Enabling Digital Medicine for Asthma – Clinical Utility of Nocturnal Cough and Sleep Quality as Digital Biomarkers

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Abstract

Globally, more than 235 million people suffer from asthma, one of the most common chronic respiratory diseases, which kills almost 500,000 people every year. This figure is expected to increase in the near future. Experts assume that half of all deaths due to asthma could be prevented. The suboptimal treatment outcomes of this highly prevalent disease are partly explained in literature as follows: Patients tend to underestimate their asthma. As a result, they do not recognize the worsening of their symptoms in time, which leads to life-threatening asthma attacks. The need for timely interventions therefore plays an important role in the prevention of asthma attacks. A "digital pill", which uses the sensors of a smartphone to automatically and objectively monitor a patient's asthma, could help to detect worsening symptoms at an early stage. An analysis of the digital asthma pills that are already available has shown that none of the 38 examined smartphone applications offers this kind of automatic monitoring system, despite the implementation feasibility with current technology. To investigate whether patients would find a digital asthma pill helpful for managing their condition, two focus groups, with a total of 15 asthma patients, and a survey of 88 asthma patients were conducted. The results suggest that the described asthma pill was perceived by patients as creating considerable value for them. However, to create medical value, the symptoms measured by means of the digital asthma pill would need to enable inferences with regard to the status of a patient's asthma. Previous research has shown that nocturnal cough and sleep quality can be automatically measured by means of a smartphone, and differ between patients depending on the status of their asthma. In order to investigate whether inferences based on these two symptoms are clinically useful, data were collected and analyzed from 79 patients over 28 nights. It was found that nocturnal cough and sleep quality enable moderately accurate assessments and short-term prognoses of a patient's asthma. Thus, while an application of the described digital pill in asthma care seems possible, the moderate accuracies would need to be taken into account when defining its intended use. In summary, a digital pill that provides patients with assessments and prognoses of their asthma based on nocturnal cough and sleep quality, is highly innovative, creates value for patients and, depending on its intended use, has the potential to also create medical value.

Zusammenfassung

Über 235 Millionen Menschen leiden weltweit an Asthma – eine der häufigsten chronischen Atemwegserkrankungen, an der jährlich knapp 500,000 Menschen mit zukünftig steigender Tendenz versterben. Experten gehen davon aus, dass die Hälfte aller Asthma-Todesfälle verhindert werden könnten. Der bisher jedoch suboptimale Behandlungserfolg dieser Volkskrankheit wird in der Fachliteratur unter anderem wie folgt erklärt: Patienten neigen dazu, ihr Asthma zu unterschätzen. Dadurch erkennen sie Verschlechterungen in ihrer Symptomatik nicht oder nur zu spät, sodass es zu lebensbedrohlichen Asthmaanfällen kommt. Von grosser Relevanz bei der Behandlung ist somit die Notwendigkeit zur rechtzeitigen Intervention. Eine „digitale Asthma-Pille“, welche die Sensorik von Smartphones nutzt, um Asthmasymptome automatisch und objektiv zu erfassen, könnte dabei helfen, Verschlechterungen frühzeitig zu erkennen. Eine Analyse bereits verfügbarer digitaler Pillen für Asthma hat ergeben, dass keine der 38 untersuchten Smartphone-Applikationen über eine solche automatische Symptommessung verfügt, obwohl eine Umsetzung mit heutiger Technologie möglich ist. Um zu untersuchen, ob Patienten eine digitale Asthma-Pille als hilfreich für den Umgang mit ihrer Erkrankung bewerten würden, wurden zwei Fokusgruppen mit insgesamt 15 Asthma-Patienten und eine Umfrage mit 88 Asthma-Patienten durchgeführt. Die Ergebnisse legen nahe, dass die beschriebene Asthma-Pille aus Sicht der Patienten einen bedeutsamen Nutzen stiften würde. Einen medizinischen Mehrwert würde die digitale Asthma-Pille erzeugen, wenn die gemessenen Symptome Aussagen über den Asthma-Status eines Patienten ermöglichen. Frühere Forschung hat ergeben, dass nächtlicher Husten und Schlafqualität mit dem Smartphone gemessen werden können und sich zwischen Patienten in Abhängigkeit von ihrem Asthma unterscheiden. Um zu untersuchen, ob Aussagen auf Basis der beiden Symptome klinisch nützlich sind, wurden Daten von 79 Patienten über 28 Nächte erhoben. Es konnte gezeigt werden, dass nächtlicher Husten und Schlafqualität Einschätzungen und kurzfristige Prognosen über das Asthma eines Patienten mit moderaten Genauigkeiten ermöglichen. Der Einsatz als digitale Pille erscheint denkbar, die medizinische Zweckbestimmung der Pille sollte jedoch den moderaten Genauigkeiten entsprechen. Zusammenfassend ist eine digitale Pille, die Patienten anhand von nächtlichem Husten und Schlafqualität Einschätzungen und Prognosen ihres Asthmas liefert, hochgradig innovativ, stiftet Patientennutzen und hat das Potential, je nach Verwendungszweck, medizinischen Mehrwert zu schaffen.

Disclaimer

Parts of this dissertation have already been published elsewhere.

Except for a few sub-sections and adaptions, Chapter 3 ("Review of Asthma Apps") has been published in the JMIR mHealth and uHealth (Tinschert, Jakob, Barata, Kramer, & Kowatsch, 2017). Instead of citing this dissertation, please directly cite the following paper:

Tinschert, P., Jakob, R., Barata, F., Kramer, J.-N., & Kowatsch, T. (2017). The Potential of Mobile Apps for Improving Asthma Self-Management: A Review of Publicly Available and Well-Adopted Asthma Apps. *JMIR mHealth uHealth, 5*(8), e113. doi: 10.2196/mhealth.7177

Chapter 5 ("Clinical Utility of Nocturnal Cough and Sleep Quality as Biomarkers") has been published in part in BMJ Open (i.e., Sections 5.1 and 0) and was presented at the 2019 conference of the International Society for Research on Internet Interventions (Sub-section 5.3.1.1; Tinschert et al., 2019a). Please also note that Sections 5.3 and 5.4 are being prepared for publication at the time of submission of this dissertation. Please cite the corresponding papers when referring to the sections:

Tinschert, P., Rassouli, F., Barata, F., Steurer-Stey, C., Fleisch, E., Puhan, M. A., . . . Kowatsch, T. (2019). Prevalence of nocturnal cough in asthma and its potential as a marker for asthma control (MAC) in combination with sleep quality: protocol of a smartphone-based, multicentre, longitudinal observational study with two stages. *BMJ Open, 9*(1), e026323. doi: 10.1136/bmjopen-2018-026323

Tinschert, P., Barata, F., Kramer, J., Rassouli, F., Steurer-Stey, C., Puhan, M. A., . . . Kowatsch, T. (2019). *Don't Lose Heart: Preliminary Engagement Results in an Ecological Momentary Assessment (EMA) Study Evaluating Digital Biomarkers for Asthma*. Paper presented at the 10th International Society for Research on Internet Interventions Scientific Meeting: The Next Generation (ISRII 2019), Auckland, New Zealand.

Furthermore, the following paper represents early work on nocturnal cough monitoring as part of a digital pill for asthma. Even though this dissertation does not cite any

sections of this paper in verbatim, it constitutes a kind of conceptual precursor for some of the ideas expressed in the dissertation. When referring to the general idea of a digital pill enabled through smartphone-based nocturnal cough monitoring, please cite the following publication:

Tinschert, P., Barata, F., & Kowatsch, T. (2017). *Enhancing Asthma Control through IT: Design, Implementation and Planned Evaluation of the Mobile Asthma Companion.* Paper presented at the 13th International Conference on Wirtschaftsinformatik, St. Gallen, Switzerland.

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List of Abbreviations

% pb	Fraction of the Personal Best
abs	Absolute Value
ACQ	Asthma Control Questionnaire
ACT	Asthma Control Test
B1 – B26	Behavior Change Technique 1 – 26
BAC	Balanced Accuracy
c/n	Coughs per Night
C1 – C5	Criterion 1 – 5
CDBs	Candidate Digital Biomarkers
CDM	Chronic Disease Management
CHF	Swiss Francs
COPD	Chronic Obstructive Pulmonary Disease
DALY	Disability-Adjusted Life Years
FDA	Food and Drug Administration
FeNO	Fraction of Exhaled Nitric Oxide
FEV_1	Forced Expiratory Volume in 1 Second
FVC	Forced Vital Capacity
G1 – G31	Gamification Technique 1 – 31
GBD 17	Global Burden of Disease Study 2017
GDP	Gross Domestic Product

GHE 16	Global Health Estimates 2016
GINA	Global Initiative for Asthma
GPS	Global Positioning System
ICC	Intraclass Correlation Coefficient
ICS	Inhaled Corticosteroids
iOS	iPhone Operating System
IQR	Interquartile Range
MAC	Marker for Asthma Control
MARS	Mobile Application Rating Scale
mHealth apps	Mobile Health Applications
NCD	Non-Communicable Disease
PEF	Peak Expiratory Flow
PSQI	Pittsburgh Sleep Quality Index
R1 – R4	Requirement 1 – 4
RQ	Research Question
SABA	Short-acting β2 Agonists
SD	Standard Deviation
USD	US Dollar
WHO	World Health Organization
YLD	Years Lived with Disability
YLL	Years of Life Lost

Chapter 1

Introduction

"Revolutions in science have often been preceded by revolutions in measurement."
Sinan Aral

1.1 Motivation

Imagine a city with the population of Zurich wiped off the face of the earth. Asthma, one of the most prevalent chronic respiratory diseases, claims 418,000 lives every single year – tragically, many of them unnecessarily (Levy, 2015; World Health Organization, 2018a, 2018b). In addition, asthma leads to an extensive amount of medical resource utilization and is therefore considered an enormous economic burden for health care systems (Bahadori et al., 2009; Braman, 2006; Murphy, McAvay, Allore, Stamm, & Simonelli, 2017; van Schayck & Boudewijns, 2017).

Medical resource utilization is driven by the fact that asthma is a chronic disease with no known cure: once a person is diagnosed with asthma, the disease usually needs to be treated continuously throughout the patient's entire life (Global Initiative for Asthma, 2018). Unsurprisingly, patients with suboptimal treatment outcomes require more frequent and more expensive care, for example, due to the need for emergency medical resource utilization (Accordini et al., 2013). A substantial share of the emergency costs, however, is preventable with today's treatment options (Pavord et al., 2018). Since asthma is a chronic disease, unnecessary treatment costs may compound over prolonged periods of time. Therefore, suboptimal outcomes in asthma are particularly alarming from a health care cost perspective (Trueman, Woodcock, & Hancock, 2017). Unfortunately, as a recent Lancet Clinical Commission has pointed out, suboptimal treatment outcomes in asthma are still common (Pavord et al., 2018). The

commissioners conclude that the progress in improving asthma outcomes "has been slow and unacceptable" (Kleinert & Horton, 2018, p. 1).

Asthma is just one instance of a chronic non-communicable disease (NCD[1]) for which suboptimal treatment outcomes have been observed (Bennett et al., 2018; World Health Organization, 2013). This fact has been recognized by the United Nations General Assembly (2015), which strives to improve prevention and treatment of NCDs to cut premature deaths by one third by 2030 as part of its Sustainable Development Goals. The need to improve prevention and treatment of NCDs is illustrated by the fact that NCDs are responsible for 71% of all deaths worldwide (World Health Organization, 2018b) and for a projected cumulative economic output loss of 47 trillion US Dollars between the years 2010 and 2030 (Bloom et al., 2012).

To understand the reasons for suboptimal outcomes in NCDs in general, and asthma in particular, considering a historical perspective on health care systems provides valuable insights.

1.1.1 Antecedents of the Non-Communicable Disease Crisis

Many health care systems were set up in the beginning of the 20th century with the objective of treating acute diseases (Sheingold & Hahn, 2014). Back then, the three leading causes of death were acute diseases, namely influenza and pneumonia, acute tuberculosis, and diarrhea/enteritis, which were responsible for 31% of deaths (Kvedar, Fogel, Elenko, & Zohar, 2016). Throughout the 20th century, however, living conditions improved drastically and the unprecedented advancements in medicine and sanitation have resulted in completely different demands on health care systems (Jones, Podolsky, & Greene, 2012). Today, the three leading causes of death are all chronic diseases (i.e., heart disease, cancer, and chronic obstructive pulmonary disease (COPD), which together account for 53% of all deaths; Kvedar et al., 2016). In contrast to acute diseases, for which curation constitutes the main treatment objective, chronic diseases like asthma, for which often no cure is available, require a fundamentally different treatment approach: continuous interventions throughout the patient's lifetime are necessary to

[1] The term *NCD* indicates that a disease is not transmitted between people, while the term *chronic* additionally specifies that a disease affects a patient long-term (i.e., for three months or more). Not all chronic diseases are NCDs (e.g., leprosy affects a patient long-term, but is transmitted from patient to patient) and not all NCDs are necessarily chronic diseases (e.g., a fatal stroke). For a more nuanced discussion of terminology, please refer to Bernell and Howard (2016).

manage the disease and its symptoms so that disease-related risks for adverse events are reduced and a patient's quality of life is restored to the fullest possible extent (Clark & Gong, 2000; Kvedar et al., 2016; Murrow & Oglesby, 1996; Reynolds et al., 2018).

The need for continuous long-term interventions in health care systems designed for short-term curative interventions places a heavy financial burden on them (Kvedar et al., 2016). It is considered one of the key reasons for the cost explosion in health care in recent decades all over the world (Ghebreyesus, 2018; World Health Organization, 2017b). Furthermore, it is exacerbated by the fact that the share of patients suffering from multiple chronic conditions, who contribute disproportionately to health care costs, steadily increases (Buttorff, Ruder, & Bauman, 2017; Gerteis et al., 2014). The question of how long health care systems will be able to bear this burden is a pressing concern for politicians and health care experts alike and is subject to heated discussions in the public sphere (e.g., Tischhauer, Fritsche, & Kolbe, 2018). Some experts even argue that alleviating this burden is essential for the continuation of health care systems in their current form (Beaglehole et al., 2011; Sigrist et al., 2016).

1.1.2 Digital Medicine as a Potential Solution

Fortunately, with the advent and maturation of the internet of things (Fleisch & Mattern, 2005; Wortmann & Flüchter, 2015) – specifically the widespread adoption of smartphones, extended network coverage with improved bandwidth, breakthroughs in artificial intelligence, and the availability of connected medical devices – mobile health technology can deliver continuous long-term interventions for NCDs (Agarwal, Gao, DesRoches, & Jha, 2010; Kvedar et al., 2016; Murray et al., 2016). In asthma, smart inhalers are a first prominent example of how connected technology can enable continuous interventions for patients (Asthma UK, 2016). Smart inhalers are sensor caps that are attached to a patient's regular inhaler, track medication adherence, and transfer the medication usage data to a connected device, such as a smartphone. The connected device can then analyze the data and deliver interventions without requiring input by medical personnel. Smart inhalers have been shown to be effective treatment supplements (Merchant, Inamdar, & Quade, 2016) and to reduce emergency medical resource utilization (Merchant et al., 2018b).

The emerging scientific field associated with developing and evaluating interventions enabled by mobile health technology is called *digital health* (World Health

Organization, 2016) or *digital medicine* (Elenko, Underwood, & Zohar, 2015). Since the broader term digital health also encompasses lifestyle, primary prevention, and public health interventions (Angerer, Schmidt, Moll, Strunk, & Brügger, 2017), this dissertation will adhere to the more specific terms digital medicine and *digital medicine interventions*. Steinhubl and Topol define digital medicine in the inaugural editorial of the eponymous *Nature Partner Journal* as follows:

> *"Using digital tools to upgrade the practice of medicine to one that is high-definition and far more individualized. It encompasses our ability to digitize human beings using biosensors that track our complex physiologic systems, but also the means to process the vast data generated via algorithms, cloud computing, and artificial intelligence."* (Steinhubl & Topol, 2018, p. 1)

Steinhubl and Topol (2018) further argue that smartphones will serve as "the hub" for health interventions by "enabling each individual to generate their own real world data" (p. 1). Since smartphones are almost ubiquitous in developed and developing countries (Deloitte, 2017), smartphone-based interventions enable extensive coverage, at least in principle. Furthermore, this mode of intervention delivery can be extremely cost-effective due to its low marginal intervention costs (Filler et al., 2015). Through the combination of the potential extensive coverage and the unrivaled cost-efficiency, scalability becomes virtually unlimited: the need for continuous, long-term interventions for a gradually increasing share of patients with NCDs no longer seems unfulfillable.

1.2 Overarching Research Question

While a few companies have already brought digital medicine interventions for asthma to the market in some countries (e.g., Propeller Health distributes smart inhalers in the United States; ResMed, 2019), these interventions require additional hardware at the expense of scalability. Furthermore, while digital medicine interventions are briefly discussed in asthma guidelines (e.g., Global Initiative for Asthma, 2018), they are not yet part of the standard of care (e.g., Buhl et al., 2017; Global Initiative for Asthma, 2018; Steurer-Stey & Beise, 2017). As of today, for example, no digital asthma intervention is reimbursed by the health care system in Switzerland (FMH Swiss

Medical Association, 2018). Without reimbursement and the endorsement of clinical guidelines, widespread adoption of digital medicine interventions seems unlikely.

Nevertheless, the potential of digital medicine has been increasingly recognized by decision makers in health care. The United States Food and Drug Administration (FDA), for example, has recently cleared the first prescription digital therapeutic (i.e., a smartphone application prescribable by a physician) in the indication of opioid use disorder (Galgay, 2018). In other countries, like Germany and the United Kingdom, pathways for the reimbursement of smartphone-based digital medicine interventions have recently been established (Federal Ministry of Health, 2019; National Health Service, 2019).

This dissertation strives to contribute to the momentum of digital medicine in asthma by establishing a foundation for smartphone-based digital interventions, also known as *digital pills* (Kowatsch et al., 2019). Such a digital pill for asthma should not only be able to exploit the potential of digital medicine in terms of scalability and thus cost efficiency, but also add value to asthma care. The broad term *value* can convey several meanings and is chosen deliberately. In the medical domain, for example, value is closely related to medical outcomes (Porter, 2010). For example, in *value-based care* a health service provider is only reimbursed for observed outcome improvements (Porter, 2009). In other literature streams, such as management literature, the term value is often related to customer experience (Gentile, Spiller, & Noci, 2007) and customer satisfaction (Kuo, Wu, & Deng, 2009). More specifically, the value proposition, which every service or product offers either implicitly or explicitly to potential customers, is considered a crucial success factor in business practice (Osterwalder & Pigneur, 2010; Osterwalder, Pigneur, Bernarda, & Smith, 2014). Based on the value proposition canvas framework, a product or a service (e.g., a digital medicine intervention) creates value for patients when it relieves *pain* or creates *gains* for its patients by solving specific tasks for them (Osterwalder et al., 2014). More abstractly, patient value is created when previously unmet patient needs are fulfilled.

The motivation behind the overarching research question of this dissertation is to examine how digital medicine could potentially create both medical value and patient value in asthma care. In other words, it examines how digital medicine can improve treatment outcomes in asthma while simultaneously fulfilling unmet patient needs. In conclusion, the overarching research question of this thesis is as follows:

> *"How can the potential of digital medicine be leveraged to create patient and medical value in asthma care in a cost-effective manner?"*

More specifically, the research objective of this dissertation is to propose a foundation for digital asthma pills that exploits the potential of digital medicine to fulfill unmet patient needs and to evaluate whether it can be used to improve asthma outcomes.

