousa-Pinto et al., 2022).

Factors for higher medication intake

To further investigate the reason for the higher medication intake in group A, the distribution across specific medication categories and the patient clusters was analyzed. According to the data, it can be inferred that the patients of the clusters FA+ or MA-, depending on the medication category, were most likely to take medication throughout the study period. One could assume that participants of these clusters were more present in group A or due to the

dropouts the distribution is skewed, and this caused the higher medication intake in group A. Based on the successful randomization and the balanced numbers of the patients of each cluster in the groups, this appears unlikely (A: FA+ = 11, MA- = 10; B: FA+ = 11, MA- = 12).

Another explanation may be that having the full app available led to a longer daily app usage and therefore an increased medication intake. The positive association of a longer duration spent in an app and the increased likelihood of taking medication was previously described with regards to controller medication in Asthma and COPD patients (Kaye et al., 2021). As no objective data of the daily usage duration was gathered via the PollDi app, a relationship with the medication intake could not be statistically analyzed in this thesis. Based on the subjective assessment in the feedback questionnaire, group A indeed indicated a longer daily app usage compared to group B, which, however, did not reach significance.
Taken together, the data suggests that there is an association between the availability of the pollen forecast and increased medication intake or medication adherence.

4.8 PERCEIVED VALUE OF THE APP USAGE

To provide an answer whether the participants perceived the app usage as positive or negative with respect to their baseline characteristics several factors must be considered.

Usability

Firstly, it is important to assess the usability of the app as it emerged to be a pivotal factor in determining whether a user engages long-term with an mHealth app. Usability has also been linked to the overall effectiveness of mHealth. (Glattacker et al., 2020; Kuhn & Amelung, 2016). These findings are also consistent with the results of this thesis, which indicated that higher ratings of user interface design (OR 2.55) were a significant predictor of participants reporting that they “liked” or “very much liked” using the app every day. Also, reporting that the app was “easy to use”, was associated with significant increased odds of reporting “most likely” or “definitively” using the app again. Overall, the PollDi app showed a good usability with 98.4% of participants rating the app as “very simple” or “simple” to use, and 79.7% rating the user interface design as “very good” or “good”. For both ratings, no significant differences between the patient clusters were observed.

Clinical impact - QOL

As presented in the Introduction of this thesis, an impairment in QOL is one of the major burdens for patients suffering from pollen allergies. Overall, 25% of participants "strongly" or "very strongly" agreed that the app usage was helpful in terms of QOL. This result is similar to the results of the Husteblume study, where 27.3% of participants answered "(mostly) true" when asked if using the app improved their QOL (Glattacker et al., 2020). Compared to the APOLLO study, only 8.8% of participants reported an improvement in QOL (Landesberger et al., 2023).

It can be emphasized that the cluster FA+ significantly benefited the most from the app usage in terms of QOL. Of this cluster, 41% "strongly" or "very strongly" agreed to have found the app usage helpful. The logistic regression revealed having a history of asthma to be the significant predictor of agreeing "strongly" or "very strongly" (OR 3.42). This finding is contrary to the APOLLO study which found no difference regarding the app ratings between asthmatic and non-asthmatic patients (Landesberger et al., 2023). However, the comparison to this study must be seen as limited as the analyzed sample size in the study of Landesberger et al. was very small (n = 35) and no pollen forecast was provided in the APOLLO app. In contrast, a systematic review supports the findings of this thesis indicating that asthmatic patients generally benefit from the use of mHealth and an improvement of symptoms was found (Marcolino et al., 2018).

With regards to helpfulness for everyday school/study/work life only 5.5% agreed "strongly" or "very strongly". The majority (74.8%) stated "hardly" or "not at all".

Clinical impact - Exacerbation

A further important clinical outcome is whether the app could help to avoid exacerbation of the pollen allergy. This may be relevant to avoid severe symptoms of AR or AC and to avoid asthmatic exacerbation. As asthmatic exacerbation was also significantly associated to the grass pollen (Annesi-Maesano et al., 2023) and ozone concentration (Huang et al., 2022) it emphasizes the potential of a pollen- and also air pollution forecast. Overall, 15.9% of participants agreed "strongly" or "very strongly" on the question whether the pollen forecast of the app was helpful to avoid exacerbation generally. In this case, no significant differences between the patient clusters were observed. However, an absence of significance may be due to the low sample size in the participant group and clusters. Regarding this analysis only group A (n = 44) could be considered as group B and C had no access to the pollen forecast. When

considering the responses “very strongly” or “strongly” a tendency towards cluster FA+ (18%) and MA+ (36%) could be observed compared to FA- (11%) and MA- (11%). These findings, thus not statistically significant, suggest that patients with a history of an asthmatic condition might have also benefited the most in terms of avoiding exacerbation. Further research with larger sample sizes is required to draw a reliable conclusion.

Adverse effects

Adverse clinical effects of the app usage appeared to be uncommon. Merely 3.9% of participants “strongly” or “very strongly” agreed to have experienced increased anxiety regarding the allergy and / or health status in general due to the app usage. The Husteblume study indicated similar results with 1.4% reporting (mostly) true on the statement that the app usage caused negative effects (Glattacker et al., 2020).

App functionalities

Overall, 18.9% “strongly” or “very strongly” agreed that the allergy information in the app was helpful in better understanding one’s allergy. 48.8% agreed “strongly or “very strongly” that the symptoms diary was useful, and 59.1% agreed “strongly or “very strongly” that the pollen forecast was useful. These findings support the potential value of a pollen forecast in allergy apps, which was also suggested in previous literature (Bastl et al., 2017). Also, according to the results, a pollen forecast appears to be the most valuable functionality of the app for the patients. This seems reasonable, as it provides a possibility to prevent symptoms and may avoid exacerbation if accurate. However, as the number of apps providing a forecast and forecasts with sufficient accuracy are very low (Bastl et al., 2017; Zhou et al., 2018) there is substantial room for further research.

Overall assessment

With 55.9% participants stating to “most likely” or “definitively” use the app again in the next pollen season, the majority of participants appeared to be overall satisfied with the app. This is also supported by the low number of dropouts (7.8%), which is considerably lower compared to

the “Husteblume” and “APOLLO” studies (Glattacker et al., 2020; Landesberger et al., 2023). Significant predictors for reporting “most likely yes” or “definitively yes” were revealed to be a good relation of time effort and personal benefit, simplicity of app usage, and a positive impact on QOL. This is consistent with the predominant reasons cited for a reluctance to reuse the app, which were: not having all functions available (being in group C), experiencing no benefit from the app usage, refusing to allow the allergy impose limitations upon oneself, a too repetitive knowledge section, and too much time effort for too little outcome. Similar findings were also described in the literature. The most common reason for discontinuing the use of mHealth apps appeared to be that the time commitment for data entry was too high (Krebs & Duncan, 2015). Regarding the question if the participants would use the app again, no differences between the patient clusters were observed.

Taken together all factors discussed, it can be inferred that the app usage was generally perceived as positive, and that especially patients with a history of asthma appeared to benefit most from the app usage.

There are also limitations regarding the feedback questionnaire and its analysis. An attrition bias may have skewed the results towards positive outcomes. Participants who were dissatisfied with the app may have been more likely to drop out leading to an affirmative bias within the feedback in the questionnaire. As the proportion of dropouts was relatively low (7.8%) and predominant reasons for dropping out were indicated to be a shortage of time and forgetting to use the app, it can be assumed that this had at the most only a minor impact on the results. With respect to other studies, a feedback questionnaire also appears to be the common method to evaluate the usability and clinical value (Glattacker et al., 2020; Landesberger et al., 2023; Maramba et al., 2019). Depending on the question, the low sample size may have also concealed statistical significance in the results of the feedback questionnaire, especially when considering aspects that could be only assessed by participants in group A (e.g. forecast-related questions).

4.9 SYMPTOM FORECAST

The symptom forecasting model was designed to test whether it is possible to predict the symptom severity caused by grass pollen allergy based on environmental data, demographic and clinical background data, and user-reported symptom severity and behavior. As described in

Chapter 2.8 a NNAR model was used, due to its combination of autoregression and machine learning.

Model evaluation

The models were firstly assessed based on the most common metrics used in machine learning studies. Of these, previous research suggested the R-squared to be the most reliable metric regarding information and truthfulness in regression analysis in the medical field (Chicco et al., 2021). Therefore, it was considered as the main metric to compare the models. The authors of this publication also reported that evaluating the metrics MAE, MASE and RMSE alone, no interpretation of the quality of the model was possible (Chicco et al., 2021). It should be noted that regarding the models of this thesis the MAPE is unusable as it produces infinite values in cases where the real value includes zeros, due to its nature of calculation (Kim & Kim, 2016). As the TSS was frequently zero in the dataset, as shown in *Figure 9A*, the MAPE shows "Infinity" for all presented models.

When comparing the personalized and generalized approaches, the personalized models clearly performed better, with the generalized approach showing a lower R-squared and higher values for MAE, MASE and RMSE. The worse performance of the generalized model appears not surprising as no data of the tested patients was used in the training dataset compared to the personalized approaches. Plus, predicting the symptoms of a completely new patient appears more difficult as symptom perception can vary widely among individuals.
In practice, if such a symptom forecast would be used by patients, showing exact values may be of limited use. It appears more reasonable to show levels of symptom severity, analogous to a visual analogue scale. Also, a "traffic light system" appears conceivable as suggested by Kiotseridis et al. to communicate the associated risk of the symptoms (Kiotseridis et al., 2013).
Based on this rationale, the models were also evaluated regarding the accuracy of predicting the correct symptom levels. In this analysis the personalized approaches also performed superior, showing an accuracy of 70.62% (1_NNAR) and 71.79% (2_NNAR) compared to the generalized approach with an accuracy of merely 57.35% (3_NNAR).