1.3 Dissertation Outline

This dissertation is the result of more than three and a half years of research. During that time, three research projects were conducted that constitute the foundation of this dissertation. Table 1.1 introduces the projects, including the data collected.

The remainder of this dissertation is structured as follows: In the second chapter, the status quo in asthma care will be presented. The first two sections are comprised of a general and a clinical introduction to asthma and will convey the basic knowledge required to follow the line of argumentation of this dissertation. The third and final section deals with patients' experiences of living with asthma. It constitutes the research background, against which three research questions will be derived.

To provide empirical insights into the current practice of digital medicine for asthma, publicly available digital pills, namely mobile health applications (mHealth apps), will be reviewed systematically in the third chapter.

The fourth chapter will examine unmet needs in asthma care from the patient perspective. For this purpose, an exploratory sequential mixed methods approach (i.e., focus groups and a subsequent survey) will be applied.

The central contribution of this dissertation will be presented in the fifth chapter. It is concerned with the empirical evaluation of the proposed digital asthma pill foundation. More specifically, patients' attitudes and medical outcomes from an observational study will be examined. Patient attitudes will be analyzed descriptively, while multiple methods from the fields of inferential statistics and predictive modelling will be employed in the analysis of medical data.

In the last chapter, all chapters will be summarized and concise answers to the research questions will be given. A conclusion will be drawn as to whether the proposed digital pill foundation can create patient value and medical value in asthma care.

As a summary, Table 1.2 indicates in which chapter the collected data will be analyzed, thereby outlining the structure of this dissertation and providing the empirical basis of each chapter.

Table 1.1. Data sources.

Project	Collaborating partners	Collected data	Sample size	Collection date
Systematic asthma app review	Technical University Munich	Ratings of review frameworks	N = 38 apps	April – November 2016
Asthma focus groups	CSS insurance, LINK AG	Qualitative insights from asthma patients	$N_1 = 7$ & $N_2 = 8$ patients	September 2016
Marker for asthma control (MAC) study	Cantonal Hospital of St. Gallen, mediX Practice Zurich, University of Zurich, Swiss Lung League, CSS insurance	Survey I: general attitudes towards digital interventions Survey II: use case evaluation Medical data: patient-reported outcomes, case report files and annotated smartphone microphone data	N = 94 patients	February 2018 – June 2019

Table 1.2. Empirical basis by chapter.

Chapter	Data source				
	App review ratings	Focus group insights	MAC study: survey I	MAC study: survey II	MAC study: medical
2. The Status Quo in Asthma Care	-	-	-	-	-
3. Review of Asthma Apps	●	-	-	-	-
4. Unmet Patient Needs	-	●	●	-	-
5. Clinical Utility of Nocturnal Cough and Sleep Quality as Digital Biomarkers	-	-	-	●	●
6. General Discussion	○	○	○	○	○

Note: ● Data source is introduced and analyzed; ○ Data source is referenced.

Chapter 2

The Status Quo in Asthma Care

2.1 Introduction to Asthma

The following chapter constitutes a general introduction to asthma. After providing a contextualized definition, prevalence and burden of disease figures will be presented to illustrate the impact of asthma on patients' lives and health care systems alike. This section focuses on the aspects relevant for the dissertation's line of argumentation and does not strive for exhaustiveness. Therefore, certain topics are omitted completely (e.g., anatomy of airways, differential diagnosis, pathogenesis, and immunopathology) or only addressed briefly (e.g., diagnosis and etiology). For a medically interested audience, please refer to the following publications for in-depth examinations of asthma from a clinical perspective: Global Initiative for Asthma (2018); Papi, Brightling, Pedersen, and Reddel (2018); and Pavord et al. (2018).

2.1.1 Definition

2.1.1.1 Definition by the Global Initiative for Asthma

In the 2018 update of the Global Strategy for Asthma Management and Prevention, one of the world's most influential asthma guidelines[2], the Global Initiative for Asthma (GINA), defines the disease as follows:

> *"Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary*

[2] While other asthma guidelines are available, for example from the British Thoracic Society (2019), this dissertation relies mostly on the GINA guidelines.

> *over time and in intensity, together with variable expiratory airflow limitation."* (Global Initiative for Asthma, 2018, p. 14)

This definition highlights several important notions, which will be discussed in more detail in the next sub-sections: the heterogeneity of asthma, the role of inflammation, and variable expiratory airflow limitations.

2.1.1.2 Heterogeneity of Asthma

Asthma varies considerably between patients in terms of its causes (i.e., pathogenesis), the course of disease over time (i.e., disease progression), visible signs and symptoms (i.e., clinical presentation), pathobiological processes that proximately cause symptoms (i.e., endotype), severity, and prognosis (Carr & Bleecker, 2016). Due to the enormous heterogeneity in asthma, experts have argued in favor of abolishing asthma as a diagnosis label altogether and instead utilizing it only as a loosely defined umbrella term for respiratory conditions (Kleinert & Horton, 2018; Pavord et al., 2018). Medical research has addressed the heterogeneity of asthma by proposing disease clusters with distinct characteristics (i.e., asthma phenotypes; for an overview refer to Hirose & Horiguchi, 2017). For example, one distinction commonly drawn in asthma phenotypes is whether symptoms are associated with allergies (i.e., allergic asthma) or not (i.e., non-allergic asthma; Moore et al., 2010). While phenotypes are useful to inform treatment decisions (Gawlik-Lipinski, 2018), addressing the heterogeneity of asthma remains a major challenge in clinical practice (Pavord et al., 2018).

2.1.1.3 The Role of Inflammation in Asthma

Chronic airway inflammation is a signature characteristic of asthma. In recent decades, several immunopathological processes and mechanisms that drive the inflammatory response have been identified (Papi et al., 2018). Eosinophilic inflammation was found to be the most prevalent type of inflammation with likely more than half of patients afflicted (Kulkarni et al., 2010). It is related to the hyperresponsiveness of patients' airways to ordinary allergens (i.e., atopy; prominent examples are pollen and dust mites), which is observed in 50% to 60% of patients (Pearce, Pekkanen, & Beasley, 1999) and constitutes a risk factor for developing asthma (Brutsche et al., 2006). However, the facts that not all patients suffering from asthma have chronically inflamed airways (Fahy, 2015) and that pathological changes in airway structure (i.e., airway remodeling) can also occur in the absence of inflammation (Fehrenbach, Wagner, & Wegmann, 2017; O'Reilly et al., 2013) suggest that asthma cannot be understood

through the lens of inflammatory processes alone. Consequently, recent conceptual models of asthma consider immunological, mechanical, and neuro-respiratory processes to explain asthma symptoms in addition to inflammatory processes (Frey & Suki, 2008).

2.1.1.4 Variable Expiratory Airflow Limitations

Asthma is not only characterized by the symptoms listed above, but also by airflow limitations. Similar to symptoms, limitations in expiratory airflow fluctuate over time (Frey et al., 2005). In one of the first books on asthma, published in 1698, Sir John Floyer, who suffered from the disease himself, already hypothesized that constricted bronchi are the cause of asthma (Gibbs, 1969). In clinical practice, this disease characteristic is utilized in the diagnosis of asthma: if a person's expiratory airflow is considerably lower than norm values from the corresponding demographic and it can be restored with rapid-acting medications that dilate airways, an asthma diagnosis is likely (Papi et al., 2018). This diagnostic procedure is referred to as the bronchodilator reversibility test (Global Initiative for Asthma, 2018).

While variable expiratory airflow limitations are the norm in asthma, in some cases airway remodeling may lead to fixed, non-reversible airflow limitations (Pascual & Peters, 2009). Fixed airflow limitations are associated with a more severe course of disease and worse outcomes (Contoli et al., 2010).

2.1.2 Prevalence

2.1.2.1 Prevalence of Asthma and Implications for its Etiology

Asthma is the second most prevalent chronic respiratory NCD after COPD[3]. Estimates for the global prevalence of asthma range from 235 million (World Health Organization, 2017a) to 339 million (Global Asthma Network, 2018) people afflicted. Recent rigorous estimates for asthma prevalence are also available from the collaborative Global Burden of Disease Study 2017 (GBD 17), which incorporated almost 70,000 data sources in its global prevalence models for 354 diseases. Based on the GBD 17 estimates, 273 million people suffer from asthma. The 95% confidence interval ranges from 242 million to 305 million. Furthermore, 36.3% of patients show very few symptoms or no symptoms at

[3] There is significant overlap in the clinical characteristics of both diseases and patients may suffer from both diseases at the same time, making differential diagnosis challenging in certain patients (Kardos et al., 2006).

all (i.e., asymptomatic asthma) while 63.7% of patients experience symptoms (James et al., 2018).

One of the reasons for the varying estimates is that different definitions of asthma are used in epidemiology research. For example, To and colleagues (2012) distinguish between physician-diagnosed asthma (i.e., whether it was diagnosed explicitly by a physician), clinical asthma (i.e., whether a person is treated for it), and symptom-defined asthma (i.e., whether a person experiences characteristic wheezing, a symptom with a high sensitivity for the diagnosis of asthma; Sistek et al., 2001). They estimate the global prevalence to be 4.27%, 4.46%, and 8.61% for physician-diagnosed asthma, clinical asthma, and symptom-defined asthma, respectively.

Arguably, the most distinct characteristic of asthma prevalence reported by To and colleagues (2012) is the enormous differences between countries. Asthma has been most prevalent in Australia with 20.96%, 21.51%, and 27.39% of the population afflicted by physician-diagnosed asthma, clinical asthma, and symptom-defined asthma, respectively. In contrast, prevalence is lowest in China with 0.19%, 1.42%, and 1.73% of the population falling under the respective asthma definitions. Figure 2.1 illustrates the prevalence of asthma for the five countries with the lowest, a median, and the highest prevalence of symptom-defined asthma. For Switzerland, data from SAPALDIA cohort study (Martin et al., 1997) indicates that 6.7% of adults and 7.4% of children have physician-diagnosed asthma (Federal Office of Public Health, 2016).

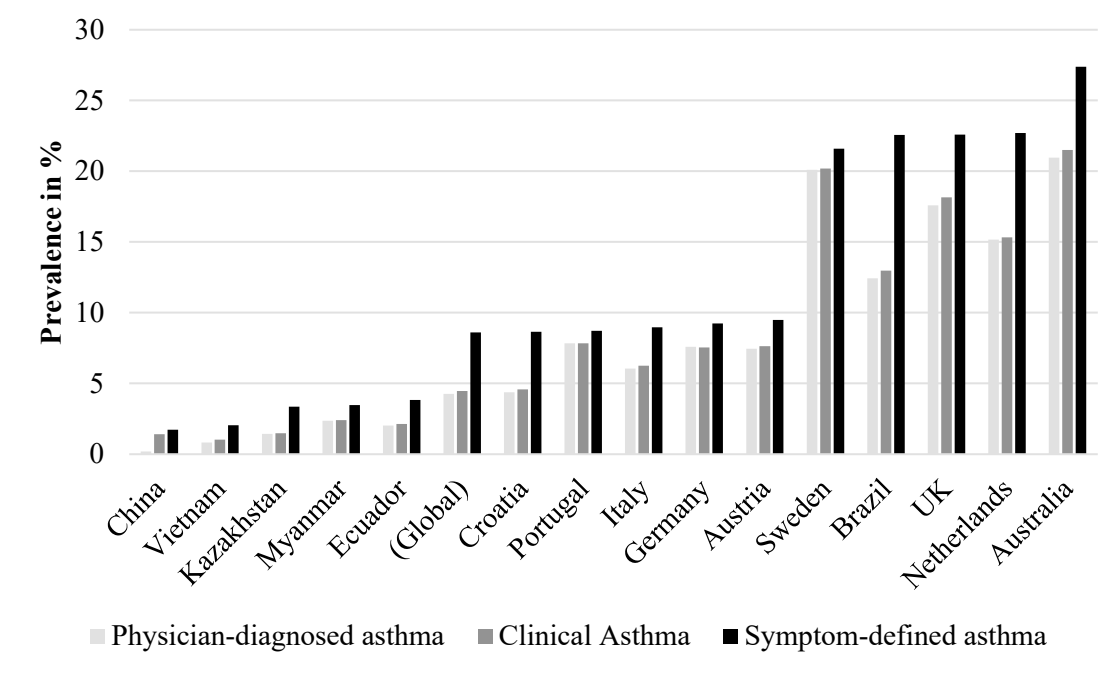


Figure 2.1. Prevalence of asthma. Figures are provided for countries with a low, medium, and high prevalence of symptom-defined asthma. Based on data from To et al. (2012).

The varying prevalence between countries demonstrates the importance of environmental factors for the incidence of asthma. It is exemplified through migration from countries with a low asthma prevalence to countries where asthma is highly prevalent: while immigrants initially have lower rates of asthma, the incidence of asthma increases continuously with the length of stay (Cabieses, Uphoff, Pinart, Antó, & Wright, 2014). However, the fact that China, a country with notoriously high levels of air pollution (e.g., Chan & Yao, 2008), exhibits the lowest asthma prevalence globally in the analyses by To and colleagues (2012), illustrates that environmental factors cannot be the sole cause of asthma. Consequently, research on etiology (i.e., causes for the onset of the disease) converges on the notion that "asthma is a consequence of complex gene–environment interactions" (Papi et al., 2018, p. 783).

However, medical research has been able to identify concrete risk factors for developing asthma: in addition to the aforementioned bronchial hyperresponsiveness (Brutsche et al., 2006), presence of mold and damp inside the living space, exposure to tobacco smoke, continuous exposure to airborne microparticles (often as a consequence of an occupation such as baking or woodworking), and obesity (Global Asthma Network, 2018) increase the likelihood of developing asthma. Particularly important are risk

factors occurring during early childhood, such as treatment with antibiotics and paracetamol (Heintze & Petersen, 2013) and caesarian sections, which increase the risk of asthma by 20% (Thavagnanam, Fleming, Bromley, Shields, & Cardwell, 2008). Furthermore, pre-natal exposure to smoke elevates a child's risk of developing the disease, rendering maternal smoking cessation an accepted primary prevention strategy for asthma (Papi et al., 2018). Interventions, which limit the exposure to other risk factors (e.g. allergens such as dust mites), are also available (Custovic et al., 2000). In contrast, breastfeeding is considered a protective factor (Dogaru, Nyffenegger, Pescatore, Spycher, & Kuehni, 2014).

2.1.2.2 Trends in Asthma Prevalence

Until recently, a substantial increase in asthma prevalence, called the "asthma epidemic" (Eder, Ege, & von Mutius, 2006, p. 2226), has been reported for multiple countries, such as the US, Scotland, and Australia. However, due to the different definitions and consequential lack of comparability of surveys and data between countries and years, clear trends in asthma prevalence are not available. Thus, it is unknown whether asthma prevalence is still rising, stagnating, or decreasing globally (Sears, 2014). To address this knowledge gap, the Global Asthma Network initiated a large-scale survey to provide reliable insights into trends of asthma prevalence. The publication of results is planned for 2020 (Global Asthma Network, 2018).

2.1.3 Burden of Disease

Several approaches are available in public health research to estimate the burden of a disease. In this sub-section, three approaches will be presented: the economic burden, the burden due to mortality, and the burden due to disability and premature mortality. Mortality and premature mortality are discussed separately because the metrics for the latter are conceptually related to disability metrics.

2.1.3.1 Economic Burden

In Switzerland, the direct treatment costs for asthma have been estimated to be between CHF 776 million and CHF 1.44 billion in 2011[4], which is equivalent to 0.12% and 0.23% of the Swiss Gross Domestic Product (GDP)[5], respectively. However, these cost

[4] The presented figures originate from Accordini et al. (2013) and Szucs, Anderhub, and Rutishauser (1999), respectively, and were converted to 2011 values by Wieser et al. (2014).
[5] Calculation based on a GDP of CHF 621.26 billion in 2011 (Federal Statistical Office, 2019).

estimates do not include indirect treatment costs (e.g., absenteeism due to asthma). For the United States, where reliable cost estimates for both direct treatment and indirect costs are available, the total asthma costs amounted to $81.9 billion in 2013 (Nurmagambetov, Kuwahara, & Garbe, 2018), which corresponds to 0.49% of the United States GDP[6]. Accordini et al. (2013) have further estimated that in 2004 the total asthma costs (i.e., the sum of direct and indirect costs) across 45 European countries were €19.3 billion in 2010 Euros. The authors conclude that asthma's cost-of-illness corresponded to 0.14% of the GDP of the considered European countries. However, while the figures presented in this section illustrate the substantial financial burden of asthma, they have to be interpreted carefully as figures may vary considerably based on the methodology behind the cost estimation (Global Asthma Network, 2014).

Interestingly, Accordini et al. (2013) also provide insights regarding cost shares: indirect costs (e.g., absenteeism due to asthma; 62%) outweigh direct costs (38%). Within direct costs, pharmacological treatment is responsible for the largest share of costs by a considerable margin, followed by hospitalizations and physician visits. The cost shares are depicted in Figure 2.2.

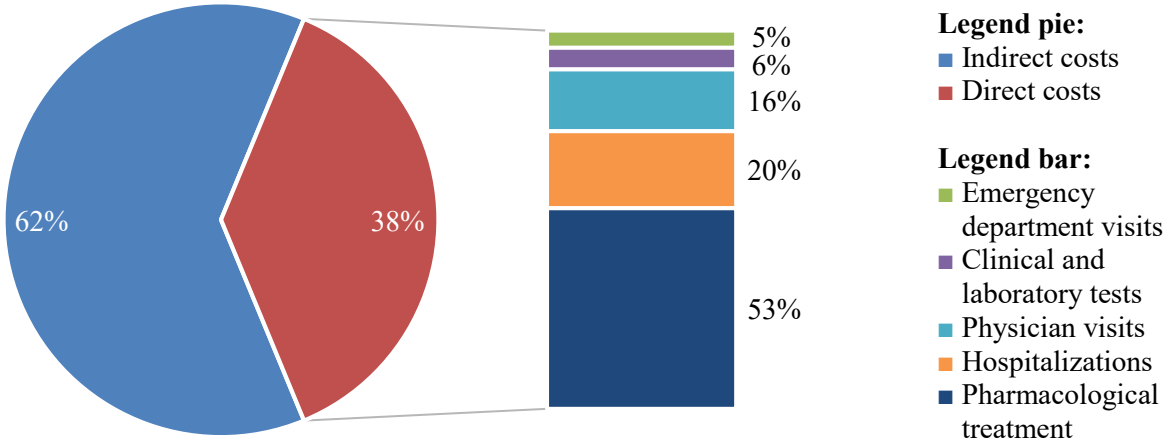


Figure 2.2. Mean annual cost share per asthma patient. Based on data from Accordini et al. (2013).

[6] Calculation based on a GDP of $16.78 trillion in 2013 (U.S. Bureau of Economic Analysis, 2019).

2.1.3.2 Burden of Mortality

Two contemporary data sources on health metrics are available, namely the Global Health Estimates (GHE 16) by the World Health Organization (WHO; World Health Organization, 2018b) and the aforementioned GBD 17. Results from the GBD 17 are published by collaborative groups of researchers for each metric: prevalence figures are published by James et al. (2018), mortality figures by Roth et al. (2018), and morbidity figures by Kyu et al. (2018). Figures from the GHE 16 and the GBD 17 will be presented throughout this sub-section as well as subsequent sub-sections.

The GHE 16 surmises 418,000 deaths due to asthma. The GBD 17, however, assumes 77,000 more deaths. Figure 2.3 illustrates these figures and compares them with figures for two communicable respiratory diseases (i.e., tuberculosis and lower respiratory infections) and COPD, the only chronic respiratory NCD more common than asthma. While the number of deaths is lower for asthma than for the three other diseases, asthma deaths are particularly tragic because they are often preventable, especially in countries with access to high quality health care (e.g., Levy et al., 2014). The recent Lancet expert commission referred to in the introductory chapter of this dissertation argues, for example, that mortality could realistically be cut in half (Pavord et al., 2018).