Observing the confusion matrices (*Figure 31*), independent of approach, the models appear to underestimate the symptom severity especially in the higher symptom range. As can be seen in the confusion matrices none of the models predicted a "severe" symptom severity. The

3_NNAR also tended to overestimate the symptom levels of “none” / “very low” (“none to minimal”). However, all approaches were rather reliable within the low-intermediate range of symptoms. For the future, a possible solution to resolve under- /overestimation may be to build an ensemble of models to counterbalance the errors.
The presented time series for the 2_NNAR and the 3_NNAR (*Figure 32*) also revealed that the models have especially difficulties to predict symptom spikes for both, low and high symptoms. This may also be caused by the nature of the calculation of the TSS, as it also incorporates general well-being and not only allergic symptoms. As the general well-being is influenced by many external and internal factors that are not included in the model, it appears difficult to predict. Future approaches may benefit from considering only the allergic symptoms. However, given that in the statistical analysis of this thesis the TSS was used, and it showed a very high correlation with the respective pollen concentration (*Figure 11A*), it was decided to evaluate the model using this metric as well in this thesis.

Limitations of the development

There are also further factors that limited the development of the symptom models: As the complete IgE profile was not available for all participants, only the sIgE g6 could be considered. Since many participants indicated to be polysensitized, potential crucial information that could have been incorporated in the model was missing. In the context of polysensitization to aeroallergens, it would also be important to incorporate other pollen allergens or fungal spores in the sensitization profile. It may be assumed that these were additional factors why the models showed limited accuracy in predicting high symptoms and spikes in the severity. Also, having data available of a longer time span, optimally data spanning over several pollen seasons, appears beneficial.

Limitations of the interpretation

There are certain limitations that must be considered for the interpretation of the results: Generally, it is important to note that the data was only available from one pollen season and the beginning of the pollen season was missing. Therefore, it was not possible to test the performance of the model on a new, “unknown”, pollen season. To draw a definite conclusion of the performance this would be crucial. Also, the 1_NNAR was already trained on

approximately 70% random datapoints of each patient. Therefore, it had to only predict unknown values in-between already known values of the training dataset, suggesting a positive bias towards more accurate results (overfitting). This was also the reason why no time series was presented of this model. The 2_NNAR was presented to emulate more "realistic" conditions for an individual approach. However, the accuracy of the 2_NNAR must also be regarded as limited, as it merely predicted the symptoms of the month August. As in August the grass pollen season is coming to an end and low pollen concentrations (*Figure 10B*) and low symptoms (*Figure 10A*) prevail, the prediction appears simpler, especially in the context of the shown inaccuracy of the model predicting more severe symptoms. Due to the lower pollen count, also spikes in the symptom severity become rarer, which also leads to a positive bias of the prediction. This can be especially seen in patient 5 (*Figure 32A*) for whom even the personalized approach has its difficulties in predicting such spikes. Considering the available data, the 2_NNAR was the closest to emulate "realistic" conditions for an individual approach.

Overall assessment

Taken together, the findings indicate that the personalized models could rather accurately forecast the symptom level of the patients. The generalized approach was limited but showing also promising accuracy and metrics suggesting the possibility of future improvements. With respect to the limitations and potential improvements, it seems likely that the development of a reliable symptom forecasts for patients suffering from pollen allergy is possible, when high quality data is available. When implementing symptom levels, such as a traffic light system (Kiotseridis et al., 2013) the accuracy of the models can even be higher.

If accurate, such a symptom forecast could provide a promising tool for patients suffering from pollen allergy. It has the potential to provide patients with useful information to alleviate symptoms and to avoid exacerbation of their allergy. Especially for patients suffering from an asthmatic condition this appears very valuable. An accurate forecast may provide a "warning" for patients that they are likely to experience asthmatic symptoms and in turn recommend allergen avoidance strategies or even preventive medication intake. As discussed, this could be based on a visual analog scale or a traffic light system. However, it appears very important to also predict the absence of symptoms and symptom spikes accurately, which was shown to be still limited.

4.10 CONCLUSION

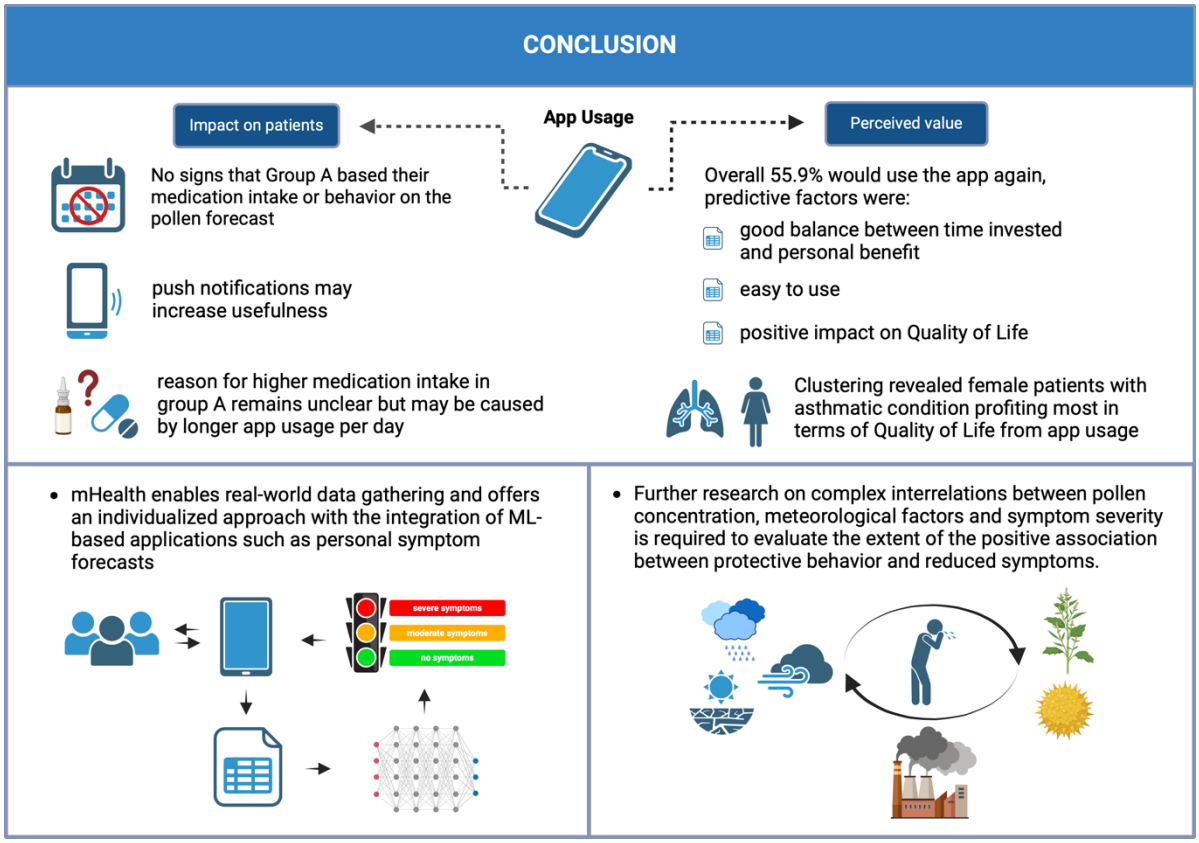


***Figure 34**: Visual summary of the conclusion.*

Taken together, there appears to be a positive association between the discussed preventive behavioral strategies and the alleviation of total and nasal allergic symptoms. Current research, as available, supports these findings. However, the extent to which the effect of the discussed behaviors can be attributed to the reduced symptom severity cannot be answered by the results of this thesis. As presented, the interrelationships of meteorological factors, pollen concentration and symptom severity are very complex and must be considered. Applying more complex statistical models such as joint mixed-effects models may present a possibility to infer causal relationships in future studies (Shardell & Ferrucci, 2018).

Further, there were no signs that participants of group A based their behavior or medication intake on the pollen forecast integrated in the app. However, in group A, the medication intake was observed to be higher. If this was caused by spending more time in the app or by the availability of the pollen forecast could not be determined with the available data.

The thesis also showed that the app usage was perceived as positive by the majority of participants, independent of patient characteristics, and negative effects were infrequently

reported. In terms of QOL, asthmatic patients, and among these especially female patients, appeared to benefit most of the app usage. Overall, participants particularly valued a good balance between time invested and personal benefit when deciding to use the app again.

With regards to the future, it can be concluded that mHealth apps present a promising tool for patients suffering from pollen allergy. Integrating push-notifications, e.g. for high pollen forecasts appear crucial and may increase the usefulness of mHealth apps for patients. Such reminders may also lower dropouts in studies and increase compliance.

Clearly, mHealth apps are very useful to collect extensive real-world datasets to uncover disease-related pattern in patients (Bousquet et al., 2020) and in providing the data for the development of new cutting-edge, machine-learning based technologies such as symptom forecasts. As pollen allergies present a complex disease entity the severity of which is influenced by environmental factors, individual parameters, and emotional factors such as perceived stress (Patterson et al., 2014), an individual symptom forecast seems promising.

In the future, providing an accurate symptom forecast appears possible and could present a valuable tool for patients to help avoiding exacerbation of allergic symptoms. Constant evaluation of the clinical efficacy and their accuracy is essential. Also, further research is required to explore the clinical efficacy of allergen avoidance strategies and preventive medication intake, as this is intrinsically linked to the efficacy of pollen forecasts and symptom forecasts.

5 ABSTRACT

5.1 ENGLISH VERSION

Seasonal AR caused by grass pollen ranks among the most common non-communicable diseases in Germany and Europe. Due to a confluence of various factors such as environmental changes, rapid urbanization, and a spreading westernized lifestyle, globally, the prevalence appears to be still on the rise. Affected patients show a substantial disease-related burden including a broad spectrum of associated co-morbidities. AR also significantly reduces QOL and work-productivity resulting in high economic costs. Yet, patients appear to often self-manage and trivialize their condition and do not seek medical supervision. This was related to a lack of knowledge about the disease and the vast accessibility of over-the-counter medications. Moreover, only a minority of patients seek causal treatments such as AIT and use strategies for allergy avoidance. Such avoidance strategies are so far also not supported by robust evidence and are subject to challenges in feasibility dependent on the allergen.

Due to the rapid advancements of digital health interventions and AI-applications in the medical field, the development of mHealth apps for AR patients is also widespread. Such apps generally aim to increase the knowledge about the disease and treatment options, increase medication adherence and offer a tool to improve the self-management. Also, depending on the app, pollen forecasts are provided to limit exposure to high pollen concentrations and mitigate symptoms. However, current research on the clinical efficacy of mHealth apps for patients suffering from pollen allergies and the impact of the different app functionalities on the behavior and medication intake of patients is very limited.

The aim of the presented thesis was therefore to provide insights into these topics and further explore the clinical efficacy of allergen avoidance strategies, as this is intrinsically linked to the efficacy of pollen forecasts. Moreover, this thesis evaluated a symptom forecasting model which was developed by the doctoral candidate based on the clinical data obtained in this study. Also, the relationship of symptom severity and QOL was addressed, but this analysis was subject to strong limitations.

The results of this thesis are based on the data of a pilot study evaluating the mHealth app “PollDi” for grass pollen allergy. The study implemented a randomized, controlled clinical trial including 167 participants, that were allocated into three groups. Each group received a different version of the app with different available functions. Group A had access to all functionalities including the pollen forecast, group B to the diary and the basic information and group C only

to the basic information. The study period took place from May 31st to August 31st in Augsburg and its greater area.

Data was analyzed using Spearman's rank correlation to investigate the relationships between symptom severity, QOL, protective behavior, meteorological factors, and medication intake. Kruskal-Wallis-rank sum tests and χ^2-tests were used to test for significant differences between groups and patient clusters regarding the behavior, medication intake and clinical efficacy of the app usage. The patient clusters were built using Gowers distance. The pollen forecasting model was developed using a neural network autoregression model (NNAR).

The results showed a positive correlation between increasing frequency of protective behavior and reduction of symptom severity across the cohort. No difference between the groups was observed regarding the frequency of the addressed behavioral strategies. Group A showed the highest medication intake throughout the study period; however, no signs were observed that group A based their medication intake or behavior on the pollen forecast. Generally, the app usage was perceived as positive by most participants without showing differences across the patient clusters. However, in terms of QOL, asthmatic patients, and among these especially female patients, appeared to benefit most of the app usage. The evaluation of the pollen forecasting model showed reasonable results for the personalized approach and yet insufficient results for the generalized approach. However, in the future, the development of accurate symptom forecasts appears possible, having high-quality data available.

Taken together, it can be concluded that mHealth apps present a promising tool for the future and can be used as a basis to provide machine-learning tools for patients to alleviate their symptom burden. The efficacy of protective behavioral strategies and further measures such as preventive medication intake on days with a forecasted high pollen load, however, require robust evidence. Also, the integration of push-notification with recommendations could provide further benefit.

As pollen allergies represent a complex disease entity, the severity of which is influenced by a variety of environmental and individual factors, mHealth apps could serve as a valuable addition to traditional treatments, offering an economic, individualized approach to mitigate symptoms.

5.2 GERMAN VERSION

Die allergische Rhinitis stellt eine der häufigsten Umwelterkrankungen in Deutschland sowie im europäischen Raum dar. Aufgrund des Zusammenspieles verschiedener Faktoren, wie dem Klimawandel, der Urbanisierung und dem sich ausbreitenden westlichen Lebensstil, scheint die

Prävalenz weltweit noch immer weiter zu steigen. Betroffene Patient*innen unterliegen einer erheblichen krankheitsbedingten Belastung und zeigen ein breites Spektrum an assoziierten Komorbiditäten. Zudem wurde nachweislich ein Zusammenhang zwischen Allergischer Rhinitis und der Verringerung der Lebensqualität sowie verminderter Produktivität festgestellt, welche mit hohen gesamtwirtschaftlichen Kosten einhergeht. Trotz der Belastung scheinen eine Vielzahl der Patient*innen die Krankheit zu bagatellisieren und bevorzugen ein Selbstmanagement anstatt einer ärztlichen Betreuung. Auch werden kausale Therapieoptionen wie die AIT nur von einer Minderheit in Anspruch genommen. Dies betrifft auch die empfohlenen Handlungsempfehlungen zur Allergievermeidung und Symptomreduktion, die jedoch auch teilweise schwer umsetzbar sind und größtenteils bisher nicht evidenz-basiert sind.

Im Zuge der rasanten technologischen Fortschritte und der Entwicklung von digitalen Hilfsmitteln und KI-Anwendungen im medizinischen Bereich, werden auch hochfrequent Apps für Pollenallergiker entwickelt. Diese beinhalten meist Information über die Krankheit und Therapiemöglichkeiten, sollen die Compliance erhöhen und das Selbstmanagement der Allergie verbessern. Auch wird in manchen Apps eine Pollenvorhersage zur Verfügung gestellt, die der Vermeidung von hohen Pollenbelastungen und damit der Symptomreduktion dienen soll.

Trotz der hochfrequenten Entwicklung und Verbreitung von Apps für Pollenallergiker ist deren klinischer Nutzen bisher nicht mit hinreichender Evidenz belegt. Auch ist die Auswirkung der verschiedenen App-Funktionalitäten, wie z.B. einer Pollenvorhersage, auf das Verhalten sowie die Medikamenteneinnahme der Patient*innen weitestgehend unbekannt.

Die vorliegende Arbeit widmete sich daher der Auseinandersetzung mit diesen Fragestellungen sowie der wissenschaftlichen Erörterung der Frage, ob bestimmte Verhaltensweisen mit einer Symptomreduktion korrelieren. Da diese in direktem Zusammenhang zum klinischen Nutzen einer Pollenvorhersage und einer Symptomvorhersage stehen, scheint dies essenziell. Auch wurde der Zusammenhang zwischen Symptomstärke und Lebensqualität untersucht, jedoch war dies nur eingeschränkt möglich. Zusätzlich wurde vom Doktoranden auf Basis von Umweltdaten und der klinischen Daten des Screenings und der App ein Symptomvorhersagemodell entwickelt, das ebenfalls in dieser Arbeit evaluiert wurde.

Die vorgestellte Studie war eine Pilotstudie im Großraum Augsburg, die den klinischen Nutzen einer speziell hierfür entwickelten App „PollDi“ evaluierte. In die Studie wurden 167 Probanden eingeschlossen, die in drei Untersuchungsgruppen randomisiert wurden und jeweils unterschiedliche Versionen der App mit den dazugehörigen freigehaltenen Funktionen erhalten haben. Gruppe A hatte alle Funktionen, inklusive der Pollenvorhersage, freigeschalten, wohingegen Gruppe B nur Zugriff auf das Symptomtagebuch und die Basis-Informationsfunktion hatte. Gruppe C, diente als Kontrollgruppe und hatte nur Zugriff auf die

Basis-Informationsfunktion. Die Datenanalyse erfolgte mit Spearman's rank correlation, um die Korrelationen zwischen meteorologischen Faktoren, Verhaltensweisen, Symptomstärke, Lebensqualität und Medikamenteneinnahme zu bestimmen. Weiterhin wurden Kruskal-Wallis rank sum tests und χ^2-Tests angewandt, um signifikante Unterschiede zwischen den Gruppen und Patientenclustern bezüglich Verhaltensweisen, Medikamenteneinnahme und dem klinischen Nutzen der App zu identifizieren. Zur Bildung der Patientencluster wurde das Verfahren Gowers distance verwendet. Das Symptomvorhersage Modell wurde unter der Verwendung eines autoregressiven neuronalen Netzwerks (NNAR) entwickelt.

Die Ergebnisse konnten eine positive Korrelation zwischen einer Zunahme der Häufigkeit der diskutierten präventiven Verhaltensweisen und abnehmender Symptomstärke in der Kohorte aufzeigen. Weiterhin zeigte sich kein signifikanter Unterschied zwischen den Gruppen bezüglich der Häufigkeit der Verhaltensweisen. Gruppe A zeigte die signifikant häufigste Medikamenteneinnahme, jedoch gab es keinen statistischen Anhalt dafür, dass Gruppe A ihre Medikamenteneinnahme oder ihr Verhalten an der Pollenvorhersage ausrichtete.

Die App-Nutzung wurde vom Großteil der Probanden als positiv wahrgenommen, jedoch zeigte sich kein signifikanter Unterschied bezüglich der Patientencluster. Im Hinblick auf die Lebensqualität konnten Probanden mit einer positiven Asthmaanamnese – und darunter speziell Frauen mit Asthma - am meisten von der App-Nutzung profitieren. Die Evaluation des Symptomvorhersagemodells zeigte gute Resultate bezüglich des „personalisierten“ Modells und eingeschränkte Resultate bezüglich des „generalisierten“ Modells. Jedoch scheint die Entwicklung eines verlässlichen Symptomvorhersagemodells auf der Basis hochqualitativer Daten möglich.