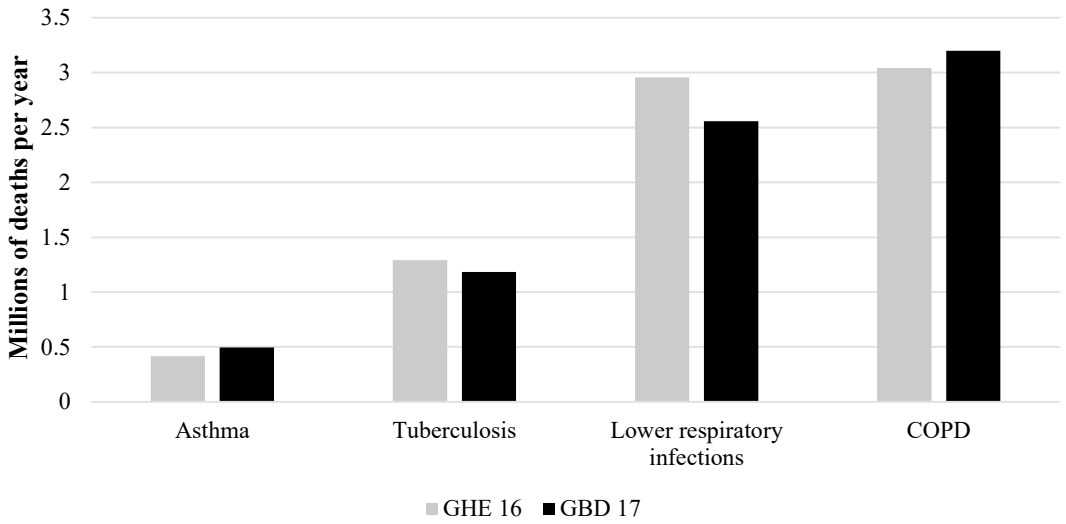


Figure 2.3. Global deaths due to asthma, tuberculosis, lower respiratory infections, and COPD. GHE 16: Global Health Estimates 2016 (based on data from the World Health Organization, 2018b); GBD 17: Global Burden of Disease study 2017 (based on data from James et al., 2018).

Furthermore, Figure 2.4 distinguishes asthma deaths by World Bank Income Group region and enriches historical data (World Health Organization, 2018b) with future projections[7] (World Health Organization, 2018d), thereby revealing two important insights. First and foremost, asthma mortality seems to have been stagnating since 2010 and will likely even increase in the near future. Second, there are substantial differences in asthma deaths between World Bank Income Group clusters. The highest relative death rates can be observed in lower-middle-income countries, followed by low-income economies. Thus, the burden of disease in terms of mortality is borne disproportionally by poorer countries. A possible explanation for the fact that mortality is higher in lower-middle-income economies than in low-income economies might be a lower prevalence of asthma as a result of less industrialization in low-income economies (Petronella & Conboy-Ellis, 2003).

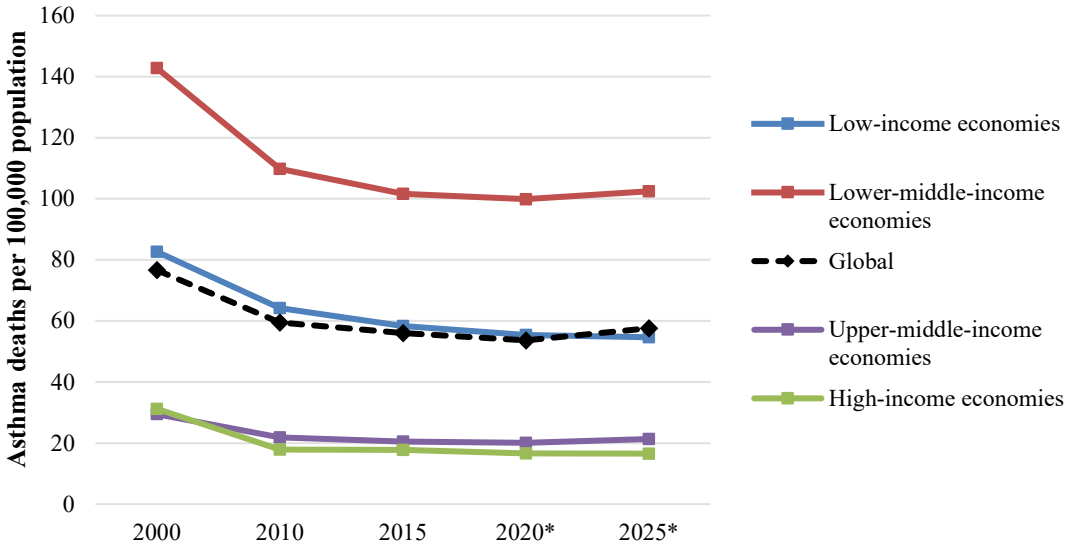


*Figure 2.4. Asthma deaths 2000 – 2025 by World Bank income group. Based on data from the WHO (World Health Organization, 2018b, 2018d). * Statistical projections.*

2.1.3.3 Burden of Premature Mortality and Disability

Three metrics are commonly used to quantify burden of disease (Institute for Health Metrics and Evaluation, 2018): disability-adjusted life years (DALY), years lived with disability (YLD), and years of life lost (YLL). YLL quantify premature mortality by estimating how many life years were lost due to the cause of death. YLD represent the

[7] The methodology behind future projections is described in Mathers and Loncar (2006).

number of years lived with the disease, weighted by the severity of disability. DALY summarize the total loss of healthy life years and are the sum of YLD and YLL. Figure 2.5 depicts the YLD and YLL (and thereby also implicitly the DALY) for the same diseases listed in Figure 2.3.

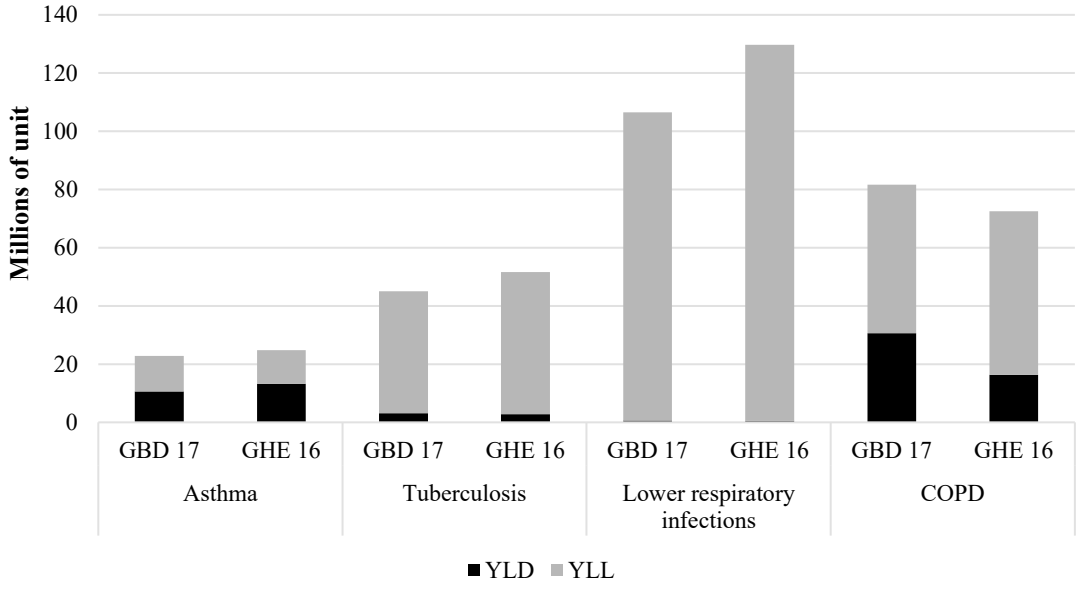


Figure 2.5. Burden of disease due to disability and premature mortality. YLD: Years lived with disability; YLL: Years of life lost; GHE 16: Global Health Estimates 2016 (based on data from World Health Organization, 2018c); GBD 17: Global Burden of Disease study 2017 (based on data from Kyu et al. (2018) and Roth et al. (2018)). The sum of YLD and YLL corresponds to the disability-adjusted life years (DALY).

As shown in Figure 2.5, asthma has the lowest DALY of all four diseases, but the highest ratio of disability to premature mortality (i.e., YLD/YLL). This finding is in line with the facts presented hitherto, namely that asthma is a chronic NCD, which usually affects patients in the long-term, but which rarely causes mortality (cf. Figure 2.3). Furthermore, Figure 2.6 illustrates that asthma is a burden for patients of all ages and does not primarily affect older patients: DALY are evenly distributed across different age segments, while COPD, for comparison, mainly affects patients older than 60 years.

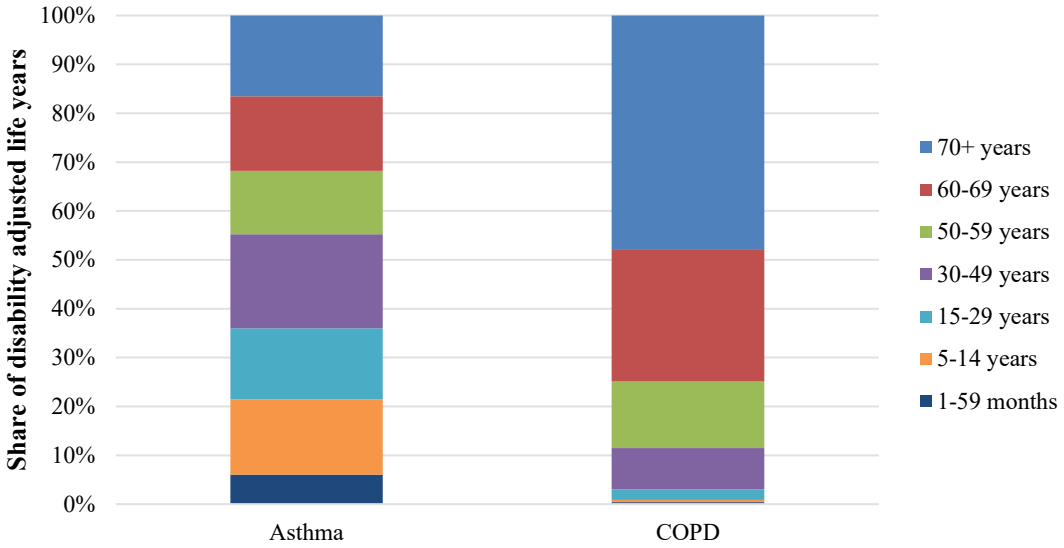


Figure 2.6. Disability adjusted life years by age segment for asthma and COPD. Based on data from the World Health Organization (2018c).

2.2 Treatment of Asthma

2.2.1 Fundamentals

To understand the rationale behind the treatment of asthma, two crucial concepts need to be introduced: *asthma attacks* and *asthma control*. In medical literature, asthma attacks are also known as asthma exacerbations, although there is some controversy around the latter term as it may mischaracterize and undermine the rapidity and severity of an asthma attack (Pavord et al., 2018). This dissertation therefore adheres to the term asthma attack instead of asthma exacerbation.

Within the section on asthma control, the notion of *control-based asthma management* will be presented, which is the default treatment approach for asthma as recommended by clinical guidelines. In addition to asthma attacks and asthma control, a third concept will be introduced, namely *asthma severity*. However, in comparison to the two other concepts, asthma severity plays a subordinate role in clinical practice (Barnes, 2004).

2.2.1.1 Asthma Attacks

Definition In 2009, the American Thoracic Society and the European Respiratory Society released a joint statement defining the terms asthma attacks and asthma control

to standardize their meaning for research and practice alike (Reddel et al., 2009). In terms of asthma attacks, it distinguishes between severe and moderate attacks. Severe attacks are defined as "events that require urgent action on the part of the patient and physician to prevent a serious outcome, such as hospitalization or death from asthma". Moderate attacks are "events that are troublesome to the patient, and that prompt a need for a change in treatment, but that are not severe. These events are clinically identified by being outside the patient's usual range of day-to-day asthma variation" (Reddel et al., 2009, p. 61).

Most asthma attacks begin gradually, with a period of five to seven days between the first signs of symptom deterioration and the manifestation of an attack (Tattersfield et al., 1999). While an asthma attack can be aborted with pharmaceutical interventions in its early stages (McKeever et al., 2018), once a tipping point is reached, an irreversible cascade of biochemical processes is triggered, propagating constrictions throughout the airways so that the manifestation of an attack becomes inevitable (Frey & Suki, 2008). Papi et al. (2018) describe the clinical presentation of mild to moderate, severe, and immediately life-threatening asthma attacks. While in mild to moderate attacks the patient remains relatively calm and responsive (e.g., generally prefers sitting to lying, is not agitated, and can speak in phrases), in severe and life-threatening attacks the patient's condition is visibly more critical (e.g., usually sits hunched forward, is agitated, drowsy or confused, and can speak only in words, or may not be able to speak at all in life-threatening attacks). One additional feature of life-threatening attacks is that patients may have a silent chest when auscultated, while in mild, moderate and severe attacks wheezing is common.

Prevalence Despite the efforts to standardize terminology in asthma attacks, a multitude of definitions and operationalizations of asthma attacks can be observed in research. Depending on the operationalization of an attack, long-term studies estimate asthma attack rates between 0.34 and 0.88 attacks per patient per year (James et al., 2018). Price, Fletcher, and Van Der Molen (2014), for example, provide prevalence figures based on different operationalizations: in the last 12 months, 44.0% of patients had to take one or more courses of corticosteroid pills, which are systemic anti-inflammatory medications administered to treat an attack; 23.9% of patients had to visit the emergency department at least once; and 11.7% of patients had one or more hospitalizations with overnight stays.

However, the likelihood of suffering an asthma attack differs substantially between patients. One study, for example, which sampled asthma patients in emergency departments, found that 21% of patients had to visit the emergency department six or more times in the last year, while 27% had no visits related to asthma attacks at all (Griswold et al., 2005). Even though these figures have to be interpreted with caution due to the sampling approach, they illustrate the enormous variance between patients at risk of asthma attacks.

Risk factors Therefore, it is crucial to stratify patients by attack risk in clinical practice. The following risk factors, inter alia, are listed in the GINA guidelines: a history of intubation or emergency care for asthma, one or more severe attacks in the last year, higher reversibility of expiratory airflow limitations in the bronchodilator test, psychological issues, low socioeconomic status, exposure to smoking or to sensitized allergens, comorbidities (e.g., obesity and food allergies), presence of eosinophilia in sputum or blood, and pregnancy (Global Initiative for Asthma, 2018).

In addition to the general risk factors for asthma attacks, research has identified several factors that indicate whether attacks have an increased risk of a fatal outcome. In their review, Alvarez, Schulzer, Jung, and Fitzgerald (2005) found that a history of intubation and mechanical ventilation, hospitalizations due to asthma within the last year, non-adherence to medication, and the (recent) intake of systemic anti-inflammatory medication are risk factors for fatal asthma attacks.

While all these factors are important for assessing a patient's risk of an attack, one factor is of particular importance for both indicating risk and guiding treatment decisions in clinical practice: a low level of asthma control substantially increases the risk of an attack (Haselkorn et al., 2009; McCoy et al., 2006; Meltzer et al., 2011; Schatz et al., 2012).

2.2.1.2 Asthma Control

Definition Asthma control is defined in the 2009 joint statement from the American Thoracic Society and the European Respiratory Society as the "extent to which the various manifestations of asthma have been reduced or removed by treatment" (Reddel et al., 2009, p. 61). More specifically, two components of asthma control were specified: first, the "level of clinical asthma control, which is gauged from features such as symptoms and the extent to which the patient can carry out activities of daily living and

achieve optimum quality of life"; and second, the "risk of future adverse events including loss of control, exacerbations, accelerated decline in lung function, and side-effects of treatment" (Reddel et al., 2009, p. 62). The GINA clinical guidelines adhere to this two-faceted conception of asthma control, namely the distinction between the current level of symptom control and the risk of future adverse events (Global Initiative for Asthma, 2018). While for many patients symptom control is a sufficient proxy for attack risk, for some patients, depending on their treatment regimen, differences between symptom control and future attack risk can be observed (Global Initiative for Asthma, 2018; Haldar et al., 2008). Measures of symptom control and asthma control will be introduced in Sub-section 2.2.2.

Importance In addition to predicting adverse outcomes, the importance of asthma control is further emphasized through its association with quality of life (Vollmer et al., 1999): lower levels of asthma control are correlated with a lower quality of life, both in terms of physical and mental well-being. In contrast, patients with controlled asthma have an almost unimpaired quality of life (Haughney et al., 2008). Apart from quality of life, asthma control is also a predictor of the cost-of-illness: patients with uncontrolled asthma cause 4.5 times the cost of a patient with controlled asthma (Accordini et al., 2013).

Application in Clinical Practice Establishing and maintaining asthma control is considered the key therapeutic objective for asthma treatment. Clinical guidelines refer to this fundamental treatment approach as *control-based asthma management* (Global Initiative for Asthma, 2018). More specifically, the GINA guidelines propose a continuous cycle for managing asthma, which consists of three stages: assessment of asthma, adjustment of treatment, and review of treatment response. The cycle is illustrated in Figure 2.7.

Several studies have found support for the effectiveness of control-based asthma management (Ait-Khaled et al., 2006; Haahtela et al., 2006; Plaza et al., 2005; Wilson et al., 2010). Haahtela et al. (2006) have shown, for example, that the introduction of control-based asthma management in Finland has reduced costs per patient by 36%. Although alternatives to control-based management are available, they are not recommended by clinical guidelines by default due to their limitations in terms of practicability, cost-effectiveness, and applicability across all patient groups (Global Initiative for Asthma, 2018). However, these alternative management approaches,

which utilize biological markers (cf. Sub-section 2.2.2.3) instead of asthma control to guide treatment, are beneficial for certain patient clusters (Haldar et al., 2008).

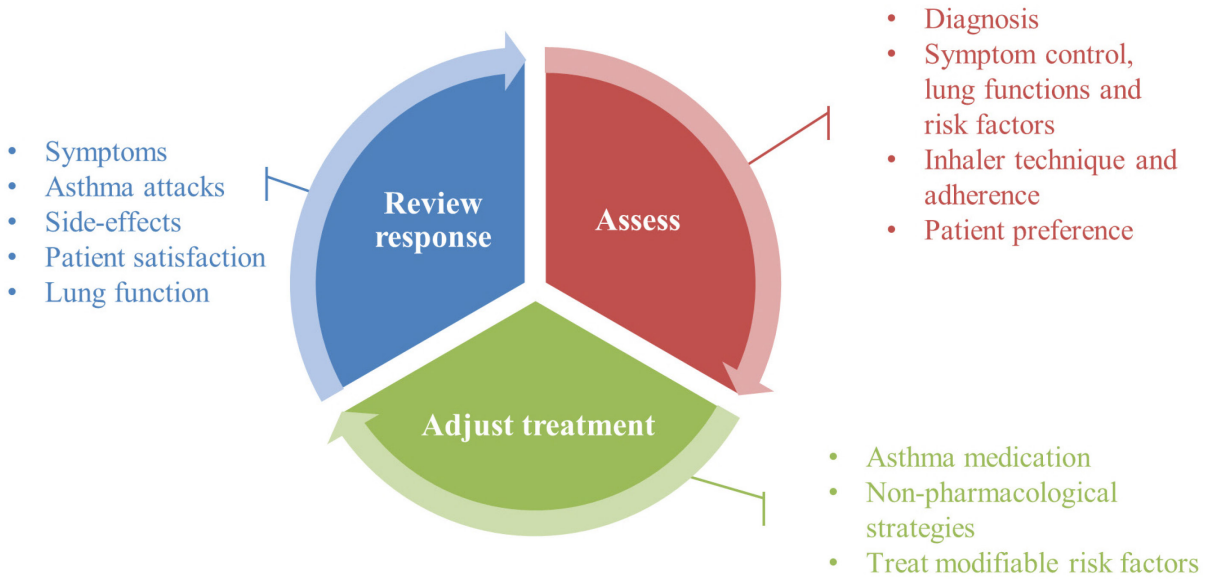


Figure 2.7. Control-based asthma management cycle. Own illustration, adapted from the Global Initiative for Asthma (2018).