Zusammenfassend wird angemerkt, dass Apps für Pollenallergiker großes Potential für die Zukunft haben, die Symptomlast von Patienten zu verringern. Hierfür ist jedoch die wissenschaftliche Evaluation des klinischen Nutzens von Handlungsweisen zur Symptomreduzierung und beispielsweise auch von präventiver Medikamenteneinnahme an Tagen mit hoher Pollenvorhersage essenziell. Auch könnte die Integration von Push-Nachrichten hilfreich sein, um die Nützlichkeit der App zu steigern. Symptomvorhersagemodelle könnten ein wertvolles Instrument für Pollenallergiker darstellen, um Exazerbationen zu vermeiden und Verhaltensweisen und Medikamenteneinnahme daran auszurichten. Da Pollenallergien eine komplexe Krankheitsentität darstellen, dessen individueller und tagesabhängiger Schweregrad von einer Vielzahl von Umweltfaktoren und individueller Faktoren abhängt, können mHealth-Apps eine wertvolle Ergänzung zu gängigen Therapieformen darstellen und einen kostengünstigen, individuellen Ansatz zur Linderung der Symptome bieten.

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APPENDIX

I. ABBREVIATIONS

AC	Allergic conjunctivitis
AIT	Allergen-specific immunotherapy
apps	Mobile applications
AR	Allergic rhinitis
ARC	Allergic rhinoconjunctivitis
DWD	Deutscher Wetterdienst (German Weather Service)
EAACI	European Academy of Allergy & Clinical Immunology
ICAR-AR	International Consensus Statement on Allergy and Rhinology
ICF	Informed consent form
IEM	Institute of Environmental Medicine
LfU	Bayerisches Landesamt für Umwelt (Bavarian Environmental State Office)
mHealth apps	Mobile health applications
ML	Machine learning
QOL	Quality of life
RCTs	Randomized, controlled trials
SCIT	Subcutaneous immunotherapy
sIgE	Allergen-specific IgE
SLIT	Sublingual immunotherapy
SPT	Skin prick test
TBSS	Total Bronchopulmonary Symptom Score
TNSS	Total Nasal Symptom Score
TOSS	Total Ocular Symptom Score
TSS	Total Symptom Score
WAO	World Allergy Organization

II. LIST OF FIGURES

III. LIST OF TABLES

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V. PUBLICATIONS AND CONGRESS PARTICIPATION

Parts of this thesis will be submitted for the publication Holzmann, Karg et.al (unpublished, manuscript in preparation) that will be dedicated to the same study. The incorporated parts of this thesis consist of Material and Methods and the results of the participant analysis, the medication analysis between groups and the symptom forecasting model. Also, the respective parts of the Discussion may be incorporated in the publication. At the time when the thesis was finished, the paper was still work in progress, and we attempted to develop the symptom forecasting model further for the paper. Therefore, the results for the symptom model presented in the paper are more comprehensive than the results presented in this thesis.

VI. QUESTIONNAIRES

A. SCREENING QUESTIONNAIRE

Screening Ehemalige	**IEM Augsburg**	
Telefonisch	**KuHeMo-AUX Pollen-App-Studie 2023**	Teilnehmer-ID |_0|_1|.|_0|_5|_8|.|__|__|__|__| Standort Studiennummer Teilnehmer-ID

Datum |__|__|.|__|__|.|__|__| Tag Monat Jahr

Gibt es Änderungen bei Ihren Allergien? ☐ Ja ☐ Nein **Wenn ja, welche:**

Pollen

Birkenpollen ☐ Ja ☐ Nein

Gräserpollen ☐ Ja ☐ Nein

Andere Pollen ☐ Ja ☐ Nein Welche _____

Ganzjährige Allergien ☐ Ja ☐ Nein **Wenn ja, welche:**

Hausstaubmilben ☐ Ja ☐ Nein

Tierhaare ☐ Ja ☐ Nein Welche _____

Aktuell Kontakt zu Tieren ☐ Ja ☐ Nein Welche _____

Sonstige: _____

Haben sich die Symptome gegen Gräserpollen geändert? ☐ Ja ☐ Nein **Wenn ja, wie:**

Die Symptome sind stärker geworden ☐ Die Symptome sind schwächer geworden ☐

Mittlere Symptomstärke 0 1 2 3 4 5

Hat sich die Art der Symptome verändert?

Augen (Konjunktivitis) ☐ Ja ☐ Nein perennial ☐ saisonal ☐

Nase (Rhinitis) ☐ Ja ☐ Nein perennial ☐ saisonal ☐

Nasenpolypen ☐ Ja ☐ Nein

Lunge (Asthma) ☐ Ja ☐ Nein perennial ☐ saisonal ☐

Haut (Atopisches Ekzem) ☐ Ja ☐ Nein

Hyposensibilisierung

Aktuell laufende Hyposensibilisierung? ☐ Ja ☐ Nein

Frühere Hyposensibilisierung? ☐ Ja ☐ Nein

Wann? |__|__| - |__|__| (Monat Jahr) Wie lange? |__|, |__| Jahre

Art? SLIT ☐ Ja ☐ Nein SCIT ☐ Ja ☐ Nein

Falls „Ja“: Trat nach der Hyposensibilisierung eine Veränderung ein?

☐ schlechter ☐ gleich ☐ besser ☐ keine Symptome mehr

Symptomstärke vor der Hypo: [0-5] |__|__|,|__| nach der Hypo: [0-5] |__|__|,|__|

Anamnese

Nikotin ☐ Ja ☐ Nein Wenn ja, wieviel? |_____| / Tag ☐ Exraucher, seit |_____| Jahren

Alkohol ☐ Ja ☐ Nein Wenn ja, wieviel? |_____| / Tag Schwangerschaft/Stillzeit ☐ Ja ☐ Nein

Autoimmunerkrankung? ☐ Ja ☐ Nein

(MS, Hashimoto, Morbus Basedow, Rheumatoide Arthritis, Psoriasis, Lupus erythemotodes, M. Crohn oder Colitis ulcerosa, M. Behcet)

Screening Ehemalige	IEM Augsburg	
Telefonisch	KuHeMo-AUX Pollen-App-Studie 2023	Teilnehmer-ID |_0|_1|.|_0|_5|_8|.|__|__|__|__| Standort Studiennummer Teilnehmer-ID

Systemische Erkrankungen? ☐ Ja ☐ Nein

(Schwere KHK, Tumorerkrankung, etc.)

Wochenenden/ Mai – August Urlaub geplant? ☐ Ja ☐ Nein

Wann? |__|__| - |__|__| bis |__|__| - |__|__| wo?|_____|
Tag Monat Tag Monat

Wann? |__|__| - |__|__| bis |__|__| - |__|__| wo?|_____|
Tag Monat Tag Monat

Proband darauf aufmerksam machen, dass Urlaub in der spezifischen Pollensaison (Gräser) u.U. nicht möglich wäre.

Täglicher Zugang zu Smartphone oder Internet? ☐ Ja ☐ Nein

Haben sich Ihre Kontaktdaten geändert?

Nachname _____

Vorname _____

Straße, Nummer _____

PLZ, Ort _____

Telefon _____ Mobil _____

E-Mail _____

Geburtsdatum |__|__|.|__|__|.|__|__|__|__| Beruf _____
Tag Monat Jahr

Geschlecht ☐ männlich ☐ weiblich

Dürfen wir diese Daten in unserer Interessentendatenbank zu späterer Kontaktaufnahme oder auch für andere Studien speichern? ☐ Ja ☐ Nein

Teilnehmerinformation/ICF verschickt? ☐ Nein ☐ Ja

Datum: |__|__|.|__|__|.|__|__|__|__|
Tag Monat Jahr

Tag Monat Jahr

Nachname Studienärztin/Studienarzt _____ Kürzel _____
Datum (tt.mm.jj)

Screening Neue	IEM Augsburg	
Telefonisch	KuHeMo-AUX Pollen-App-Studie 2023	Teilnehmer-ID |_0|_1|.|_0|_5|_8|.|__|__|__|__| Standort Studiennummer Teilnehmer-ID

Datum |__|__|.|__|__|.|__|__|
Tag Monat Jahr

Woher haben Sie die Information zu dieser Studie?

Haben Sie Allergien?	☐ Ja	☐ Nein	**Wenn ja, welche:**
Pollen			
Birkenpollen	☐ Ja	☐ Nein	
Gräserpollen	☐ Ja	☐ Nein	
Andere Pollen	☐ Ja	☐ Nein	Welche _____
Lebensmittelallergien	☐ Ja	☐ Nein	**Wenn ja, welche:**
Äpfel	☐ Ja	☐ Nein	
Nüsse	☐ Ja	☐ Nein	
Sonstige: _____			
Ganzjährige Allergien	☐ Ja	☐ Nein	**Wenn ja, welche:**
Hausstaubmilben	☐ Ja	☐ Nein	
Tierhaare	☐ Ja	☐ Nein	Welche _____
Aktuell Kontakt zu Tieren	☐ Ja	☐ Nein	Welche _____
Sonstige: _____			
Insektengiftallergie	☐ Ja	☐ Nein	
Arzneimittelunverträglichkeit	☐ Ja	☐ Nein	**Wenn ja, welche:**
Andere Allergien	☐ Ja	☐ Nein	**Wenn ja, welche:**
Sind Sie bereits getestet worden?	☐ Ja	☐ Nein	**Wenn ja, wie?** Prick-Test ☐ Blut ☐ Anderes ☐
			Wann?
Haben Sie Symptome?	☐ Ja	☐ Nein	
Ganzjährig	☐ Ja	☐ Nein	
In welcher Jahreszeit			|__|__| - |__|__| (Monat Monat) |__|__| - |__|__| (Monat Monat)
Seit wann bestehen die Symptome?			|__|__| - |__|__| (Monat Jahr)
Art der Symptome			
Augen (Konjunktivitis)	☐ Ja	☐ Nein	perennial ☐ saisonal ☐
Nase (Rhinitis)	☐ Ja	☐ Nein	perennial ☐ saisonal ☐
Nasenpolypen	☐ Ja	☐ Nein	
Lunge (Asthma)	☐ Ja	☐ Nein	perennial ☐ saisonal ☐
Haut (Atopisches Ekzem)	☐ Ja	☐ Nein	

Screening Neue	IEM Augsburg	
Telefonisch	KuHeMo-AUX Pollen-App-Studie 2023	Teilnehmer-ID |_0|_1|.|_0|_5|_8|.|__|__|__|__| Standort Studiennummer Teilnehmer-ID

Wie schwer sind Ihre mittleren Symptome gegen Gräserpollen?