Challenges Despite the importance of establishing and maintaining asthma control as the key therapeutic objective in asthma care, many patients are afflicted by partially controlled or even uncontrolled asthma. For example, a European-wide study with almost 3,000 patients has revealed that only 5.3% of patients met all clinical guideline criteria for fully controlled asthma (Rabe, Vermeire, Soriano, & Maier, 2000). In a study with 2,500 patients in the United States, Murphy et al. (2012) found that the majority of patients suffered from partially controlled asthma (23.8%) or uncontrolled asthma (46.9%), while only a minority of patients had controlled asthma (29.2%). Similar results were observed in one of the most extensive surveys on this topic: out of 8,000 European patients, 20.1%, 34.8%, and 45.1% of patients had controlled, partially controlled, and uncontrolled asthma, respectively (Price et al., 2014). However, it is important to point out that while the majority of patients can achieve high levels of symptom control and absence of attacks with proper treatment, it seems unfeasible for some patients to achieve asthma control, even with maximum therapy (Bateman et al., 2004).

In a recent Swiss study by Dürr et al. (2017), well-controlled asthma was most prevalent (65.3%), followed by partially controlled (20.3%) and uncontrolled asthma (14.4%).

While the higher share of controlled patients in this study should not be misinterpreted as evidence of better asthma care in Switzerland (due to an unrepresentative sample and limited sample size (N = 222)), differences in asthma control between countries are indeed common: Vermeire, Rabe, Soriano, and Maier (2002), for example, have found that among adult patients who suffer from more severe asthma symptoms, the share of controlled asthma ranges from 29.4% in the United Kingdom to 68.4% in France.

In his review on the widespread prevalence of uncontrolled asthma, Braido (2013) distinguishes between disease-related, physician-related, and patient-related reasons for uncontrolled asthma. Disease-related reasons are comorbidities[8], which complicate the treatment of asthma and are associated with worse outcomes, continuous presence of triggers[9], and refractory asthma[10]. Limited knowledge and implementation of asthma guidelines, as well as misdiagnosis, were identified as physician-related reasons. Patient-related reasons will be discussed later (cf. Sub-section 2.3.2).

In conclusion, while the share of patients with uncontrolled, partially controlled, and controlled asthma varies substantially between studies and countries, evidence suggests a consistent pattern of considerable shortcomings in establishing and maintaining asthma control.

2.2.1.3 Asthma Severity

Asthma severity is defined as the "intensity of treatment required to achieve good asthma control" (Reddel et al., 2009, p. 86). Like asthma control, severity does not necessarily remain constant through the course of the disease, but may vary over time (Global Initiative for Asthma, 2018). It can only be assessed retrospectively after a patient has received the same medication at the same dosage for several months. For this reason, it is considered to be impractical in clinical practice (Barnes, 2004).

International guidelines on asthma severity from the European Respiratory Society and the American Thoracic Society differentiate between mild, moderate, and severe asthma depending on the medication needed to achieve controlled asthma (Chung et al., 2014). The authors of the guidelines argue that severe asthma might be phenotypically different than mild and moderate asthma in terms of its genetic basis and expression, airway tissue

[8] Notable examples are rhinitis, gastroesophageal reflux, obstructive sleep apnea, and obesity.
[9] Triggers are stimuli, microparticles, or sensitized allergens that may trigger a distressing reaction in the patient's airways (e.g., house dust mites, pets, occupational exposure, exercise, certain drugs, and second-hand smoke).
[10] In refractory asthma, the symptoms and/or inflammation does not respond to the majority of the available pharmacological treatment options (Pavord et al., 2018).

composition, lung function, and patient factors. However, even in patients with mild asthma, who achieve asthma control with low medication doses, it is still possible for fatal asthma attacks to occur (Levy et al., 2014).

Other authors additionally distinguish between mild persistent and mild intermittent asthma, whereby patients suffering from the intermittent form have fewer symptoms. Vermeire et al. (2002) estimate that mild persistent asthma is most prevalent in Europe (37.0%), followed by moderate (23.2%), severe (20.5%), and mild intermittent asthma (19.3%). Figure 2.9 in Sub-section 2.2.3.3 provides additional figures for severity and maps it on to medication regimens.

Finally, it is important to distinguish between uncontrolled and severe asthma in clinical practice, as in most cases the former is responsible for symptoms and attacks and can be more effectively treated (Global Initiative for Asthma, 2018). To confirm asthma severity as the reason for suboptimal treatment outcomes, all factors that could cause uncontrolled asthma symptoms despite high dose treatment have to be ruled out (e.g., lack of adherence or wrong inhaler technique; Chung et al., 2014).

2.2.2 Monitoring of Asthma

Reviewing the treatment response is one of the three fundamental components of control-based asthma management. To this end, multiple categories of *markers* (i.e., measurable parameters that provide meaningful information about the state of the disease) are available. These markers allow patients and physicians to monitor asthma. Expanding the marker categories proposed by Tartibi and Bahna (2014), this section will present *clinical markers* (i.e., standardized, predominantly subjective symptom assessments that are easy to apply in clinical practice and research), *lung function markers* (i.e., respiratory performance indicative of airway obstructions), *biological markers* (which will be defined in the corresponding sub-section), and *digital markers* (i.e., digital versions of markers from the three preceding categories).

2.2.2.1 Clinical Markers

Three types of clinical markers are used to assess asthma control: questionnaires, diaries, and checklists based on clinical criteria. They mostly record the severity of symptoms and impairments in everyday life due to asthma.

Notable examples of reliable and validated questionnaires include the *Three Questions* tool from the Royal College of Physicians (Pinnock et al., 2012; Thomas, Gruffydd-

Jones, Stonham, Ward, & Macfarlane, 2008), the *Asthma Control Test* (ACT; Nathan et al., 2004; Schatz et al., 2006), the *Asthma Control Questionnaire* (ACQ; Juniper, Bousquet, Abetz, Bateman, & Goal, 2006; Juniper, O'Byrne, Guyatt, Ferrie, & King, 1999), and the *Asthma Control Scoring System* (Boulet, Boulet, & Milot, 2002). In addition to questionnaires, physician-administered criteria checklists are available. The Global Initiative for Asthma (2018), for example, provides a checklist with four dichotomous criteria for classifying uncontrolled, partially controlled, and controlled asthma. While questionnaires and checklists refer to symptoms experienced within a time frame of one week or longer, daily symptom diaries are also in use (Hyland, Kenyon, Allen, & Howarth, 1993; Jansen, McCaffery, Hayen, Ma, & Reddel, 2012; Santanello et al., 1997; Santanello et al., 1999). However, several studies have found that diaries suffer from limited reliability due to low adherence and self-invented measurements (Kamps, Roorda, & Brand, 2001; Rhee, Fairbanks, & Butz, 2014).

Table 2.1 provides an overview of conceptual differences between the ACT, the ACQ, the Asthma Control Scoring System, and the GINA checklist. The limited importance of lung functions in clinical markers is noteworthy. Of the four presented markers, only two consider lung functions explicitly. Even in these tests, poor lung functions can be outweighed by the other items. In the ACQ, for example, lung function is one of seven equally weighted items. The minor role of lung functions in clinical markers reflects the two facets of asthma control: level of symptom control and risk of attacks. While lung function parameters are predictors for future adverse events like asthma attacks (Fuhlbrigge et al., 2001; Osborne et al., 2007), they are not strongly correlated with the current level of symptom control (Brand et al., 1999; Kerstjens, Brand, de Jong, Koeter, & Postma, 1994). The level of symptom control, however, is also a predictor of asthma attacks on its own. Haselkorn et al. (2009) have found, for example, that poor symptom control increases the risk of an attack by a factor of 6.4 in children and a factor of 3.2 in adults and adolescents[11]. In conclusion, clinical markers focus predominantly on assessing symptom control.

[11] However, as mentioned in Sub-section 2.2.1.2, symptom control alone might be an insufficient marker for patients under certain treatment regimens or with severe asthma (Global Initiative for Asthma, 2018).

Table 2.1. Clinical asthma control markers. Adapted from Tartibi and Bahna (2014).

	ACT	**ACQ**	**ACSS**	**GINA**
Time frame for assessment	4 weeks	1 week	4 weeks	4 weeks
Includes daytime symptoms?	Yes	Yes	Yes	Yes
Includes nighttime symptoms?	Yes	Yes	Yes	Yes
Includes lung functions?	No	Yes	Yes	No
Includes biological markers?	No	No	Yes	No
Intended for patient self-administration?	Yes	No	No	No

Note: ACT: Asthma Control Test; ACQ: Asthma Control Questionnaire; ACSS: Asthma Control Scoring System; GINA: Global Initiative for Asthma checklist

2.2.2.2 Lung Function Markers

A spirometer, which is the clinical gold standard for assessing lung functions, can identify two types of respiratory performance impairments: obstructions and restrictions (Moore, 2012). Restrictions are characterized by a loss of lung volume and are rare in clinical practice. They occur, for example, in pulmonary fibrosis. The two most common chronic respiratory NCDs, asthma and COPD, are both obstructive diseases, which means that while lung volume is usually not affected, airflow is limited due to obstructions, such as mucus plugging, inflammation, or contraction of the smooth airway muscles. While airflow limitations in asthma can usually be restored to normal levels with medication, they are not fully reversible in COPD, and worsen as the disease progresses (Global Initiative for Asthma, 2018).

The most relevant lung function markers for asthma are the forced expiratory volume in 1 second (FEV_1), the peak expiratory flow (PEF), and the forced vital capacity (FVC). The three parameters are illustrated schematically in Figure 2.8. To facilitate the interpretation of lung function parameters, they are commonly stated as the ratio of the patient's measurement to norm values based on age, sex, height, and ethnicity (referred to as % predicted or, for example, FEV1%; e.g. Moore, 2012). Alternatively, values are also expressed as the fraction of the personal best (referred to as % pb; e.g. Papi et al., 2018).

As discussed above, poor lung function, or more specifically an FEV_1% of less than 60%, is an attack risk factor (Fuhlbrigge et al., 2001; Osborne et al., 2007). During an attack, lung function is severely impaired. In mild to moderate attacks, the PEF is > 50%

pb, in severe attacks it ranges between 33% pb and 50% pb, and in life-threatening attacks it is less than 33% pb (if the patient is able to perform the measurement at all; Papi et al., 2018).

While the assessment of FEV_1 and FVC requires a spirometer and is therefore limited to a clinical setting (Pellegrino et al., 2005), the PEF can also be measured by patients in-situ with a low-cost dedicated peak flow device, the so-called peak flow meter (Miller, 2004). The GINA guideline recommends patient self-monitoring of lung functions in the short term (i.e., two weeks up to three months), especially after the initial diagnosis of asthma, as it is useful to assess treatment response, to identify triggers, and to ascertain a baseline for future interventions. Long-term PEF monitoring is only warranted in patients with severe asthma or those with a compromised perception of asthma control. As considerable PEF variations within one day indicate low asthma control and an elevated risk of attacks, two measurements per day are recommended in PEF monitoring (Global Initiative for Asthma, 2018).

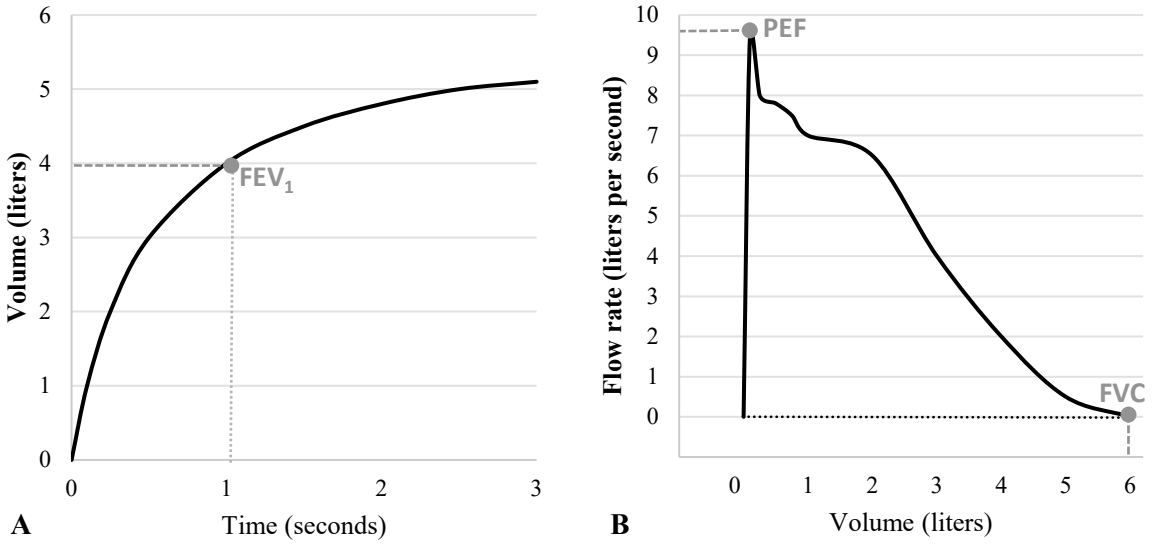


Figure 2.8. Schematic illustration of lung function markers. Graph A depicts the forced expiratory volume in one second (FEV_1) in a volume-time graph, and graph B portrays the peak expiratory flow (PEF) and the forced vital capacity (FVC) in a flow-volume graph based on fictitious measurement data.

2.2.2.3 Biological Markers

Coravos, Khozin, and Mandl (2019, p. 1) define biological markers *(biomarkers)* as "physiologic, pathologic, or anatomic characteristics that are objectively measured and evaluated as an indicator of normal biologic processes, pathologic processes, or biological responses to therapeutic interventions".[12] There are a number of biomarkers available for asthma, for example the blood and sputum eosinophil count, fraction of exhaled nitric oxide (FeNO), and levels of immunoglobulin E in the serum (Pavord et al., 2018). While eosinophil counts and FeNO are useful to assess airway inflammation, the latter biomarker provides additional insights regarding the allergic response (Burrows, Martinez, Halonen, Barbee, & Cline, 1989).

It is important to distinguish between so-called *predictive markers*, which can be used to guide treatment decisions as they predict a patient's response to medication, and *prognostic markers*, which indicate the likelihood of a prospective clinical event (e.g., an asthma attack) or disease progression (e.g. airway remodeling; Nalejska, Mączyńska, & Lewandowska, 2014; Sechidis et al., 2018). FeNO is an example of a biomarker that is both prognostic and predictive: a high FeNO level indicates both an increased risk of asthma attacks as well as a high likelihood of responding to anti-inflammatory pharmacological treatment. Coravos et al. (2019) further distinguish between, inter alia, diagnostic biomarkers for confirming the presence of a disease and monitoring biomarkers for assessing disease status over time (e.g., changes in asthma control). To take FeNO as an example again, it is not particularly useful as a diagnostic biomarker due to the fact that not all patients with asthma necessarily have inflamed airways (cf. Sub-section 2.1.1.3). However, for asthma patients suffering from eosinophilic airway inflammation, FeNO can be utilized as a monitoring marker, even though it is not recommended by guidelines by default due to practicability concerns and mixed outcomes in clinical studies of FeNO-guided self-management (Global Initiative for Asthma, 2018).

Table 2.2 summarizes the utility, advantages, and disadvantages of the most commonly administered biomarkers. Other biomarkers, whose application in clinical practice is less common (e.g., biomarkers that measure the expression of genes associated with atopic reactions; Brutsche et al., 2002), are also available. In summary, while multiple

[12] Please note that based on this definition the lung function markers described in the preceding section could also be considered biomarkers. However, as lung function marker is a common and useful descriptive label, this dissertation treats lung function markers as a distinct category of markers.

biological markers exist, clinical and lung function markers are more commonly administered due to their ease of use, cost-efficiency, and applicability in clinical practice (Tartibi & Bahna, 2014). Furthermore, each biomarker captures different aspects of asthma's pathophysiology (Tiotiu, 2018). Therefore, while biomarkers provide valuable insights for medical research and are becoming increasingly important in this domain (Pavord et al., 2018), the lack of an all-purpose biomarker, which can be used for all patients equally, limits clinical applicability (Tartibi & Bahna, 2014).

Table 2.2. Overview of available biomarkers for asthma. Adapted from Tiotiu (2018).

Biomarker	Utility	Advantages	Disadvantages
Blood eosinophils	• Prognostic marker for attacks, poor control, and airway obstruction • Predictive marker for corticosteroids and biologics	• Minimal-invasive • Requires low patient effort • Practicable in clinical settings • Correlates with sputum eosinophilia	• Measurement difficult and painful for some patients • Unclear performance due to varying cut-offs • Low specificity (can be elevated due to other causes)
Sputum eosinophils	• Predictive marker for corticosteroids and biologics	• Not invasive • Higher specificity due to focus on upper airways	• Limited availability • Demanding collection requirements (training, equipment etc.)
Serum IgE	• Prognostic marker for asthma severity and airway remodeling	• Easy measurement • Identifies candidates for Anti-IgE therapy	• Better markers for inflammation and allergen specific IgE are available
FeNO	• Prognostic marker for attacks and airway hyper-reactivity • Predictive marker for anti-inflammatory treatment	• Not invasive • Requires low patient effort • Practicable in clinical settings	• Limited reliability (due to multiple confounders) • Requires special equipment

Note: IgE: Immunoglobulin E; FeNO: Fraction of exhaled nitric oxide.

2.2.2.4 Digital Markers

The advent of mobile health technology described in Sub-section 1.1.2 also enables novel disease monitoring approaches. Advances in mobile sensing (i.e., the exploitation of sensors in wearables and smartphones to derive meaningful information about the environment and users; Lane & Georgiev, 2015), for example, have led to the development of smartphone-based monitoring in the fields of physical activity and mental health (Trifan, Oliveira, & Oliveira, 2019). As smartphones are companions in

the everyday life of most patients, their computational power and sensing capabilities can further enable *passive monitoring*, in which health-related parameters are continuously measured without any patient effort required (Cornet & Holden, 2018; Schatz, 2018).

Such novel monitoring approaches, however, require valid digital markers. While the term marker was defined in the last sub-sections, the prefix *digital* expresses that they are measured by sensors and processed computationally, so that they are available in a digital format (i.e., stored as ones-and-zeros; Coravos et al., 2019). However, to the best of the author's knowledge, no digital markers are used in clinical practice hitherto for the in-situ disease monitoring of asthma. For example, digital markers are not mentioned in any of the clinical guidelines or review articles that have served as the theoretical background for this chapter (e.g., British Thoracic Society, 2019; Global Initiative for Asthma, 2018; Papi et al., 2018; Pavord et al., 2018; Steurer-Stey & Beise, 2017). The only technology-based monitoring approach that is at least somewhat adopted in asthma are online and smartphone-based versions of the clinical markers discussed in Sub-section 2.2.2.1 (Larson, Saba, Kaiser, Goel, & Patel, 2017).

Digital Biomarkers Although a lack of biochemical sensors in smartphones prohibits digital versions of the biomarkers presented in Sub-section 2.2.2.3, mobile sensing can enable other useful *digital biomarkers* for asthma. As indicated in Table 2.1, clinical markers of asthma control rely mainly on the assessment of symptoms. While these assessments are subjective in nature, mobile sensing technology can enable their automatic detection. In this way, objective and reliable measurements of symptoms could become available for asthma monitoring. In other words, mobile sensing technology has the potential to objectively quantify asthma symptoms, so that hitherto subjective symptom assessments can become objective digital biomarkers[13].

In mobile sensing, cough is one of the most extensively researched symptoms relevant for asthma. Barata et al. (2019), for example, have found that a convolutional neural network is able to detect cough consistently across different smartphones from their built-in microphones with mean accuracies between 85.9% and 90.9%. This finding is

[13] Please note that digital biomarkers based on the objective quantification of symptoms may have different characteristics than the conventional biological markers presented in Sub-section 2.2.2.3. For example, parameters falling under the category of digital biomarkers do not necessarily map directly onto biochemical processes (but onto their effects measurable through smartphone sensors; e.g., symptoms), so that they may be inherently less specific than conventional biological markers.

in line with earlier work on cough detection, which substantiates the claim that smartphone-based cough detection is indeed feasible. One of the most cited papers on cough detection by Larson, Lee, Liu, Rosenfeld, and Patel (2011) has shown in a laboratory setting that automatic cough detection of smartphone audio recordings can exceed sensitivities and specificities of 90%.

Sleep quality is a second potential digital biomarker, which attracted the attention of mobile sensing research (Consolvo et al., 2008). The inclusion of nocturnal symptoms in many clinical markers for asthma (cf. Table 2.1) foreshadows the relevance of sleep quality for asthma monitoring. Research has found that sleep disturbances, such as awakenings in the early morning and nocturnal wakefulness, are very prevalent in asthma (Janson, Gislason, Boman, Hetta, & Roos, 1990). Furthermore, sleep quality is associated with asthma control even after controlling for comorbidities (Luyster et al., 2012). These findings suggest that smartphone-based detection of sleep quality can indeed be a valid digital biomarker for asthma. Min et al. (2014) have delivered the proof of concept for sleep quality detection with an accuracy of 81% in a binary classification task (i.e., good vs. poor sleep quality).

Digital Lung Function Markers In addition to asthma symptoms, mobile sensing can also be used for quantifying lung functions introduced in Sub-section 2.2.2.2. While the status quo of asthma lung function monitoring relies on dedicated peak-flow devices or costly spirometers, recent advances in mobile sensing have delivered the proof of concept for population-wide, highly cost-efficient smartphone-enabled spirometry (Larson et al., 2017).

Goel et al. (2016), for example, have shown that the PEF, FEV_1, FEV_1%, and FVC can be estimated by means of the smartphone's built-in microphone with a measurement error of less than 10%. For FEV_1%, a mean error rate across multiple devices of less than 6% was achieved, which, according to the authors, is within the required margin for a clinical spirometer. However, in addition to the observed systematic overestimation of lung functions, these results were achieved in a laboratory environment and lack clinical validation. Similar results with the same approach had already been reported by the same research group: Larson et al. (2012) were able to show that for FVC, FEV_1, and PEF a mean error of 5.1% could be achieved with a smartphone's built-in microphone compared to a clinical spirometer. In both studies, the computation for estimating spirometry results was not performed on the smartphone itself, but on a

dedicated server (Larson et al., 2012) or as a call over the mobile phone network (Goel et al., 2016).

Furthermore, notable attempts at developing mobile, phone-based spirometry through additional, low-cost hardware were made by Carspecken, Arteta, and Clifford (2013) and by Gupta, Chang, Anyigbo, and Sabharwal (2011). However, patients still need to perform the same deliberate measurement maneuver to measure their lung functions, regardless of whether they use a dedicated spirometer, a connected spirometer, or a smartphone's microphone. Therefore, passive monitoring as described above is not feasible.

2.2.3 Pharmacological Interventions

Three categories of medication are available for the management of asthma: controller, reliever, and add-on therapies (Global Initiative for Asthma, 2018). Most medications are dispensed through inhalers to enable the delivery of the active substances directly to the airways. While different types of inhalers are available to accommodate patient needs (e.g., pressurized metered-dose inhaler with or without spacers or dry powder inhaler; see National Asthma Council Australia (2019) for an exhaustive list), incorrect inhaler technique remains common in practice and is associated with poor asthma control and frequent attacks (Hamdan et al., 2013).

In this chapter, controller and reliever medication will be briefly introduced and the treatment algorithm will be outlined. Add-on therapies, which are employed in the treatment of severe asthma, will not be covered directly. Furthermore, a number of non-pharmacological interventions are also available for asthma (e.g., smoking cessation). Since these treatment options will not be discussed further, please refer to the GINA guidelines for additional information. However, for many of the non-pharmacological interventions, in particular those based on complementary and alternative medicine, evidence demonstrating their efficacy is limited (Györik & Brutsche, 2004).

2.2.3.1 Controller Medication

Controller medications are used on a regular basis for the long-term maintenance of asthma (Papi et al., 2018). They decrease airway inflammation, so that symptoms are kept under control and the risk of future attacks and airway remodeling is reduced (O'Byrne, Pedersen, Lamm, Tan, & Busse, 2009). The most prominent controller medications are inhaled corticosteroids, which need two to three months to take full

effect (Reddel et al., 2000). Other available controller medication options are Leukotriene receptor antagonists and theophylline (Global Initiative for Asthma, 2018).

The determined introduction of anti-inflammatory controller medication to asthma care in the 1980s has substantially reduced asthma attacks and mortality due to asthma (Pavord et al., 2018). Tragically, inhaled corticosteroids continue to be underused, which results in otherwise preventable attacks and deaths (Levy & Winter, 2015).

2.2.3.2 Reliever Medication

Reliever medications, also referred to as rescue medications, are used on an as-needed basis for short-term symptom relief during asthma deteriorations, asthma attacks, or in everyday life (Global Initiative for Asthma, 2018; Papi et al., 2018). They dilate the airways rapidly, but only work in the short term and do not treat underlying causes for the bronchoconstriction (Kerstjens et al., 1992). The two most common reliever medications are short-acting β2 agonists (SABA) and long-acting β2 agonists. They take effect within 15 to 20 minutes and provide symptom relief for up to four hours or 15 hours, respectively (Global Initiative for Asthma, 2018). While reliever medications contribute significantly to patients' quality of life (Pavord et al., 2018), the frequent usage of reliever medication is a risk factor for asthma attacks and is associated with asthma mortality (Patel et al., 2013). Therefore, successful asthma management should aim for reducing or, if possible, even eliminating the necessity for reliever medication in the treatment of a patient (Global Initiative for Asthma, 2018).

2.2.3.3 Treatment Algorithm

The treatment algorithm for asthma is characterized through its stepwise logic (Papi et al., 2018): if a patient's symptoms persist after treatment with controller medication for 2–3 months and other non-disease-severity-related reasons for persisting symptoms can be ruled out (i.e., incorrect inhaler technique, poor adherence, continuously ongoing exposure to triggers, comorbidities, or incorrect diagnosis), the GINA guidelines recommend a therapy *step up* (Global Initiative for Asthma, 2018). In addition to these *sustained* step ups, the guidelines also allow for short-term step ups (e.g., in the case of viral infections or during allergy season) and for day-to-day adaptations (depending on current symptoms and for certain treatment options). However, if a patient's asthma can be considered as controlled by the current treatment regimen, a *step down* is warranted. In this way, a patient's minimum effective treatment can be identified (Global Initiative for Asthma, 2018). In total, the GINA guidelines list five treatment steps, which are

illustrated in Figure 2.9. An alternative controller medication option is available for each step to account for patient preferences (e.g., anxiety related to corticosteroids).

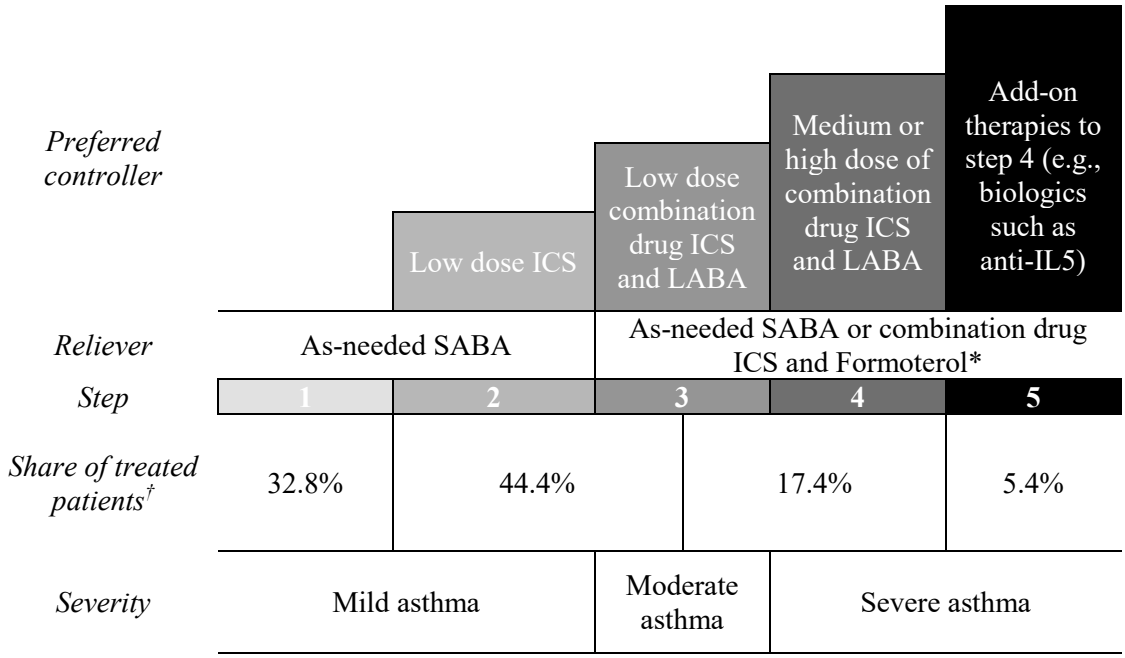


*Figure 2.9. Stepwise approach for adjusting asthma treatment. Modified from Global Initiative for Asthma (2018). * Depending on controller medication; † Estimates adapted from the REALISE survey (n = 8'000 from 11 European countries; Price et al., 2014); ICS: Inhaled corticosteriods; SABA: Short-acting beta-2 agonists; LABA: Long-acting beta-2 agonists; IL5: Interleukin-5.*

2.3 Living with Asthma

After introducing asthma and focusing on its treatment, this section puts the patient in the foreground. In the 1990s, chronic disease management (CDM) emerged as a patient-centric treatment approach for chronic NCDs like diabetes, depression, or COPD (Peytremann-Bridevaux, Arditi, Gex, Bridevaux, & Burnand, 2015). As discussed by Schrijvers (2009, p. 2), multiple definitions of CDM are available, for example from the Disease Management Association of America: "Disease management is a system of coordinated health care interventions and communications for populations with conditions in which patient self-care efforts are significant". Most definitions converge on the notions that CDM addresses patients who are suffering from chronic diseases by systematically providing cost-effective preventive and curative interventions, usually in

a multidisciplinary setting, with the goal of improving outcomes and a patient's quality of life.

A Cochrane review on this topic found low to moderate evidence that CDM for asthma improves quality of life, lung functions, and asthma severity (Peytremann-Bridevaux et al., 2015). However, not enough homogenous study results were available for the meta-analytic estimation of CDM's effect on asthma-related emergencies, such as emergency department visits and asthma attacks. The authors therefore conclude that CDM is probably effective, but the optimal combination of interventions remains unclear. In their review on CDM for asthma, Lemmens, Nieboer, and Huijsman (2009, p. 670) distinguish between "double interventions (patient-related and organisational interventions)" and "triple interventions (patient-related, professional-directed and organisational interventions)". While both were effective for improving a patient's quality of life, triple interventions also reduced hospital admissions. However, due to the heterogeneous combination of interventions, specifying the optimal configuration was not possible.

In conclusion, further research is needed to identify the optimal configuration of interventions for CDM asthma programs. Therefore, it seems more promising to focus on individual interventions for asthma, for which evidence is more conclusive, instead of on comprehensive CDM programs. Since patient-related interventions are central to the overarching question posed in Section 1.2, they will be discussed at length in the next sub-section. Later on, patient risk factors, coping styles, perceptions, and patient attitudes will be covered. In addition, three specific research questions, which will be examined in chapters three to five, will be derived.

2.3.1 Asthma Self-Management

Patient-related interventions for the management of chronic diseases are often referred to as patient *self-management*. They are considered to be "a key to effectiveness and efficiency in care of chronic diseases" (Holman & Lorig, 2004, p. 239). Self-management for asthma is a vibrant field of research: a search in the PudMed data base[14] revealed that of the 439 publications available with the terms "asthma" and "self-management" in the title, more than a quarter were published only in the last five years.

[14] PubMed search was conducted on July 10, 2019 using the search phrase "(Asthma[Title]) AND Self-Management[Title]"

2.3.1.1 Efficacy

Asthma self-management is endorsed by clinical guidelines (Global Initiative for Asthma, 2018) and its utility is undisputed in clinical practice and medical research alike. A systematic meta-review encompassing 27 reviews with a total of 244 randomized controlled trials has demonstrated conclusively that asthma self-management improves asthma control and patients' quality of life, and reduces adverse events such as attacks (Pinnock et al., 2017). In terms of emergency medical resource utilization, for example, patients who received asthma self-management had on average between 0.50 and 0.79 times the risk of a hospitalization, between 0.66 and 0.82 times the risk of an emergency department visit, and 0.68 times the risk of unscheduled consultations in comparison to control groups. However, while the costs of offering asthma self-management were mostly offset by a reduction in emergency medical resource utilization, a marginal (but statistically insignificant) increase in costs due to self-management has been observed (Cohen's d = 0.12; 95% CI [-0.09, 0.34]).

2.3.1.2 Effective Ingredients

In contrast to general CDM asthma programs, the effective ingredients in asthma self-management are well understood. In their seminal review on asthma self-management, Gibson and colleagues (2003) identified the following four effective components: asthma education, regular medical reviews, self-monitoring of either peak-flow or symptoms, and a written action plan. In the following sub-sections, each component will be introduced.

Asthma Education Interventions for providing asthma education can contain, for example, basic information about the respiratory system (e.g., the role of oxygen and the anatomy of the airways), asthma in general (e.g., symptoms, impairments in everyday life, medication, triggers, and attacks), techniques for symptom relief (e.g., pursed-lip breathing), coping strategies, recommendations for improving quality of life, and emergency responses in the case of asthma attacks (Möller et al., 2017). While interventions exclusively providing asthma education are not improving asthma outcomes, asthma education reduces hospitalizations, emergency department visits, and unscheduled physician visits, and improves quality of life when administered in conjunction the other three components of asthma self-management (Powell & Gibson, 2003).

In their review, Rosas-Salazar, Apter, Canino, and Celedón (2012) identified multiple factors that affect a patient's level of asthma knowledge. Among others, health literacy (i.e., the aptitude to apply general cognitive skills such as reading to a health context) emerged as an important predictor of asthma knowledge. However, despite its role in acquiring asthma knowledge, it is unclear whether health literacy is causally associated with actual asthma treatment outcomes (Berkman, Sheridan, Donahue, Halpern, & Crotty, 2011).

Regular Medical Reviews The second component of self-management is regular consultations with health care professionals. These medical reviews should be performed according to the control-based treatment cycle introduced in Sub-section 2.2.1.2. More specifically, asthma control should be assessed and treatment adjusted if necessary (Global Initiative for Asthma, 2018). Additionally, two aspects of asthma treatment should be reviewed explicitly: inhaler technique and non-adherence to medication.

Inhaler technique is important because incorrect inhaler usage is not only associated with, among other outcomes, increased hospitalizations and emergency department visits, but it is unfortunately also very common. Depending on the type of inhaler, between 12% and 44% of all patients commit critical errors that limit or inhibit the effect of the dispensed medicine (Melani et al., 2011). Other estimates for incorrect inhaler use range between 28% and 68% of all patients affected (Fink & Rubin, 2005). Furthermore, the latter study has found that between 39% and 67% of all nurses, physicians, and respiratory therapists were not able to describe correct inhaler use or to use the inhaler correctly themselves. The consequence of widespread incorrect inhaler use is that 20% to 28% of financial resources spent on inhalers are wasted (Fink & Rubin, 2005).

The second important aspect to review is adherence to medication. Non-adherence to prescribed controller medication, namely inhaled corticosteroids (ICS), is notoriously high in asthma (Pavord et al., 2018). In clinical practice, only 30% to 40% of patients are consistently adherent to the prescribed medication regimen, and even in the context of well-monitored studies the adherence rate does not exceed 70% (Sumino & Cabana, 2013). Non-adherence naturally has similar consequences to incorrect inhaler use, namely poor asthma control and an increase in emergency medical resource utilization due to asthma attacks (Sumino & Cabana, 2013). The reasons for non-adherence and incorrect inhaler technique are discussed in Sub-section 2.3.2.1.

Symptom or PEF Monitoring A crucial part of self-management is the systematic monitoring of PEF or symptoms. In their review, Powell and Gibson (2003) found that the monitoring of either parameter produces equivalent outcomes.

McKeever et al. (2018) have shown in a pragmatic trial that 20% of attacks in adults can be prevented by increasing the ICS dose four-fold after the detection of first symptom deteriorations. While the high dose ICS therapy used to abort asthma attacks seems to be less effective in children – and potential side-effects of ICS are more severe in this age group (Jackson et al., 2018) – the ICS escalation strategy is considered effective for the abortion of imminent asthma attacks in adults (Reddel & Barnes, 2006). However, clinical guidelines emphasize that the effectiveness of the escalation strategy for asthma attack abortion depends decisively on whether the medication dosage was escalated soon enough (Steurer-Stey & Beise, 2017). Therefore, regular monitoring of PEF or symptoms can support patients in identifying the window of opportunity for stopping impeding asthma attacks (Honkoop, Taylor, Smith, Snoeck-Stroband, & Sont, 2013). However, despite the utility of regular monitoring for asthma care and preventing asthma attacks, only 5% of patients measure their PEF at least once a week (Murphy et al., 2012). Furthermore, even if patients are explicitly instructed to measure their PEF regularly, the corresponding diary entries are correct in less than 50% of cases (Kamps et al., 2001).

Asthma Action Plan While written plans are generally recommended (Global Initiative for Asthma, 2018), verbal instructions were found to be equally effective (Powell & Gibson, 2003). Even though there are many different versions of asthma action plans available, all action plans tend to have similar content: "objective cues to promote early detection of deteriorating asthma symptoms, medications prescribed and action to take in the event of an acute episode, with particular reference to step-up and step-down therapy, along with health service access" (Gatheral et al., 2017, p. 7). Research has demonstrated that independently performed treatment adjustments based on a pre-defined action plan are as effective as ad-hoc adjustments by the physician (Powell & Gibson, 2003).