Mittlere Symptomstärke 0 1 2 3 4 5

Hyposensibilisierung

Aktuell laufende Hyposensibilisierung? ☐ Ja ☐ Nein

Frühere Hyposensibilisierung? ☐ Ja ☐ Nein

Wann? |__|__| - |__|__| (Monat Jahr) Wie lange? |__|, |__| (Jahre)

Art? SLIT ☐ Ja ☐ Nein SCIT ☐ Ja ☐ Nein

Falls „Ja“: Trat nach der Hyposensibilisierung eine Veränderung ein?

☐ schlechter ☐ gleich ☐ besser ☐ keine Symptome mehr

Symptomstärke vor der Hypo: [0-5] |__|__|,|__| nach der Hypo: [0-5] |__|__|,|__|

Anamnese

Nikotin ☐ Ja ☐ Nein Wenn ja, wieviel? |_____| / Tag ☐ Exraucher, seit |_____| Jahren

Alkohol ☐ Ja ☐ Nein Wenn ja, wieviel? |_____| / Tag Schwangerschaft/Stillzeit ☐ Ja ☐ Nein

Autoimmunerkrankung? ☐ Ja ☐ Nein

(MS, Hashimoto, Morbus Basedow, Rheumatoide Arthritis, Psoriasis, Lupus erythemotodes, M. Crohn oder Colitis ulcerosa, M. Behcet)

Systemische Erkrankungen? ☐ Ja ☐ Nein

(Schwere KHK, Tumorerkrankung, etc.)

Wochenenden/ Mai- August Urlaub geplant? ☐ Ja ☐ Nein

Wann? |__|__| - |__|__| (Tag Monat) bis |__|__| - |__|__| (Tag Monat) wo?|_____|

Wann? |__|__| - |__|__| (Tag Monat) bis |__|__| - |__|__| (Tag Monat) wo?|_____|

Proband darauf aufmerksam machen, dass Urlaub in der spezifischen Pollensaison (Gräser) u.U. nicht möglich wäre.

Laboranforderung? ☐ Ja ☐ Nein

Inhalations-Allergene ☐ Ja ☐ Nein

Datum der Blutabnahme |__|__|.|__|__|.|__|__|__|__| (Tag Monat Jahr)

Abgabe im Labor am |__|__|.|__|__|.|__|__|__|__| (Tag Monat Jahr)

Urin-Aufkleber Laboranforderung

Serologie ☐ Ja ☐ Nein

Screening Neue	IEM Augsburg	
Telefonisch	**KuHeMo-AUX Pollen-App-Studie 2023**	Teilnehmer-ID |_0|_1|.|_0|_5|_8|.|__|__|__|__| Standort Studiennummer Teilnehmer-ID

Datum der Blutabnahme |__|__|.|__|__|.|__|__|__|__|
Tag Monat Jahr

Abgabe im Labor am |__|__|.|__|__|.|__|__|__|__|
Tag Monat Jahr

Stuhl-Aufkleber Laboranforderung

Täglicher Zugang zu Smartphone oder Internet? ☐ Ja ☐ Nein

Screening-Untersuchung ☐ Ja ☐ Nein

Besteht Bereitschaft zur Blutabnahme für ein Screening vorbei zu kommen?

Kontaktdaten

Nachname _____

Vorname _____

Straße, Nummer _____

PLZ, Ort _____

Telefon _____ Mobil _____

E-Mail _____

Geburtsdatum |__|__|.|__|__|.|__|__|__|__| Beruf _____
Tag Monat Jahr

Geschlecht ☐ männlich ☐ weiblich

Dürfen wir diese Daten in unserer Interessentendatenbank zu späterer Kontaktaufnahme oder auch für andere Studien speichern? ☐ Ja ☐ Nein

Screening-Termin vereinbart? ☐ Nein ☐ Ja

Datum: |__|__|.|__|__|.|__|__|__|__| Uhrzeit |__|__|:|__|__|
Tag Monat Jahr Uhrzeit

Teilnehmerinformation/ICF verschickt? ☐ Nein ☐ Ja

Datum: |__|__|.|__|__|.|__|__|__|__|
Tag Monat Jahr

Termin in Datenbank eingetragen? ☐ Nein ☐ Ja

Datum: |__|__|.|__|__|.|__|__|__|__|
Tag Monat Jahr

Screening Neue	IEM Augsburg	
Telefonisch	KuHeMo-AUX Pollen-App-Studie 2023	Teilnehmer-ID |_0|_1|.|_0|_5|_8|.|__|__|__|__| Standort Studiennummer Teilnehmer-ID

Mitteilung IgE-Laborergebnisse? ☐ Nein ☐ Ja

Befunde besprochen: |__|__|.|__|__|.|__|__| Datum (tt.mm.jj)

Befunde versandt: |__|__|.|__|__|.|__|__| Datum (tt.mm.jj)

Einschluss? ☐ Nein ☐ Ja

Datum: |__|__|.|__|__|.|__|__|__|__|
Tag Monat Jahr

Wenn nein, Begründung Ausschluss:

_____

Nachname Studienärztin/Studienarzt _____ Kürzel _____

B. SYMPTOM DIARY

Beginn des Blocks: Allgemeinzustand

Q3.1 **Wie ging es Ihnen im Allgemeinen?**

	sehr schlecht									sehr gut
	0	1	2	3	4	5	6	7	8	9	10
Bitte verschieben Sie den Balken ()											

Q3.2 **Wie bewerten Sie Ihre Stressbelastung auf einer Skala von 0 bis 10 (zu Hause und in der Arbeit)?**

	kein Stress									extremer Stress
	0	1	2	3	4	5	6	7	8	9	10
Bitte verschieben Sie den Balken ()											

Ende des Blocks: Allgemeinzustand

Beginn des Blocks: Allergiebezogenes Verhalten

X→

Q4.1 **Haben Sie bei offenem oder geschlossenem Fenster geschlafen?**

- ○ offen (1)
- ○ geschlossen (2)
- ○ teilweise offen, teilweise geschlossen (3)

X→

Q4.2 **Haben Sie vor dem Schlafengehen die Bettwäsche / den Kopfkissenbezug gewechselt?**

- ○ Ja (1)
- ○ Nein (0)

Q4.3 **Haben Sie sich die Haare gewaschen?**

- ○ Ja (1)
- ○ Nein (0)

Diese Frage anzeigen:

If Q4.3 = Ja

Q4.4 **Wann haben Sie sich die Haare gewaschen?**
Mehrfachantwort ist möglich. Bitte Zutreffendes ankreuzen!

- ☐ Morgens (1)
- ☐ Gleich nach dem Heimkommen (2)
- ☐ Vor dem Schlafengehen (3)
- ☐ Zu einer anderen Tageszeit (4)

Q4.5
Haben Sie Ihre Kleidung und Schuhe gewechselt, nachdem Sie sich im Freien aufgehalten haben?

- ○ Ja, ich habe Kleidung **und** Schuhe gewechselt (1)
- ○ Ich habe nur die Schuhe **oder** nur die Kleidung gewechselt (2)
- ○ Nein, ich habe **weder** Kleidung **noch** Schuhe gewechselt (3)
- ○ Ich war **nicht** im Freien (4)

Ende des Blocks: Allergiebezogenes Verhalten

Beginn des Blocks: Beschwerden

X→

Q5.1 **Hatten Sie Symptome?**

Bitte geben Sie an, ob Sie körperliche oder psychische Beschwerden hatten.

- ○ Ja (1)
- ○ Nein (0)
- ○ Kann ich nicht sagen, bin mir nicht sicher (2)

Überspringen bis: Ende des Blocks Wenn Q5.1 = Nein

X→

Q5.2 **Hatten Sie eine Erkältung oder einen viralen Infekt?**

- ○ Ja (1)
- ○ Nein (0)
- ○ Kann ich nicht sagen, bin mir nicht sicher (2)

Seitenumbruch

Q5.3 **Belastung der Augen**

- ○ keine (0)
- ○ geringe (1)
- ○ mäßige (2)
- ○ starke (3)

Überspringen bis: Q5.5 Wenn Q5.3 = keine

Q5.4 **Symptome der Augen**
Mehrfachantwort ist möglich. Bitte Zutreffendes ankreuzen!

- ☐ Juckreiz (1)
- ☐ Fremdkörpergefühl (2)
- ☐ Rötung (3)
- ☐ Tränenfluss (4)
- ☐ Schwellung (5)
- ☐ Trockenheit (6)

Seitenumbruch

Q5.5 **Belastung der Nase**

- ○ keine (0)
- ○ geringe (1)
- ○ mäßige (2)
- ○ starke (3)

Überspringen bis: Q5.7 Wenn Q5.5 = keine

Q5.6 **Symptome der Nase**
Mehrfachantwort ist möglich. Bitte Zutreffendes ankreuzen!

- ☐ Nasenjucken (1)
- ☐ Niesen (2)
- ☐ rinnende Nase (3)
- ☐ verstopfte Nase (4)

Seitenumbruch

Q5.7 **Belastung der Ohren**

- ○ keine (0)
- ○ geringe (1)
- ○ mäßige (2)
- ○ starke (3)

Überspringen bis: Q5.9 Wenn Q5.7 = keine

Q5.8
Symptome der Ohren
Mehrfachantwort ist möglich. Bitte Zutreffendes ankreuzen!

- ☐ Druckgefühl (1)
- ☐ Ohrenjucken (2)
- ☐ Ohrenschmerzen (3)
- ☐ vorübergehende Hörminderung (4)

Seitenumbruch

X→

Q5.9 **Belastung des Rachenraums**

- ○ keine (0)
- ○ geringe (1)
- ○ mäßige (2)
- ○ starke (3)

Überspringen bis: Q5.11 Wenn Q5.9 = keine

X→

Q5.10 **Symptome des Rachenraums**
Mehrfachantwort ist möglich. Bitte Zutreffendes ankreuzen!

- ☐ Gaumenjucken (1)
- ☐ Schwellung (2)
- ☐ Trockenheitsgefühl (3)
- ☐ Halsschmerzen / Schluckbeschwerden (4)
- ☐ Heiserkeit (5)
- ☐ Verschleimung (6)

Seitenumbruch

X→

Q5.11 **Belastung der Lunge**

- ○ keine (0)
- ○ geringe (1)
- ○ mäßige (2)
- ○ starke (3)

Überspringen bis: Q5.13 Wenn Q5.11 = keine

X→

Q5.12 **Symptome der Lunge**
Mehrfachantwort ist möglich. Bitte Zutreffendes ankreuzen!

- ☐ Pfeifen (1)
- ☐ Kurzatmigkeit (2)
- ☐ Husten (3)
- ☐ asthmatische Reaktion (4)

Seitenumbruch

Q5.13 **Belastung der Haut**

- ○ keine (0)
- ○ geringe (1)
- ○ mäßige (2)
- ○ starke (3)

Überspringen bis: Q5.15 Wenn Q5.13 = keine

Q5.14
Symptome der Haut
Mehrfachantwort ist möglich. Bitte Zutreffendes ankreuzen!

- ☐ Ausschlag (1)
- ☐ Rötung (2)
- ☐ Juckreiz (3)
- ☐ örtliche Schwellung (4)

Seitenumbruch

Q5.15 **Magen-Darm-Beschwerden**

- ○ Ja (1)
- ○ Nein (0)

Seitenumbruch

Q5.16 **Hatten Sie allgemeine körperliche Beschwerden?**

- ○ keine (0)
- ○ geringe (1)
- ○ mäßige (2)
- ○ starke (3)

Überspringen bis: Q5.19 Wenn Q5.16 = keine

Q5.17 **Allgemeine körperliche Beschwerden**
Mehrfachantwort ist möglich. Bitte Zutreffendes ankreuzen!

- ☐ Abgeschlagenheit und Müdigkeit (1)
- ☐ Appetitlosigkeit (2)
- ☐ erhöhte Temperatur / Fieber (3)
- ☐ Kopfschmerzen (4)
- ☐ Gliederschmerzen (5)
- ☐ Schlafstörungen (6)

Seitenumbruch

Q5.18 **Sonstige Beschwerden**

- ○ Ja und zwar: (1) _____
- ○ Nein (0)

Seitenumbruch

Q5.19
Wie sehr haben Ihre Symptome / Beschwerden den Umgang mit anderen Menschen (Ihre sozialen Kontakte) beeinträchtigt?

- ○ überhaupt nicht (0)
- ○ ein bisschen (1)
- ○ ziemlich (2)
- ○ sehr (3)

Q5.20 **Konnten Sie trotz der Beschwerden Ihren Alltag wie üblich gestalten?**

- ○ Ja (1)
- ○ Nein (0)
- ○ Teilweise (2)

Q5.21 **Wie sehr haben die Beschwerden Ihren Alltag beeinträchtigt?**

- ○ überhaupt nicht (0)
- ○ ein bisschen (1)
- ○ ziemlich (2)
- ○ sehr (3)

Ende des Blocks: Beschwerden

Beginn des Blocks: Pollenexposition

Q6.1
Unsere Pollendaten gelten für den Augsburger Raum. Falls Sie weiter als 100km von Augsburg entfernt waren, würden wir uns freuen, wenn Sie uns angeben, wo Sie waren, damit wir Ihre Pollenbelastung schätzen können.

Die Antwort ist freiwillig.

_____

X→

Q6.2 **Haben Sie sich im Freien aufgehalten?**

- ○ Ja (1)
- ○ Nein (0)

Überspringen bis: Ende des Blocks Wenn Q6.2 = Nein

Q6.3 **Wie viele Stunden haben Sie sich im Freien aufgehalten?**
Bitte verschieben Sie den Balken entsprechend der ungefähren Stundenanzahl. Klicken Sie den Balken bitte auch an, wenn Sie ihn nicht verschieben möchten.

	0 1 2 3 4 5 6 7 8
morgens/ mittags 6-14 Uhr ()	
nachmittags / abends 14-22 Uhr ()	
nachts 22-6 Uhr ()	

Ende des Blocks: Pollenexposition

Beginn des Blocks: Sport und Bewegung

Q7.1
Haben Sie Sport betrieben oder sich körperlich aktiv betätigt?

- ○ Ja (1)
- ○ Nein (0)

Überspringen bis: Ende des Blocks Wenn Q7.1 = Nein

Q7.2 **Wie viele Stunden haben Sie im Freien Sport betrieben oder sich körperlich aktiv betätigt?**
Bitte verschieben Sie den Balken entsprechend der ungefähren Stundenanzahl. Klicken Sie den Balken bitte auch an, wenn Sie ihn nicht verschieben möchten.

	0 1 2 3 4 5 6 7 8
morgens / mittags 6-14 Uhr ()	
nachmittags / abends 14-22 Uhr ()	
nachts 22-6 Uhr ()	

Q7.3 **Wie viele Stunden haben Sie in Innenräumen Sport betrieben oder sich körperlich aktiv betätigt?**
Bitte verschieben Sie den Balken entsprechend der ungefähren Stundenanzahl. Klicken Sie den Balken bitte auch an, wenn Sie ihn nicht verschieben möchten.

	0 1 2 3 4 5 6 7 8
morgens / mittags 6-14 Uhr ()	
nachmittags / abends 14-22 Uhr ()	
nachts 22-6 Uhr ()	

Ende des Blocks: Sport und Bewegung

Beginn des Blocks: Medikamente

X→

Q8.1 **Haben Sie Medikamente eingenommen, die Sie normalerweise nicht täglich einnehmen?**

- ○ Ja (1)
- ○ Nein (0)

Überspringen bis: Q8.3 Wenn Q8.1 = Nein

Q8.2 **Welche Medikamente haben Sie aus sonstigen Gründen eingenommen?**
Bitte geben Sie den Handelsnamen des Medikaments an.

_____

X→

Q8.3 **Welche Medikamente haben Sie aufgrund der Pollenbelastung eingenommen?**
Mehrfachantwort ist möglich. Bitte Zutreffendes ankreuzen!

- ☐ Augensalbe / Augentropfen (1)
- ☐ Nasenspray / Nasentropfen (2)
- ☐ Antiallergische Tabletten (3)
- ☐ Homöopathisches (4)
- ☐ Sonstiges: (5)

_____

Ende des Blocks: Medikamente

Beginn des Blocks: Bemerkungen

Q9.1 **Bemerkungen: Hier können Sie Hinweise auf Besonderheiten an diesem Tag oder zu Ihren Symptomen geben**

_____

Ende des Blocks: Bemerkungen

Beginn des Blocks: Vielen Dank!

Q10.1 **Vielen Dank für Ihre Unterstützung!**
Bitte füllen Sie dieses Tagebuch auch morgen wieder aus!

Wenn Sie auf " >> " klicken, werden Ihre Daten gespeichert!

Ende des Blocks: Vielen Dank!

C. FEEDBACK QUESTIONNAIRE

Received by all groups:

Q2n1 Wie einfach bewerten Sie die Handhabung der App?

- ○ Sehr einfach (5)
- ○ Einfach (4)
- ○ Weder einfach noch kompliziert (3)
- ○ Kompliziert (2)
- ○ Sehr kompliziert (1)

Display This Question:

If Wie einfach bewerten Sie die Handhabung der App? = Kompliziert

Or Wie einfach bewerten Sie die Handhabung der App? = Sehr kompliziert

Q2n2 Sie haben angegeben, dass die Handhabung der App für Sie kompliziert oder sehr kompliziert war. Können Sie uns mitteilen warum?

_____

_____

_____

_____

_____

Page Break

Q3 Wie schnell haben Sie sich beim Navigieren in der App zurechtgefunden?

- ○ Sehr schnell (5)
- ○ Schnell (4)
- ○ Normal (3)
- ○ Langsam (2)
- ○ Sehr langsam (1)

Q4 Wie bewerten Sie die Gestaltung der Benutzeroberfläche der App?

- ○ Sehr gut (5)
- ○ Gut (4)
- ○ Neutral (3)
- ○ Nicht besonders gut (2)
- ○ Überhaupt nicht gut (1)

Q5n1 War es einfach für Sie, die App-Nutzung in Ihren täglichen Tagesablauf zu integrieren?