Asthma action plans are usually personalized and differentiate treatment based on color-coded zones: green for regular care, yellow for noticeable symptom deteriorations, and red for acute attacks (e.g. Asthma UK, 2018). They are used in conjunction with PEF and/or symptom diaries to ensure availability of treatment adjustment cues. Honkoop et

al. (2013) have shown that useful objective cues are changes in symptom severity of more than two standard deviations and PEFs of less than 60% predicted or 70% pb. If a PEF of less than 70% pb and changes in symptom severity of two standard deviations or more occur within seven days of each other, asthma attacks can be detected up to 5.1 days before manifestation with a sensitivity of 75% and a specificity of 98%. While this combination of parameters provides patients with the largest window of opportunity for attack abortion, other combinations are more accurate. A PEF of less than 60% pb, for example, has a sensitivity of 100% and a specificity of 98%. However, with only 1.8 days remaining until its manifestation, it is doubtful whether the attack could still be aborted.

2.3.1.3 Digital Implementations

In line with the main theme of this dissertation, asthma self-management seems like a particularly well-suited target to leverage the potential of digital medicine: the effectiveness of the four components is not only well documented, but a digital version of each effective component can also be intuitively envisioned. For example, asthma education and written action plans could be delivered directly to the patient's smartphone, regular medical reviews could be performed by means of telemedicine, symptoms could be tracked manually with smartphone questionnaires, and the PEF could be measured by means of a clinical-grade connected spirometer (e.g., Nuvoair spirometer, https://www.nuvoair.com/).

Consequently, *digital self-management interventions*[15] for asthma have been subject to a considerable amount of research. In one of the first reviews in this field, Marcano Belisario, Huckvale, Greenfield, Car, and Gunn (2013) were only able to identify two studies of sufficient quality on *smartphone-based self-management interventions*[14]. While one study found no effect on asthma outcomes, the other study has shown improvements in quality of life, lung functions, and a reduction in emergency department visits. Due to the mixed results, Marcano Belisario et al. (2013) concluded that, at that point in time, not enough evidence was available to recommend smartphone-based self-management interventions for clinical practice. However, a thematically similar review with more positive results regarding the efficacy of smartphone apps has

[15] Instead of the general terms *digital medicine intervention* and *digital pill* (cf. Section 1.2), the terms *smartphone-based self-management intervention* and *digital self-management intervention* are used in this section to be more precise with regard to the intervention category.

since been published: in comparison with control groups, lung functions improved significantly in two out of three studies, asthma/symptom control improved in five out of six studies, and quality of life improved in three out of four studies (Farzandipour, Nabovati, Sharif, Arani, & Anvari, 2017). However, as this review had more modest inclusion criteria for published studies, a direct comparison to Marcano Belisario et al. (2013) is not possible.

Morrison et al. (2014) conducted a broader meta-review in which all digital self-management interventions were included (e.g., web-based interventions), not just smartphone-based interventions. However, only ten of the 29 identified reviews were of sufficient quality to be included. These ten reviews were comprised of 19 clinical trials. Similar to the review by Marcano Belisario and colleagues (2013), mixed results were found: self-care (n = 5/6), quality of life (n = 4/7), and medication adherence (n = 2/3) were improved in more than half of the studies that measured these outcomes; better symptom control (n = 6/12) and less absenteeism due to asthma (n = 2/4) was reported in half of the studies; and lung functions (n = 2/16) and health service utilization (n = 2/15) remained mostly unaffected by the interventions. Due to the heterogeneity and insufficient reporting of interventions, a meta-analysis could not be performed. The authors conclude that digital asthma self-management interventions show promise, but further high-quality research is warranted.

A similar conclusion was reached by McLean et al. (2016), who, in their review of interactive digital self-management interventions, identified only two studies that could be analyzed in a meta-analysis. Other studies had to be excluded because they either failed to meet the eligibility criteria for the analysis or induced considerable heterogeneity. For the two remaining studies, a moderate positive effect of interactive digital self-management interventions was found for quality of life (Cohen's d = 0.45; 95% CI [0.13, 0.77]) and asthma control (Cohen's d = 0.54; 95% CI [0.22, 0.86]). Additionally, McLean et al. (2016) and Morrison et al. (2014) found no evidence of harm resulting from digital self-management interventions.

A review of digital asthma self-management interventions also investigated the role of psychological theory for the effectiveness of interventions (Lycett et al., 2018). Fourteen studies, which were most commonly build upon Social Cognitive Theory, the Health Belief Model, and Self-Efficacy Theory, were included in this review. The review found that medication adherence increased in all studies (n = 5), self-management and asthma control was improved in half of the studies (n = 4/8), but a higher quality of life and less

health care utilization was achieved in less than half of the studies (n = 3/8 and n = 3/7, respectively). Furthermore, the authors found a strong positive relationship between the extent of theory use and study outcomes.

Despite issues regarding the heterogeneity of interventions and the poor quality of the available studies, the reviews indicate the potential of digital self-management interventions for improving asthma outcomes. However, published studies are not necessarily reflective of the interventions offered in real life, namely asthma smartphone apps. With more than 318,000 health apps available (Byambasuren, Sanders, Beller, & Glasziou, 2018) – apps that can be designed without the involvement of medical experts and published without any quality control measures – a question arises about the status quo of digital asthma self-management interventions in practice, namely publicly available asthma apps. Against this background, the first research question of this dissertation is as follows:

> ***RQ1:*** *"What is the potential of publicly available asthma apps for improving asthma self-management?"*

Answering this question is highly relevant for the overarching research question of this dissertation because it enriches the academic perspective with insights from the practice of digital medicine. In particular, it can help to detect currently untapped potential, which can then be leveraged to improve asthma care.

2.3.2 Patient Factors

As demonstrated by the importance and effectiveness of asthma self-management, patients contribute significantly to the success of asthma care. This sub-section is dedicated to patient factors that affect asthma outcomes, for example, risk factors, coping styles, perceptions, and attitudes. The objective of this sub-section is to provide a better understanding of patients and their disease-related behavior. In line with the overarching research question and objective, the research questions derived in the remainder of this sub-section are concerned with unmet patient needs.

Figure 2.10 provides a schematic, non-exhaustive overview of patient-related risk factors for non-adherence, poor asthma control, and increased likelihood of death due to asthma. The risk factors were synthesized from multiple reviews (Braido, 2013; Dima, Hernandez, Cunillera, Ferrer, & de Bruin, 2015; Haughney et al., 2008; Levy et al., 2014), the GINA guideline (Global Initiative for Asthma, 2018), a survey about

asthma control from 2,238 adults (Stanford et al., 2010), and a case-control encompassing 533 asthma deaths (Sturdy et al., 2002). Physician-related and disease-related risk factors for suboptimal asthma outcomes were already discussed in earlier sections (e.g., Sub-section 2.2.1).

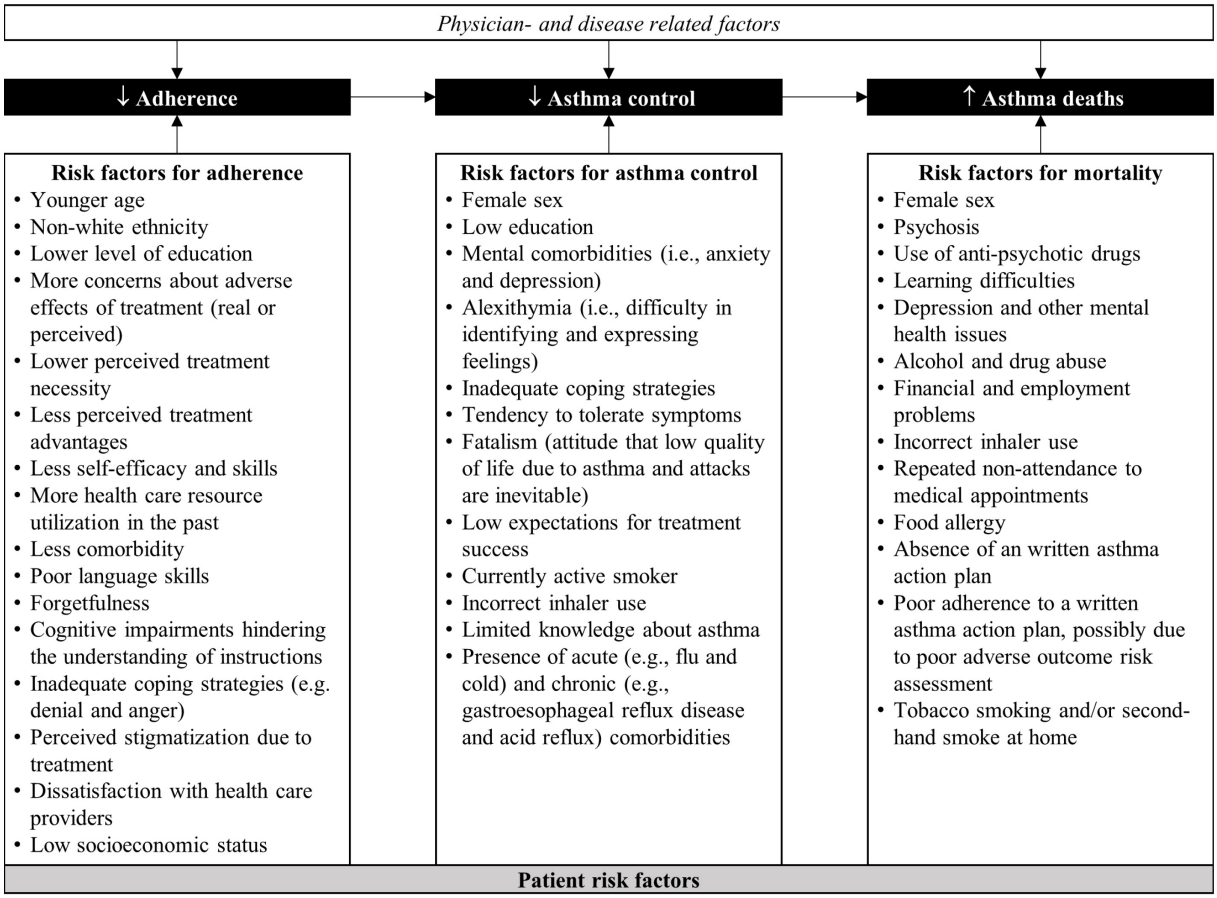


Figure 2.10. Patient-related risk factors for non-adherence, poor asthma control, and asthma deaths. Factors are synthesized from literature (Braido, 2013; Dima et al., 2015; Global Initiative for Asthma, 2018; Haughney et al., 2008; Levy et al., 2014; Stanford et al., 2010; Sturdy et al., 2002). Note: Up- and down-pointing arrows specify the relationships between risk factors, adherence, asthma control, and asthma deaths (e.g., young age is associated with lower adherence, which in turn is associated with lower levels of asthma control, which in turn increases the likelihood of death due to asthma).

2.3.2.1 Intentional Adverse Health Behavior

In their analyses on risk factors for non-adherence, Haughney et al. (2008) differentiate between unintentional (e.g., language barriers and forgetfulness) and intentional reasons for non-adherence. While unintentional non-adherence is intuitively comprehensible,

deliberate non-adherence to medication that improves quality of life and reduces the likelihood of life-threatening asthma attacks is astounding and seems highly irrational. However, psychological theory offers explanations for why patients might intentionally behave in a way that jeopardizes their health.

The *health belief model* (Becker & Maiman, 1975), for example, provides useful insights into the health behavior of humans. In summary, this model explains health behavior as a risk-benefit analysis, in which the belief in a health threat (e.g., asthma is a serious illness with life-threatening attacks) and the belief that the threat can be reduced (e.g., ICS decreases the risk of an attack) determine whether a specific health behavior (e.g., adherence to an ICS regimen) is performed. Clark, Jones, Keller, and Vermeire (1999) argue, for example, that patients suffering from asthma balance the necessity of medication (resulting from belief in the health threat) with concerns about the side-effects and the effectiveness of medication (which are potential barriers to the belief that the threat can be reduced). Based on this risk-benefit analysis, non-adherence by patients may actually be a rational decision, in a sense that it is a logical consequence based on underlying, but incorrect, beliefs (e.g., the belief that the side-effects of ICS are more dangerous than health risks due to asthma).

A different explanation for non-adherence stems from the literature on cognitive biases and heuristics. One well-investigated heuristic for judging the probability of an event (e.g., an asthma attack) is the *availability heuristic*: if instances of an event come to one's mind easily, the probability of this event to occur is judged to be high (and vice versa; Tversky & Kahneman, 1973). This heuristic could explain why the National Review on Asthma Deaths in the United Kingdom found that the majority of patients who died from asthma were treated only for mild (9%) or moderate (49%) asthma (Levy et al., 2014): due to the fact that asthma symptoms fluctuate over time and attacks tend to occur infrequently in these comparatively healthy patients, it can be argued that patients might underestimate the probability of an attack due to the limited cognitive availability of prior adverse asthma events (e.g., attacks). In line with the health belief model, this would diminish the perceived health threat due to asthma and could result in non-adherence, which in turn is a risk factor for potentially fatal asthma attacks.

An alternative cognitive bias, which might contribute to the explanation of non-adherence, is the *present bias*: immediate rewards are overvalued at the expense of long-term rewards (Benhabib, Bisin, & Schotter, 2010). Based on the present bias, non-adherence might be explained by the fact that controller medications like ICS tend not

to take effect immediately, so no reward is experienced in the present. As future rewards (e.g., better symptom control in the future) are inherently discounted, there is no incentive for adherence to the controller medication regimen in the present. Support for this reasoning comes from the substantial overuse of reliever medications by asthma patients – medications that provide an immediate reward (i.e., symptom relief) at the expense of an increase in future risk of attacks (O'Byrne, Jenkins, & Bateman, 2017). Unsurprisingly, survey studies also indicate that 90% of patients with asthma prefer treatments with immediate effects (Partridge, van der Molen, Myrseth, & Busse, 2006).

Additional psychological theories could be invoked, and further explanations based on biases and heuristics could be proposed. However, the purpose of providing examples of the potential theoretical explanations for intentional adverse health behavior is to illustrate that humans are inherently cognitively ill-equipped to manage chronic long-term diseases, despite the necessity and importance of doing so.

2.3.2.2 Coping Styles

Figure 2.10 revealed that coping styles, which are the result of psychological adjustment to chronic disease (De Ridder, Geenen, Kuijer, & van Middendorp, 2008), are important factors for non-adherence and asthma control. In a study of 3,464 patients, Aalto, Harkapaa, Aro, and Rissanen (2002) identified the following six asthma-specific coping strategies, sorted from most common to least common: positive reappraisal, information seeking, ignoring asthma, restricted lifestyle, hiding asthma, and worrying about asthma. A restricted lifestyle, hiding asthma, information seeking, and asthma worry were positively correlated with asthma severity. Furthermore, hiding asthma and asthma worry were associated with worse psychological health, while positive reappraisal was the only coping style associated with a better psychological constitution. A longitudinal study has found further evidence for the association of hiding and worry about asthma with emotional problems, namely anxiety, depression, and stress (Tiggelman, van de Ven, van Schayck, Kleinjan, & Engels, 2014). In terms of medical resource utilization, information seeking and asthma worry are positively correlated with the number of general physician visits. All coping styles were further negatively associated with physical health, implying that patients with good physical health cope less strongly with their asthma overall. Restricted lifestyle, which resembles a state of resignation, is a particularly common coping style in long-term and elderly patients with suboptimal treatment outcomes, who often accept the impairments of their quality of life as

inevitable and stop seeking care improvements (O'Conor et al., 2017). However, restricting lifestyle due to asthma was also observed in younger patients (e.g., avoiding physical activity; Al-Kalemji, Johannesen, Dam Petersen, Sherson, & Baelum, 2014).

In their review of coping styles in asthma, Barton, Clarke, Sulaiman, and Abramson (2003) point out that the coping style of ignoring asthma, characterized by denial, was more prevalent in patients with a severe course of disease (i.e., history of hospitalization and near-fatal attacks). Tragically, this coping style was also associated with medication non-adherence. The authors emphasize the role of social support, family factors, and socioeconomic status for the development of healthy coping styles. Fortunately, coping strategy interventions are available and have shown improvements in psychological well-being and asthma control.

2.3.2.3 Perceptions

A prerequisite for the success of control-based management is that patients assess their asthma control continuously and, if necessary, take action (e.g., visit their physician for treatment adjustment). For this reason, one component of self-management is self-monitoring of either symptoms or PEF. While PEF is an objective value (even though measurement errors may occur if the manoeuvre is carried out incorrectly; Moore, 2012), the assessment of symptom severity is highly subjective. The success of asthma (self-)management therefore often depends on a patient's perceptions of symptoms and asthma control, even more so for patients who do not explicitly self-monitor asthma (e.g., by recording their symptoms or PEF in a diary) but rather rely on their day-to-day ad-hoc self-assessments. In the following, patient perceptions of symptoms and asthma control will be discussed.

Symptoms Price et al. (2014) have systematically investigated patients' asthma-related perceptions in the REALISE survey with 8,000 European asthma patients. In terms of symptoms, breathlessness was ranked by 29% of the patients as the symptom with the greatest impact on everyday life, followed by cough (20%), wheezing (18%), chest tightness (15%), and night-time awakenings (5%). Furthermore, in a sample of adolescent patients, Rhee et al. (2014) found three symptoms that were experienced by the majority of patients: 98% reported cough, followed by wheeze (79%), and shortness of breath (72%). Additionally, the authors found that adolescent patients associated their symptoms with negative feelings, such as fatigue, exhaustion, and anxiety. In a different survey of 3,415 adults with asthma from eleven countries (INSPIRE study, Partridge et

al., 2006), the majority of patients perceived their worsening symptoms as impacting their daily activities, namely exercise and physical activity (73%), leisure time (49%), social interactions (39%), intimacy in their relationship (29%), work (28%), and family time (16%).

Asthma Control One of the most consistent (and unfortunately also most alarming) findings in the literature on patients' perceptions is the systematic overestimation of asthma control (Gillissen, 2015). The 2009 Asthma Insight and Management survey found that while 71% of patients considered their asthma to be controlled, in fact only 29% of patients had controlled asthma as defined by clinical guideline criteria. The same study found that only 26% of patients with uncontrolled asthma visited a specialist on a regular basis (Murphy et al., 2012), even though specialists deliver better asthma outcomes in comparison to general physicians (Harmsen, Nolte, & Backer, 2010; Schatz et al., 2005). The INSPIRE study provides further compelling evidence for the patients' overestimation of asthma control: 95.4% and 83.7% of patients with partially and uncontrolled asthma, respectively, perceived their asthma as being under control. Furthermore, the majority of patients with uncontrolled asthma were not concerned about their disease (58.3%).

As a possible explanation for the overestimation of asthma control, Von Leupoldt, Brassen, Baumann, Klose, and Büchel (2011) have found evidence of long-term structural brain changes due to asthma. More specifically, the authors were able to show that neural habituation, which is correlated with the years lived with the disease, results in a systematic underestimation of symptom severity. In other words, the longer a patient suffers from asthma, the more the brain becomes accustomed to the symptoms, leading to a false perception of asthma control. Al-Kalemji et al. (2014) have gathered converging evidence in interview studies: patients state that they struggle to estimate the severity of symptoms correctly because over the years they have gradually adapted to them.

In summary, considering the high risks associated with uncontrolled asthma and the limited window of opportunity for stopping asthma attacks, the systematic overestimation of asthma control is very alarming and must be addressed. However, the monitoring of asthma control falls within the personal responsibilities of patients and thus cannot be improved without their involvement. Therefore, a crucial question is whether patients actually recognize it as an unmet need in their asthma care, or whether

they prioritize other disease-related needs. For this reason, this dissertation sets out to answer the following research question:

> ***RQ2a:*** *"What unmet needs do patients perceive in asthma care?"*

Together with its follow-up question, which will be derived in the next sub-section, this research question is of immediate importance for the overarching research question of the dissertation: only if patient needs are investigated and understood comprehensively, can additional value for patients in asthma care be created through digital medicine.