- ○ Sehr einfach (5)
- ○ Einfach (4)
- ○ Weder einfach noch schwierig (3)
- ○ Schwierig (2)
- ○ Sehr schwierig (1)

Display This Question:

If War es einfach für Sie, die App-Nutzung in Ihren täglichen Tagesablauf zu integrieren? = Schwierig

Or War es einfach für Sie, die App-Nutzung in Ihren täglichen Tagesablauf zu integrieren? = Sehr schwierig

Q5n2 Sie haben angegeben, dass es für Sie schwierig oder sehr schwierig war, die App-Nutzung in Ihren täglichen Tagesablauf zu integrieren. Können Sie uns mitteilen warum?

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Q6 Wie lange haben Sie die App täglich im Schnitt genutzt?

- ○ <1 min (1)
- ○ 1-5 min (2)
- ○ 5-10 Minuten (3)
- ○ 10-15 Minuten (4)
- ○ >15 Minuten (5)

Q7 Wie bewerten Sie den täglichen Zeitaufwand für die App-Nutzung?

- ○ Sehr kurz (5)
- ○ Kurz (4)
- ○ Normal (3)
- ○ Lang (2)
- ○ Sehr Lang (1)

Q8 Haben Sie die App täglich gerne genutzt oder mussten Sie sich dazu überwinden?

- ○ Ich habe die App sehr gerne genutzt (5)
- ○ Ich habe die App gerne genutzt (4)
- ○ Weder gern noch ungern (3)
- ○ Ich habe die App ungerne genutzt (2)
- ○ Ich habe die App sehr ungerne genutzt (1)

Page Break

Q9n1 Wie hilfreich bewerten Sie die Nutzung der App hinsichtlich Ihrer Lebensqualität?

- ○ Sehr hilfreich (5)
- ○ Ziemlich hilfreich (4)
- ○ Etwas hilfreich (3)
- ○ Wenig hilfreich (2)
- ○ Überhaupt nicht hilfreich (1)

Display This Question:

If Wie hilfreich bewerten Sie die Nutzung der App hinsichtlich Ihrer Lebensqualität? = Wenig hilfreich

Or Wie hilfreich bewerten Sie die Nutzung der App hinsichtlich Ihrer Lebensqualität? = Überhaupt nicht hilfreich

Q9n2 Sie haben angegeben, dass die App Nutzung für Sie wenig hilfreich oder überhaupt nicht hilfreich für Sie war. Können Sie uns mitteilen warum?

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Q10 Wie bewerten Sie die Relation von Zeitaufwand für die App-Nutzung zu persönlichem Nutzen für Ihr Allergiemanagement/Symptomkontrolle?

- ○ Sehr gut (5)
- ○ Gut (4)
- ○ Neutral (3)
- ○ Nicht besonders gut (2)
- ○ Überhaupt nicht gut (1)

Q11 Hatten Sie manchmal das Gefühl, Sie würden sich aufgrund der App-Nutzung zu viel mit Ihrer Allergie beschäftigen?

- ○ Sehr stark (5)
- ○ Stark (4)
- ○ Teilweise (3)
- ○ Kaum (2)
- ○ Gar nicht (1)

Q12 Hat die App-Nutzung dazu geführt, dass Sie sich generell mehr Sorgen bezüglich Ihrer Allergie und/oder Ihres Gesundheitszustands gemacht haben, als gewohnt?

- ○ Sehr stark (5)
- ○ Stark (4)
- ○ Teilweise (3)
- ○ Kaum (2)
- ○ Gar nicht (1)

Page Break

Q13 Wie hilfreich sind die Tipps innerhalb der App, um Ihre Symptome zu lindern?

- ○ Sehr hilfreich (5)
- ○ Ziemlich hilfreich (4)
- ○ Etwas hilfreich (3)
- ○ Nicht besonders hilfreich (2)
- ○ Überhaupt nicht hilfreich (1)

Q14 Wie gut war die App darin, Ihnen Empfehlungen und Tipps zur Bewältigung hoher Pollenbelastungen zu geben?

- ○ Sehr gut (5)
- ○ Gut (4)
- ○ Neutral (3)
- ○ Nicht besonders gut (2)
- ○ Überhaupt nicht gut (1)

Page Break

Q15n1 Haben Sie durch die App-Nutzung, häufiger als gewohnt, auf gängige präventive Alltagsmaßnahmen wie Haare waschen, Kleidung wechseln etc. geachtet?

- ○ Sehr stark (5)
- ○ Stark (4)
- ○ Teilweise (3)
- ○ Kaum (2)
- ○ Gar nicht (1)

Display This Question:

If Haben Sie durch die App-Nutzung, häufiger als gewohnt, auf gängige präventive Alltagsmaßnahmen wi... = Sehr stark

Or Haben Sie durch die App-Nutzung, häufiger als gewohnt, auf gängige präventive Alltagsmaßnahmen wi... = Stark

Or Haben Sie durch die App-Nutzung, häufiger als gewohnt, auf gängige präventive Alltagsmaßnahmen wi... = Teilweise

Or Haben Sie durch die App-Nutzung, häufiger als gewohnt, auf gängige präventive Alltagsmaßnahmen wi... = Kaum

Q15n2 Auf welche Alltagsmaßnahmen haben Sie insbesondere geachtet?

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Q16n1 Haben Sie während der Verwendung der App während der Allergiesaison zur Behandlung Ihrer Allergie weniger **Medikamente** eingenommen als gewohnt?

- ○ Ich habe deutlich weniger Medikamente benötigt (5)
- ○ Ich habe weniger Medikamente benötigt (4)
- ○ Ich habe teilweise weniger Medikamente benötigt (3)
- ○ Ich habe genauso viele Medikamente benötigt (2)
- ○ Ich habe mehr Medikamente eingenommen als gewohnt (1)

Display This Question:

If Haben Sie während der Verwendung der App während der Allergiesaison zur Behandlung Ihrer Allergie... = Ich habe deutlich weniger Medikamente benötigt

Or Haben Sie während der Verwendung der App während der Allergiesaison zur Behandlung Ihrer Allergie... = Ich habe weniger Medikamente benötigt

Or Haben Sie während der Verwendung der App während der Allergiesaison zur Behandlung Ihrer Allergie... = Ich habe teilweise weniger Medikamente benötigt

Q16n2 Welche Medikamente haben Sie weniger eingenommen als gewohnt?

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Display This Question:

If Haben Sie während der Verwendung der App während der Allergiesaison zur Behandlung Ihrer Allergie... = Ich habe mehr Medikamente eingenommen als gewohnt

Q16n3 Welche Medikamente haben Sie mehr eingenommen also gewohnt?

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Page Break

Q17n1 Hat sich Ihr **Freizeitverhalten** durch die App-Nutzung in der Allergiesaison verändert im Vergleich zur Allergiesaison ohne App?

- ○ Sehr stark (5)
- ○ Stark (4)
- ○ Teilweise (3)
- ○ Kaum (2)
- ○ Gar nicht (1)

Display This Question:

If Hat sich Ihr Freizeitverhalten durch die App-Nutzung in der Allergiesaison verändert im Vergleich... = Sehr stark

Or Hat sich Ihr Freizeitverhalten durch die App-Nutzung in der Allergiesaison verändert im Vergleich... = Stark

Or Hat sich Ihr Freizeitverhalten durch die App-Nutzung in der Allergiesaison verändert im Vergleich... = Teilweise

Or Hat sich Ihr Freizeitverhalten durch die App-Nutzung in der Allergiesaison verändert im Vergleich... = Kaum

X→ X→

Q17n2 Wie hat sich Ihr Freizeitverhalten verändert?

- ○ Positiv (3)
- ○ Negativ (1)
- ○ Positiv und negativ (2)

Display This Question:

If Wie hat sich Ihr Freizeitverhalten verändert? = Positiv

Or Wie hat sich Ihr Freizeitverhalten verändert? = Positiv und negativ

Q17n21 Sie haben angegeben Ihr Freizeitverhalten hat sich positiv verändert. Können Sie uns mitteilen wie? (mehrere Antwortmöglichkeiten möglich)

- ☐ Ich konnte meinen Hobbies besser nachgehen (1)
- ☐ Ich konnte meine Freizeit besser planen (2)
- ☐ Ich konnte besser sozialen Kontakten nachgehen (3)
- ☐ Ich habe mehr Zeit im Freien verbracht (4)
- ☐ Ich hatte mehr Spaß an Tätigkeiten im Freien (5)
- ☐ weitere oder andere positive Veränderungen: (6) _____

Display This Question:

If Wie hat sich Ihr Freizeitverhalten verändert? = Negativ

Or Wie hat sich Ihr Freizeitverhalten verändert? = Positiv und negativ

Q17n22 Sie haben angegeben Ihr Freizeitverhalten hat sich negativ verändert. Können Sie uns mitteilen wie? (mehrere Antwortmöglichkeiten möglich)

- [ ] Ich habe weniger Zeit im Freien verbracht (1)
- [ ] Ich habe mich ständig auf meine Allergie konzentriert (2)
- [ ] Ich habe mir mehr Sorgen bezüglich der Pollenbelastung als üblich gemacht (3)
- [ ] Ich hatte weniger Spaß an Tätigkeiten im Freien (4)
- [ ] Ich konnte weniger meine sozialen Kontakten nachgehen (5)
- [ ] weitere oder andere negative Veränderungen: (6) _____

Page Break

Q18n1 Wie hilfreich war die App-Nutzung für die Bewältigung Ihres Schul-/ Studium- oder Berufsalltags?