2.3.2.4 Attitudes

In addition to perceptions, attitudes towards asthma are important drivers of patient behavior and will be examined in the following. While this sub-section discusses general attitudes towards asthma and specific attitudes towards medication, the final section on patients' attitudes towards self-management is most relevant for this dissertation's overarching research question due to the suitability of self-management for digital medicine interventions (cf. Sub-section 2.3.1.3).

General attitudes The overall theme of patients' attitudes in the REALISE study was that patients do not want to make asthma an issue in their everyday lives: the majority of patients stated that they do not want to be labelled as sick (82%), they do not consider their symptoms to be serious (71.6%; 57.6% for patients with uncontrolled asthma), and they have a similar or better level of health than other people their age (70.6%). Furthermore, similar to the coping strategy of ignoring asthma, 42.8% of patients ignore asthma symptoms intentionally to feel normal and to fit in with their peers and friends (Price et al., 2014).

In the INSPIRE study, the authors investigated the perceived hassles of asthma: the panic when symptoms start to deteriorate, interferences with everyday life (both 73%), fear of requiring emergency medical attendance (54%), and attacks in front of other people (51%) were named as pain points by the majority of patients (Partridge et al., 2006). The study further revealed that while 85% of patients feel competent enough to intervene in time to prevent the deterioration of symptoms, 49% of patients are still afraid of severe asthma attacks despite using their medication as prescribed by a physician. Nevertheless, when symptoms deteriorate, 71% of patients reported to try to manage their asthma themselves instead of consulting a physician.

Medication In their qualitative synthesis review of 56 papers, Miles et al. (2017) found that patients often believe their asthma medications to have severe adverse side-effects, to be generally unsafe, and to lead to addiction and long-term dependence. Patients further reported that they are reluctant to use medication in high doses, even if prescribed by a physician. These findings are in line with the INSPIRE study, which found that 59% of patients are afraid of possible side-effects due to high doses, and that only 35% of patients would be willing to increase the dose of their controller medication to have as few symptoms as possible (Partridge et al., 2006).

Furthermore, trial and error approaches to medication dosage adjustment based on currently perceived symptoms are common, which was also observed by Al-Kalemji et al. (2014) in their interview study. Symptom-dependent adaption of medication dosage was also found in the REALISE study (i.e., 18% of patients only take their controller medication when they have symptoms; Price et al., 2014) and in the INSIPRE study (i.e., 34% of patients use their controller medication less than prescribed when they feel well, while 45% of patients use it more than prescribed when symptoms get worse; Partridge et al., 2006). In the latter study, 68% of patients stated that they adjust their controller medication based on symptom levels, 54% are worried about using too much medication when they feel well, and 39% do not believe that taking medication every day is necessary. Additionally, the REALISE study found that 41% of patients consider it a "real nuisance" to use their inhalers, 36% are ashamed of using inhalers in front of others, 26% are embarrassed carrying around an inhaler, and 14% find the inhaler difficult to use (Price et al., 2014, p. 6).

In summary, considering all these primarily negative attitudes towards medication, it is understandable that, contrary to the recommendations of the GINA guidelines, only 53% of patients with uncontrolled asthma and 48% of all patients use their controller medication daily (Price et al., 2014).

Self-management As argued in Sub-section 2.3.1.3, asthma self-management is well-suited for digitization. Therefore, patients' attitudes towards self-management are of particular interest for this dissertation. In their review, Miles et al. (2017) synthesize patients' attitudes towards self-monitoring. Skepticism about self-management was observed as a result of patients lacking the necessary training and materials to perform self-management properly. In a similar vein, patients did not believe that PEF monitoring provides any benefit to them, and assess their self-efficacy to be low for self-

management. Furthermore, patients were concerned that action plans were too general to apply in their specific situations, and therefore tended to rely on their own plans instead of the action plan. While the authors do not provide frequency figures for these sentiments due to their qualitative approach, these results suggest worrying attitudes towards self-management.

Miles et al. (2017) have also covered attitudes towards digital self-management interventions. They report that patients were often not willing to use digital interventions, also as a result of poor computer operating skills. This is somewhat contrary to Merchant et al. (2018a), who, in their evaluation of a smart inhaler intervention with 207 participants, found that 72% of patients were interested in continuing the intervention beyond the duration of the study. Furthermore, patients in this study stated that digital health interventions improve their self-efficacy for self-management. Nevertheless, many patients remain skeptical regarding the usage of digital health interventions. In their survey study of 186 patients with asthma, Simpson et al. (2017) have shown that only 12% would be willing to accept the recommendations of a digital self-management intervention for adjusting their treatment. This share of patients increases to 30% and 41% if the data basis for the recommendation is presented and the interventions are endorsed by a physician, respectively.

In conclusion, previous research has led to somewhat contradictory results in terms of patient attitudes towards digital self-management. Considering the relevance of digital self-management for the overarching research question of this dissertation, it is necessary to examine the conflicting findings in more detail and to comprehensively understand patient attitudes towards this topic. Therefore, this dissertation sets out to clarify the patients' attitudes towards digital self-management interventions and poses the following research question:

> ***RQ2b:*** *"What are the patients' attitudes towards digital self-management interventions for asthma?"*

In conjunction with RQ2a, this research question is part of the endeavor to identify opportunities for leveraging digital medicine's potential to create patient value in asthma care.

2.3.3 Value Creation for Patients through Digital Medicine

The objective of this dissertation is to propose a foundation for a digital pill for asthma that creates patient value by fulfilling unmet needs and creates medical value by potentially improving treatment outcomes. As discussed in the preceding sections, research and clinical practice consider asthma control and asthma attacks to be the two key outcomes for demonstrating medical value. With regard to asthma control, one major problem on the patient-side has been identified: patients' incorrect perceptions of asthma control puts them at risk of asthma attacks. Theoretically, solutions for this problem already exist (i.e., explicit self-monitoring of symptoms and/or objective lung function markers like PEF). However, the prevalence of regular self-monitoring and the reliability of patient-recorded measurements and assessments were found to be alarmingly low. The research presented in the last sub-sections suggests that this could be, at least in part, a consequence of coping styles, patients' disease perceptions, and patients' attitudes towards medication, self-management, and asthma in general.

2.3.3.1 Smartphone-based Passive Nocturnal Monitoring

Digital medicine may offer an innovative and promising solution for the above-mentioned issues: by exploiting a smartphone's sensing capabilities and computational power, digital biomarkers for asthma can be automatically measured to enable passive and unobtrusive disease monitoring. This monitoring approach, which was introduced in Sub-section 2.2.2.4, has the potential to improve asthma control overestimation, low adherence to self-monitoring, and low reliability of patient-recorded data. More specifically, smartphone-based passive monitoring is objective, it requires very little effort or motivation, and it is largely independent of any patient factors that often undermine self-monitoring adherence.

This dissertation argues that passive and unobtrusive monitoring could create both medical value and patient value. Medical value can be created by providing objective and reliable intervention cues to patients when their asthma worsens, so that the often-observed overestimation of asthma control (Gillissen, 2015) can be corrected. In this way, a patient's window of opportunity for attack abortion can be restored without the need for costly interventions. For example, following the treatment adjustment instructions in a written asthma plan could be performed independently by patients in a cost- and time-effective manner. Indeed, interventions based on passive asthma control monitoring seem promising considering patients' confidence in the self-adjustment of

their medication (cf. Sub-section 2.3.2.4) and the fact that the key intervention requirements are already in place (e.g., written asthma action plans as part of the standard of care, the widespread adoption of smartphones, and the availability of asthma medication in-situ).

Patient value, on the other hand, can be created by addressing two of the most prominent pain points for patients, namely the impairments in their everyday life due to unnoticed gradual symptom deteriorations and the widespread fear of unexpected asthma attacks. Contrary to all currently available alternatives for monitoring asthma, the proposed passive and unobtrusive approach would only require minimal effort, thereby making it compatible with virtually all coping styles and attitudes towards asthma. Even for patients who tend to ignore their asthma and trivialize their symptoms, such an approach could be attractive due to its suitability for everyday use.

2.3.3.2 Proposition of a Digital Asthma Pill Foundation

To enable passive monitoring, digital biomarkers are required that can be measured automatically by means of a smartphone. As described in Sub-section 2.2.2.4, research in mobile sensing has identified two symptoms fulfilling this criterion: cough and sleep quality. Marsden and colleagues (2016), for example, were able to show that cough in general, and nocturnal cough in particular, are associated with asthma control. This also holds for sleep quality (Luyster et al., 2012). Therefore, this dissertation proposes the following foundation of a digital pill for asthma: *a smartphone-based system to monitor a patient's cough and sleep quality passively at night with the objectives of assessing asthma control and predicting asthma attacks*.

Besides potentially creating patient value and medical value, such a digital pill foundation also seems promising from a research and technology perspective.

From a research perspective, nocturnal cough and sleep quality could serve as proximal outcomes for just-in-time adaptive interventions (Nahum-Shani, Hekler, & Spruijt-Metz, 2015) or as surrogate endpoints (Fleming & DeMets, 1996) in asthma research. This could facilitate future studies in asthma as the efficacy of interventions could be continuously assessed, thereby enabling adaptive clinical trials (Pallmann et al., 2018).

From a technology perspective, such a system could be incorporated into digital interventions that employ devices with similar sensing and computational capabilities – without any additional substantial development costs. This opportunity clearly

illustrates the scalability of digital medicine since the system could be scaled not only to smartphones, but also to other devices such as smart home assistants.

The importance of scalable technology in enabling innovative research is evident in the domain of physical activity. In recent years, the emergence and widespread adoption of technology capable of counting steps in a scalable way (i.e., smartphones and wearables) has led to an explosive growth in physical activity research (Vandelanotte et al., 2016). Furthermore, connected pedometer technology has enabled research to gain additional insights into interventions for elevating physical activity in everyday life through micro-randomized controlled trials (e.g., Kramer et al., 2019).

2.3.3.3 Nocturnal Cough and Sleep Quality as Candidate Digital Biomarkers

Mobile sensing research has demonstrated the feasibility of passively measuring nocturnal cough and sleep quality by means of a smartphone (cf. Sub-section 2.2.2.4). However, the medical usefulness of the two candidate digital biomarkers (CDBs) is less understood. The association strengths between the two CDBs and asthma control reported by prior research (i.e., Luyster et al., 2012; Marsden et al., 2016) can only be considered weak to moderate based on Cohen's (1988) and Evans' (1996) rules of thumb[16]. Furthermore, prior research was conducted cross-sectionally, which means it was investigating between-patient research questions. Therefore, both CDBs and their associations with asthma control remain uninvestigated on a within-patient level (e.g., trends and changes over time).

However, within-patient analyses are particularly important for the proposed digital pill foundation, as disease monitoring is a continuous task with a focus on within-patient changes in disease status (Coravos et al., 2019). Therefore, it remains unclear how useful these CDBs actually are for asthma control monitoring and asthma attack prediction in patients' everyday lives. Against this background, the third research question of this dissertation is as follows:

> ***RQ3:*** *"To what extent are nocturnal cough and sleep quality clinically useful digital biomarkers for asthma control?"*

[16] The correlation between nocturnal cough and asthma control is .30 (Marsden et al., 2016). For sleep quality, correlations with asthma control range from .31 to .36 (Luyster et al., 2012). Cohen classifies correlation strengths as follows: weak (r = .10 – .30), moderate (r = .30 – .50), and strong (r > .50). Evans' classification is as follows: very weak (r < .20), weak (r = .20 – .39), moderate (r = .40 – .59), strong (r = .60 – .79), and very strong (r > .80).

Please note that while RQ3 is concerned with the *clinical utility* of both CDBs, technological feasibility is not considered explicitly. Whether the two CDBs can be measured by a smartphone under real-life conditions to a sufficient degree of accuracy is beyond the scope of this dissertation. Nevertheless, the positive results of prior work in mobile sensing, which in the case of cough have also already been implemented in real-life conditions (e.g., Hoyos-Barceló et al., 2019), allow for an optimistic outlook in this regard.

2.3.3.4 Criteria of Clinical Utility

In contrast to RQ1 and RQ2, RQ3 is substantially more comprehensive due to the scope of the term *clinically useful*. Lesko, Zineh, and Huang (2010, p. 729) have described *clinical utility* as related to the "relevance and usefulness of an intervention in patient care" and that its evaluation is "[…] multidimensional and may include economic, clinical, and/or humanistic domains". However, as "[…] there is no consensus on its definition or how to robustly demonstrate it to the satisfaction of multiple stakeholders" (p. 729), this dissertation assesses clinical utility based on five criteria that are specific to the digital pill foundation proposed in this sub-section. The five assessment criteria for CDBs, their corresponding research questions, and their relation to clinical utility are illustrated in Figure 2.11 and Figure 2.12. In the following, the five criteria, namely *patient acceptance*, *persistence*, *statistical significance*, *monitoring performance*, and *prognostic performance*, will be introduced.

Patient acceptance Dillon (2001) defined acceptance as the "willingness within a user group to employ information technology for the tasks it is designed to support" (p. 1). Thus, patients must be willing to use a digital pill based on automated nocturnal monitoring in everyday life, despite the inherent privacy invasion. Without patient acceptance, the proposed foundation is unlikely to be adopted in practice and is therefore of very limited clinical utility.

Persistence In econometric literature, persistence is defined as the extent to which shocks to a serially measured variable propagate over time (Nelson, 1990). It is particularly relevant for the suitability of nocturnal cough and sleep quality as *monitoring biomarkers*. Califf (2018) emphasizes that monitoring biomarkers serves the purpose of serially inferring disease status (e.g., asthma control). While asthma control may change over time, it is usually assessed over a span of one or multiple weeks (cf. Table 2.1), which suggests a certain temporal stability of asthma control. For sensible

serial and continuous monitoring, the measured CDBs need to be persistent – a biomarker that fluctuates unpredictably between consecutive days is not useful for the serial assessment of disease status and is hence not suitable for disease monitoring.

Statistical Significance The first two criteria are insufficient to demonstrate clinical utility, as associations of the biomarkers with disease outcomes are not yet considered. Starting with the third criterion, namely statistical significance, clinical utility emerges. However, a statistically significant association between the CDBs and asthma outcomes will not suffice to fulfill this criterion – additional requirements regarding variance decomposition need to be satisfied: in contrast to diagnosis (and diagnostic biomarkers), where variance between patients is decisive, monitoring and prognosis requires a statistically significant association between biomarker and outcomes on a within-patient level (Collins, Reitsma, Altman, & Moons, 2015). To demonstrate an association between biomarker and outcome on a within-patient level, longitudinal data with repeated measurements per patient are required (Collins et al., 2015).

Monitoring Performance and Prognostic Performance Monitoring performance (fourth criterion) and prognostic performance (fifth criterion) advance the notion of associations between the CDBs and asthma outcomes. More specifically, these two criteria examine the extent to which intervention-oriented classifications of disease status or events are possible. For monitoring performance, the disease status to assess occurs in the same time frame as the biomarker measurement, while for prognostic performance the biomarker measurement has to precede the event (Califf, 2018; Coravos et al., 2019). For prognostic performance, the time factor is particularly important: if biomarkers enable valid classifications, but only after the tipping point for irreversible asthma attacks has passed, they are hardly of any use for asthma care (Honkoop et al., 2013). Furthermore, prognostic performance in particular increases clinical utility (cf. Figure 2.11): a sufficiently early detection of asthma attacks may serve as an unambiguous intervention cue for restoring a patient's window of opportunity for attack abortion.

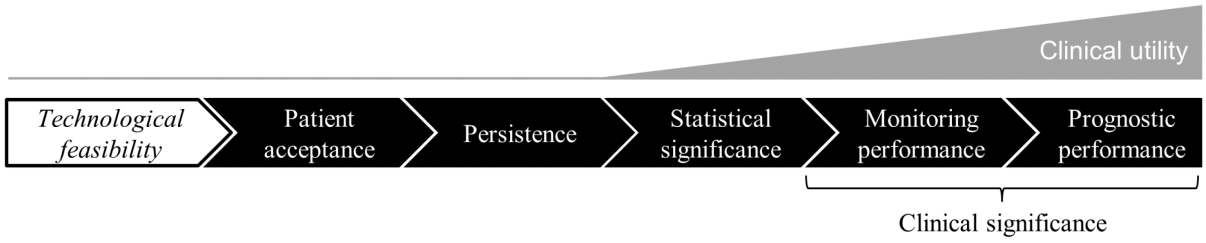


Figure 2.11. Assessment of clinical utility.

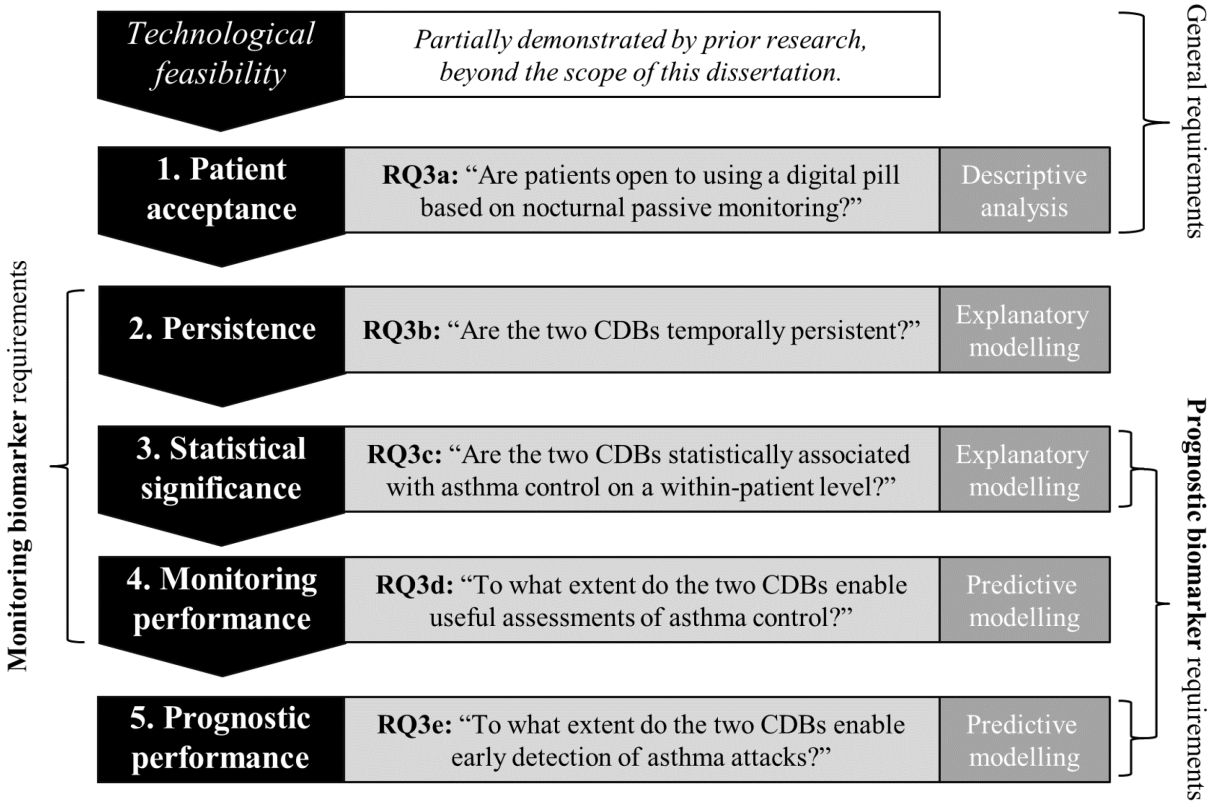


Figure 2.12. The five postulated clinical utility criteria and their corresponding research questions for evaluating the clinical utility of the two condidate digital biomarkers (CDBs).