- ○ Sehr hilfreich (5)
- ○ Ziemlich hilfreich (4)
- ○ Etwas hilfreich (3)
- ○ Wenig hilfreich (2)
- ○ Überhaupt nicht hilfreich (1)

Display This Question:

If Wie hilfreich war die App-Nutzung für die Bewältigung Ihres Schul-/ Studium- oder Berufsalltags? = Sehr hilfreich

Or Wie hilfreich war die App-Nutzung für die Bewältigung Ihres Schul-/ Studium- oder Berufsalltags? = Ziemlich hilfreich

Or Wie hilfreich war die App-Nutzung für die Bewältigung Ihres Schul-/ Studium- oder Berufsalltags? = Etwas hilfreich

Q18n2 Sie haben angegeben, dass die App Nutzung Ihnen für die Bewältigung Ihres Schul-/ Studium- oder Berufsalltags geholfen hat. Können Sie uns mitteilen wie?

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Q19 Im folgenden stellen wir Ihnen Fragen zu den einzelnen Funktionen der App.

Fragen zum Bereich **Wissen:**

Q20 Hat Ihnen der Bereich „Wissen“ innerhalb der App geholfen Ihre Allergie besser zu verstehen?

- ○ Sehr stark (5)
- ○ Stark (4)
- ○ Teilweise (3)
- ○ Kaum (2)
- ○ Gar nicht (1)

Q21 Wie nützlich bewerten Sie den Themenbereich „Information zur Pollenallergie“ für Ihr Allergiemanagement?

- ○ Sehr nützlich (5)
- ○ Ziemlich nützlich (4)
- ○ Etwas nützlich (3)
- ○ Wenig nützlich (2)
- ○ Überhaupt nicht nützlich (1)

Q22 Wie nützlich bewerten Sie den Themenbereich „Allergie-Quiz“ für Ihr Allergiemanagement?

- ○ Sehr nützlich (5)
- ○ Ziemlich nützlich (4)
- ○ Etwas nützlich (3)
- ○ Wenig nützlich (2)
- ○ Überhaupt nicht nützlich (1)

Q23 Wie nützlich bewerten Sie den Themenbereich „ChatGPT über Allergien“ für Ihr Allergiemanagement?

- ○ Sehr nützlich (5)
- ○ Ziemlich nützlich (4)
- ○ Etwas nützlich (3)
- ○ Wenig nützlich (2)
- ○ Überhaupt nicht nützlich (1)

Q24 Wie nützlich bewerten Sie den Themenbereich „Fragen & Antworten“ für Ihr Allergiemanagement?

- ○ Sehr nützlich (5)
- ○ Ziemlich nützlich (4)
- ○ Etwas nützlich (3)
- ○ Wenig nützlich (2)
- ○ Überhaupt nicht nützlich (1)

Q25 Wie nützlich bewerten Sie den Themenbereich „Erstaunliche Fakten“ für Ihr Allergiemanagement?

- ○ Sehr nützlich (5)
- ○ Ziemlich nützlich (4)
- ○ Etwas nützlich (3)
- ○ Wenig nützlich (2)
- ○ Überhaupt nicht nützlich (1)

Page Break

Only group A and B:

Q26 Im folgenden stellen wir Ihnen Fragen zum **Symptomtagebuch**:

Q27 Wie einfach war es für Sie, Ihre Symptome in die App einzutragen und zu verwalten?

- ○ Sehr einfach (5)
- ○ Ziemlich einfach (4)
- ○ Weder einfach noch kompliziert (3)
- ○ Kompliziert (2)
- ○ Sehr kompliziert (1)

X→ X→

Q28 Wie gut sind die Symptomkategorien in der App auf Ihre Beschwerden zugeschnitten?

- ○ Sehr gut (5)
- ○ Gut (4)
- ○ Neutral (3)
- ○ Nicht besonders gut (2)
- ○ Überhaupt nicht gut (1)

X→ X→

Q29n1 Wie hilfreich bewerten Sie das Symptomtagebuch für Ihr Allergiemanagement?

- ○ Sehr hilfreich (5)
- ○ Ziemlich hilfreich (4)
- ○ Etwas hilfreich (3)
- ○ Wenig hilfreich (2)
- ○ Überhaupt nicht hilfreich (1)

Display This Question:

If Wie hilfreich bewerten Sie das Symptomtagebuch für Ihr Allergiemanagement? = Wenig hilfreich

Or Wie hilfreich bewerten Sie das Symptomtagebuch für Ihr Allergiemanagement? = Überhaupt nicht hilfreich

Q29n2 Sie haben angegeben, dass das Symptomtagebuch für Ihr Allergiemanagement wenig hilfreich oder überhaupt nicht hilfreich war. Können Sie uns mitteilen warum?

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Only group A:

Q30 Im folgenden stellen wir Ihnen Fragen zur **Pollenvorhersage**:

X→ X→

Q31 Wie hilfreich bewerten Sie die Pollenvorhersage für Ihr Allergiemanagement?

- Sehr hilfreich (5)
- Ziemlich hilfreich (4)
- Etwas hilfreich (3)
- Wenig hilfreich (2)
- Überhaupt nicht hilfreich (1)

Q32 Wie verständlich war die Interpretation der Pollenvorhersage für Sie?

- Sehr verständlich (5)
- Verständlich (4)
- Neutral (3)
- Nicht besonders verständlich (2)
- Überhaupt nicht verständlich (1)

Q33 Wie gut waren die visuellen Darstellungen der Symptomverläufe in Bezug zur Pollen- und Schadstoffvorhersage in der App?

- Sehr gut (5)
- Gut (4)
- Neutral (3)
- Nicht besonders gut (2)
- Überhaupt nicht gut (1)

Q34 Wie stark hat die Pollenvorhersage der App mit der Stärke Ihrer tatsächlichen Symptome übereingestimmt?

- ○ Sehr stark (5)
- ○ Stark (4)
- ○ Teilweise (3)
- ○ Kaum (2)
- ○ Gar nicht (1)

Q35 Konnten Sie mit Hilfe der Pollenvorhersage häufiger starke Allergieschübe vermeiden als normalerweise in der Allergiesaison?

- ○ Sehr stark (5)
- ○ Stark (4)
- ○ Teilweise (3)
- ○ Kaum (2)
- ○ Gar nicht (1)

Q36 Wie häufig haben Sie bei starker Pollenvorhersage vermieden lange draußen zu sein?

- ○ Sehr häufig (5)
- ○ Ziemlich häufig (4)
- ○ Manchmal (3)
- ○ Selten (2)
- ○ Nie (1)

Q37 Haben Sie dazu tendiert, an Tagen mit starkem Pollenflug laut der App, präventiv nicht nach draußen zu gehen?

- ○ Sehr stark (5)
- ○ Stark (4)
- ○ Teilweise (3)
- ○ Kaum (2)
- ○ Gar nicht (1)

Q38 Haben Sie dazu tendiert, an Tagen mit mittlerem Pollenflug laut der App, präventiv nicht nach draußen zu gehen?

- Sehr stark (5)
- Stark (4)
- Teilweise (3)
- Kaum (2)
- Gar nicht (1)

Q39 Haben Sie dazu tendiert, an Tagen mit starkem Pollenflug laut der App, präventiv Medikamente einzunehmen?

- Sehr stark (5)
- Stark (4)
- Teilweise (3)
- Kaum (2)
- Gar nicht (1)

Q40 Haben Sie dazu tendiert, an Tagen mit mittlerem Pollenflug laut der App, präventiv Medikamente einzunehmen?

- ○ Sehr stark (5)
- ○ Stark (4)
- ○ Teilweise (3)
- ○ Kaum (2)
- ○ Gar nicht (1)

Page Break

Received by all groups:

Q41 Fragen **allgemein** zur App:

Q42 Wie zufrieden sind Sie insgesamt mit der PollDi App?

- ○ Sehr zufrieden (5)
- ○ Ziemlich zufrieden (4)
- ○ Weder zufrieden noch unzufrieden (3)
- ○ Ziemlich unzufrieden (2)
- ○ Sehr unzufrieden (1)

Q43n1 Würden Sie die App in der nächsten Allergiesaison wieder nutzen?

- ○ Definitiv Ja (5)
- ○ Wahrscheinlich Ja (4)
- ○ Weder ja noch nein (3)
- ○ Wahrscheinlich Nein (2)
- ○ Definitiv Nein (1)

Display This Question:

If Würden Sie die App in der nächsten Allergiesaison wieder nutzen? = Wahrscheinlich Nein

Or Würden Sie die App in der nächsten Allergiesaison wieder nutzen? = Definitiv Nein

Q43n2 Sie haben angegeben, dass Sie die App wahrscheinlich nicht nochmal oder definitiv nicht nochmal nutzen würden. Können Sie uns die wichtigsten Gründe mitteilen warum nicht?

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Q44 Abschließend stellen wir Ihnen noch zwei Fragen bezüglich Ihrer allergischen Beschwerden:

Q45 Bitte geben Sie die Stärke Ihrer Symptome an, und zwar:

	0 = keine Symptome 0 1 1 2 2 3 3 4 4 5 = Stärkste vorstellbare Symptome
Während einer durchschnittlichen Allergiesaison (ohne App-Nutzung) ()	
Während der diesjährigen Allergiesaison (während der App-Nutzung) ()	

Q46 Bitte geben Sie die Belastung im Alltag durch Ihre Allergie an, und zwar:

	0 = keine Symptome 0 1 1 2 2 3 3 4 4 5 = Stärkste vorstellbare Symptome
Während einer durchschnittlichen Allergiesaison (ohne App-Nutzung) ()	
Während der diesjährigen Allergiesaison (während der App-Nutzung) ()	

Q47 Haben Sie Kritik, Verbesserungsvorschläge oder Wünsche für Funktionen, die Sie gerne in der App sehen würden? (Optionales Feld, Sie müssen hier nichts angeben)

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