In addition to the criteria and their research questions, Figure 2.12 contains two additional pieces of information. Firstly, the general analysis approach differs by criterion. For patient acceptance, a descriptive analysis of patient attitudes will be employed to gather the necessary insights. In the second and third criteria, the objectives are statistical inferences, therefore explanatory modelling will be applied (i.e., exploit all available data to explain relationships between variables by means of statistically significant patterns; Shmueli, 2010). The fourth and fifth criteria, however, are concerned with *biomarker performance* (Bossuyt, 2010) and thus should be analyzed by means of predictive modelling (i.e., split the data set, use one part of it to build classification models, and evaluate their performance subsequently on the remaining, unseen data; Breiman, 2001; Shmueli, 2010). Secondly, while the first criterion, patient acceptance, is required for both monitoring and prognostic biomarkers, the importance of later criteria differ by type of biomarker. As argued in the previous paragraphs, persistence, statistical significance, and monitoring performance are requirements for

monitoring biomarkers. Prognostic biomarkers also require statistical significance and prognostic performance, but not necessarily persistence: risk assessments for future events, like asthma attacks, can, for example, be based on singular anomalies (e.g., Honkoop et al., 2013).

2.3.3.5 Biomarker Development Pipeline

In summary, RQ3 examines the clinical utility of nocturnal cough and sleep quality as monitoring biomarkers and prognostic biomarkers for asthma care by virtue of five criteria. By evaluating biomarker performance for monitoring (fourth criterion) and prognosis (fifth criterion), this dissertation strives to assess whether the two CDBs are sufficiently performant to trigger interventions. In this way, the fourth and fifth criterion quantify the CDBs' potential for application in practice, or, in other words, their clinical significance (Collins, 2019). However, the criteria outlined in the last sub-section do not represent a conclusive evaluation of the two CDBs. Since biomarker performance tends to differ considerably between contexts (e.g., based on care setting (inpatient vs. outpatient), reference standard, and definition of the target condition; Bossuyt, 2010), biomarker development traditionally encompasses multiple stages and studies (Institute of Medicine, 2010). Figure 2.13 illustrates an exemplary biomarker development pipeline following Collins and colleagues (2015), and contextualizes the clinical utility criteria listed in Figure 2.11 and Figure 2.12.

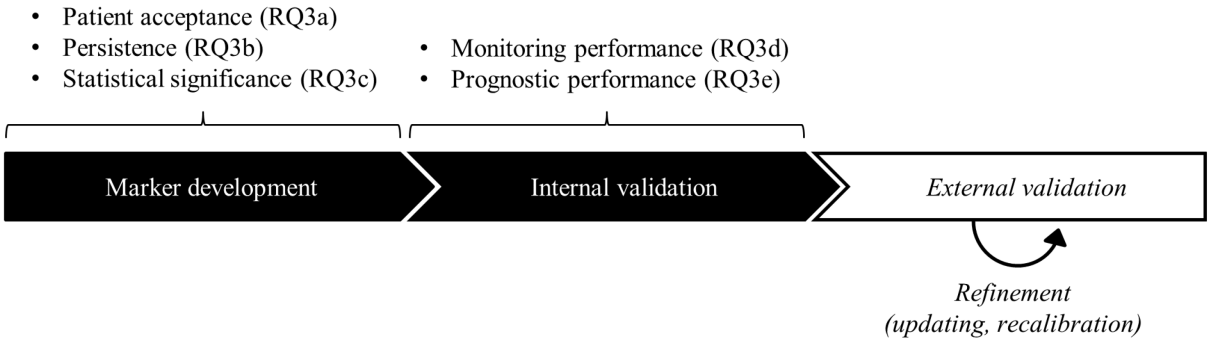


Figure 2.13. Biomarker development pipeline. Adapted from Collins et al. (2015)

In conclusion, RQ3 is concerned with biomarker development and internal validation (i.e., predictive modelling based on, for example, cross-validation with unseen cases; Collins et al., 2015). External validation, which is the application of a CDB to a novel data set (and not only on unseen observations from the same data set it was developed with), as well as refinement of both CDBs for novel contexts are beyond the scope of this dissertation.

Chapter 3

Review of Asthma Apps

3.1 Introduction and Related Work

The objective of this chapter is to provide insights into the practice of smartphone-based self-management interventions that have already been adopted, namely asthma apps[17]. More specifically, the research presented in this chapter investigates the potential of publicly available asthma apps to improve asthma self-management, thereby addressing RQ1 derived in Sub-section 2.3.1.3.

Whereas single studies have indicated that asthma apps can indeed be effective tools for supporting patients in their self-management (Ahmed et al., 2016; Cook, Modena, & Simon, 2016), reviews of asthma apps come to either ambiguous (Marcano Belisario et al., 2013) or rather disappointing conclusions regarding the value of apps for improving asthma self-management (Huckvale, Car, Morrison, & Car, 2012; Huckvale, Morrison, Ouyang, Ghaghda, & Car, 2015). These reviews mainly based their conclusions on a lack of methodologically sound studies (Marcano Belisario et al., 2013) and the limited application of medical guidelines (Huckvale et al., 2012; Huckvale et al., 2015).

Although an evidence base is highly desirable for health apps in general, it is unrealistic to expect app developers to conduct clinical studies or to hire clinical experts as consultants. The reasons for this are, among others, the high costs and difficulty of clinical research (Hulley, Cummings, Browner, Grady, & Newman, 2013). Additionally, app stores do not require developers to disclose the evidence base of an app (e.g., Apple App store; Apple Inc., 2016). MHealth apps are also not always

[17] In this chapter, the term *asthma apps* is used to specify smartphone-based self-management interventions that work on a stand-alone basis (i.e., outside of clinical studies and without physician involvement). Please refer to Sub-section 2.3.1.3 for further clarification of the terminology.

comprehensively regulated by public authorities (e.g., in the United States, the FDA (2015) only regulated a subset of the available apps when this research was conducted). Even though patients tend to consider the evidence base as an important selection criterion for mHealth apps (Dennison, Morrison, Conway, & Yardley, 2013), they are often not able to make an informed judgment regarding these characteristics of an app (Anderson, Burford, & Emmerton, 2016). All these factors contribute to the fact that patients continue to use publicly available asthma apps regardless of missing validation studies or an app's limited application of medical guidelines.

Therefore, it is necessary for clinical practice to develop a more comprehensive understanding of the value that publicly available asthma apps might offer for patients. Research pursuing this objective would need to address the limitations of the aforementioned reviews, which have focused exclusively on peer-reviewed papers and not on publicly available apps (Marcano Belisario et al., 2013), or have focused on qualitative analysis of app content without applying review frameworks with quantifiable results (Huckvale et al., 2012; Huckvale et al., 2015).

To overcome these shortcomings, this review applies review frameworks, such as behavior change techniques (Abraham & Michie, 2008) and gamification taxonomies (Thiebes, Lins, & Basten, 2014). Thereby, it quantifies the characteristics of asthma apps. By making use of such frameworks, it investigates the potential of well-adopted asthma apps to support patients in their self-management, even if clinical evidence is not available. In the next section, a functional definition of the term *app potential* is provided. The definition consists of specific requirements that an asthma app should fulfill in order to enable a positive effect on a patient's asthma self-management.

3.2 Methods

3.2.1 Overview

In this review, an app's potential to support patients in their disease management is defined as the degree to which an app fulfills the following four requirements: an app has to contain some kind of *active ingredient*, that is, functions supporting patients in their disease management (R1); similar to traditional asthma self-management programs offered by health care entities (Global Initiative for Asthma, 2018), an app should be able to change or guide behavior relevant for effective asthma self-management (R2);

an app should motivate the patient to use the app to deliver the active ingredients (R3); and an app has to be of adequate quality (e.g., functionality and aesthetics of an app) to guarantee a sufficient implementation quality of the other postulated requirements (R4).

More specifically, this review addresses R1 by reviewing available functions (similar to Huckvale et al. (2012) and Huckvale et al. (2015)), R2 by applying a taxonomy of behavior change techniques (Abraham & Michie, 2008), R3 by rating a taxonomy of gamification components (Thiebes et al., 2014), and R4 by using the Mobile Application Rating Scale (MARS; Stoyanov et al., 2015).

3.2.2 Systematic Search

The second author of the published manuscript searched the term "asthma" in the US versions of the two most popular app stores: Google Play store and Apple App store (IDC Research, 2016). The latest app search was conducted on April 10, 2016. In total, 523 apps were identified (Figure 3.1).

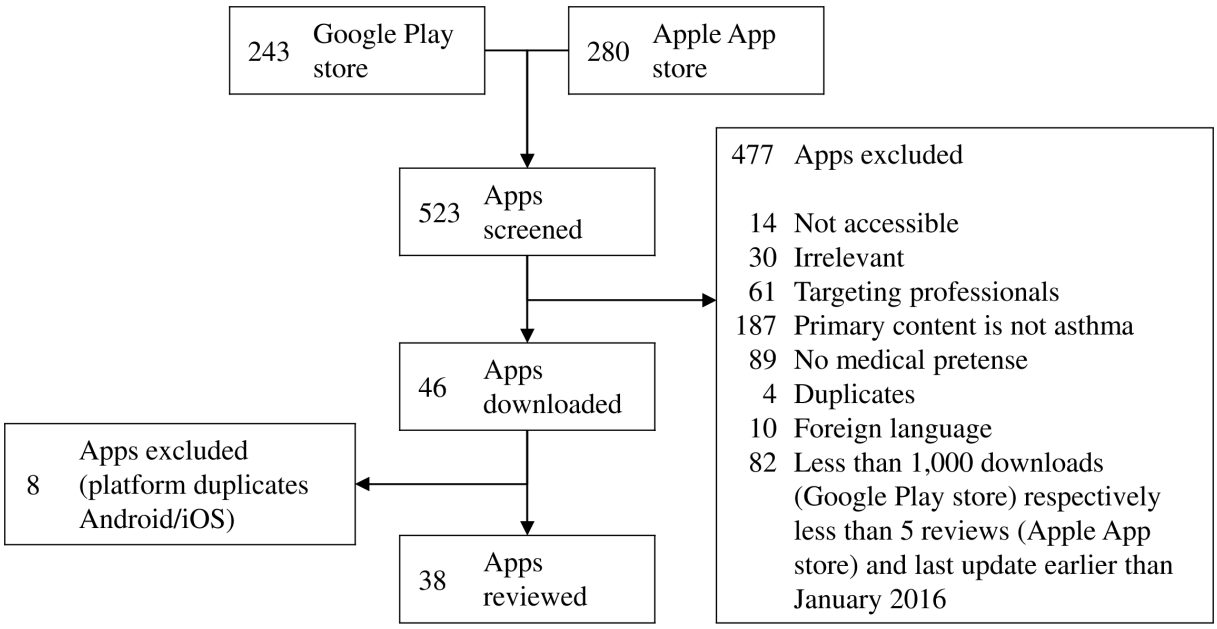


Figure 3.1. Systematic search and exclusion criteria.

3.2.3 Inclusion and Exclusion Criteria

The strategy for app selection was to include publicly available and well-adopted apps that are designed specifically for asthma. To identify these apps, the following exclusion criteria were applied: no access (e.g., only accessible through a special health program),

irrelevance (i.e., apps completely unrelated to asthma), target group are professionals (e.g., apps supporting physicians), primary content is not asthma (e.g., general weather or nutrition apps with very limited ancillary functions dedicated to asthmatics), no medical pretense (e.g., yoga and acupressure apps), duplicates (i.e., different versions of the same app with marginally different functions), and foreign language (i.e., apps not in English). To ensure that relatively well-adopted apps are reviewed, apps with less than 1000 downloads (Google Play store) or less than five reviews (Apple App store) were excluded.

Because the number of downloads or reviews of an app depends on its release date, apps with less than 1000 downloads (Google Play store) or five reviews (Apple App store) were not excluded if they were updated in 2016. Otherwise, a selection bias against recently released apps would have occurred. In fact, ten otherwise excluded apps remained in this review due to this criterion (i.e., four Android and six iPhone operating system (iOS) apps).

Based on the specified criteria, 477 apps were excluded. The remaining 46 apps were checked for duplicates between the two platforms (i.e., Android and iOS). After excluding eight duplicates, the systematic search yielded 38 apps to review.

3.2.4 Review Process

The review process consisted of two main steps. First, basic information about the app was gathered from the corresponding app store (e.g., app description, date of last update, developer, number of downloads if available, number of user reviews, and average rating). Only publicly available data, which was directly extracted from the app stores, was used in this process. Additionally, an app's website was consulted if available.

Second, the four requirements for app potential were evaluated. Except for the MARS framework, for which multiple mobile phones and tablets were used (i.e., Huawei P9 Lite, HTC M9, LG Leon 4G LTE, iPad Air 2, and iPhone 6), apps were reviewed on a LG Leon 4G LTE (Android) and iPhone 6 (iOS). In the next section, the measures of the four app potential requirements are introduced in more detail.

3.2.5 Measures of App Potential Requirements

3.2.5.1 App Functions (R1)

An exhaustive list of all existing functions was developed through a bottom-up review approach: whenever a function was encountered that was not yet specified in the list, it was expanded accordingly. In this way, a total of 42 functions was identified. Afterwards, the available functions were assessed in all apps based on the complete list.

Additionally, functions were grouped post hoc into four categories: tracking (e.g., of peak flow values), information (e.g., about asthma symptoms), assessment (e.g., indicating asthma control by color-coding peak flow values), and notification functions (e.g., medication intake reminder). These function categories are conceptually identical to prior app reviews (Huckvale et al., 2012; Huckvale et al., 2015), except for one difference: the category of therapeutic tools was replaced with notification functions. Reasons for this are the low prevalence of therapeutic tools in asthma apps (Huckvale et al., 2015) and the potential utility of notification functions for asthma self-management (e.g., as reminders for physician appointments; Ornstein, Garr, Jenkins, Rust, & Arnon, 1991).

3.2.5.2 Potential to Change Behavior (R2)

Many reviews have applied behavior change technique taxonomies as measures of behavior change efforts in health interventions and apps (Gardner, Smith, Lorencatto, Hamer, & Biddle, 2016; Martin, Chater, & Lorencatto, 2013; Mercer, Li, Giangregorio, Burns, & Grindrod, 2016). However, to the best of the authors' knowledge, they have not yet been applied to the domain of asthma apps.

In this review, the application of the 26 behavior change techniques proposed by Abraham and Michie (2008) was rated for each app. Ratings were dummy coded (1 = "technique fully applied", 0 = "technique not applied"). The first and second author of the published manuscript agreed on explicit rating criteria and related functions for all behavior change techniques (e.g., social network functions enable the application of the behavior change techniques "provide information about other's approval," "provide opportunities for social comparison," and "plan social support or social change"). This approach addressed the issue of mediocre interrater reliability for some of the behavior change techniques (i.e., whereas the mean kappa values ranged from .74 to .82 in the original publication, 20 out of 71 kappa scores (28%) were below .70 (Abraham &

Michie, 2008)). By applying explicit and objective rating criteria, the process of rating behavior change techniques was facilitated, and rating ambiguity was reduced. Differences in ratings between the first and second author were resolved in discussions.

In some instances, a behavior change technique was rated as partially applied (.50). This was the case if an app fulfilled the application criteria only partially (e.g., nonadjustable task reminder for "time management") or if an agreement between the first and second author could not be reached.

3.2.5.3 Potential to Promote App Use (R3)

Gamification is a promising way to promote the use of information technology (IT) systems such as mobile apps (Hamari, Koivisto, & Sarsa, 2014; Thiebes et al., 2014). A taxonomy of 31 gamification components (Thiebes et al., 2014) was applied to rate an app's potential for motivating app use. Similar to the rating process of behavior change techniques, the first and second author agreed on an explicit list of relevant rating criteria and related functions for gamification components. Again, dummy coding was used for rating gamification components and partially implemented components were considered (1 = "gamification component fully applied", .5 = "gamification component partially applied", and 0 = "gamification component not applied"). Differences in ratings were resolved in discussions between the first and second author and may have resulted in rating a gamification component as "partially applied".

In addition to listing individual gamification components, the applied taxonomy groups individual gamification components into five categories: system design (seven components), challenges (three components), rewards (six components), social influences (eleven components), and user specifics (four components). The original publication provides comprehensive definitions of each category (Thiebes et al., 2014).

3.2.5.4 App Quality (R4)

Four of the authors of the published manuscript participated in rating app quality by means of the MARS framework (Stoyanov et al., 2015). However, the ratings of the first and second author were averaged due to their close cooperation in the rating process, thereby preserving independency of ratings. The MARS framework contains 19 items on a 5-point Likert scale (1 = inadequate, 2 = poor, 3 = acceptable, 4 = good, and 5 = excellent) to assess app quality. Items are grouped into four subscales: engagement (5

items), functionality (4 items), aesthetics (3 items), and information quality (7 items). The average of the four scales determines the app quality score.

One item from the information quality scale requires a literature search regarding clinical efficacy. PubMed and Google Scholar were searched using the following term: [%app name%] AND [“randomized controlled trial”/”RCT”] OR [“study”]. Literature inclusion criteria were published in a peer-reviewed journal, clearly defined outcome construct that is a valid measure for asthma (e.g., peak flow values) and description of the applied study design.

Additionally, MARS contains a subjective quality scale that measures the subjectively perceived app quality. This scale consists of four 5-point Likert scale questions regarding personal recommendation, potential future usage, willingness to pay for an app, and an overall star rating.

MARS is an objective (intraclass correlation coefficient (ICC) between raters = .79) and highly reliable scale (alpha = .90). As recommended by the authors of MARS (Stoyanov et al., 2015), all raters participated in a workshop regarding the application of the framework. This workshop was based on the MARS training video (Stoyanov, 2016).

3.2.6 Statistical Methods

To assess the status quo of app potential in asthma apps, ratings were analyzed descriptively. ICC between raters were computed as a measure for interrater reliability of the MARS scales. Finally, correlations between the aggregated framework scores were calculated.

3.3 Results

3.3.1 General App Characteristics

Out of the 38 reviewed apps, 13 apps were available for both iOS and Android (34%). The remaining apps were exclusively developed for either iOS (16/38, 42%) or Android (9/38, 24%). The vast majority of apps was free of charge (36/38, 95%). In-app purchases were offered in seven apps (18%, 7/38). Additionally, eight apps contained some form of advertising (21%, 8/38).

Most apps were developed in the United States (14/38, 37%), followed by Switzerland (4/38, 11%), Australia, India, Spain, the United Kingdom (each 2/38, 5%), Germany, Portugal, Lithuania, Latvia, and the Czech Republic (each 1/38, 3%). Private companies accounted for the development of half of the apps (n = 19), independent developers for nine apps (24%, 9/38), and university hospitals and health-related foundations for four apps each (11%, 4/38). Both nonprofit organizations and governmental nonprofit bodies were responsible for one app each (3%, 1/38). Almost half of the apps claimed that they involved health care entities in the development process (16/38, 42%).

In general, a wide range in the distinct app characteristics became apparent (Table 3.1). The range was particularly noticeable in the category "days since last update": one app was updated just two days before the review deadline ("e-symptoms"), whereas "Asthma Journal Free" was last modified over 6 years ago. On average, apps were not updated for approximately more than 1 year and 4 months.

Table 3.1. Overview general app characteristics.

App characteristics	n (%)	Mean (SD)	Median (IQR)	Range
Paid apps and price (USD)	2 (5)	3.49 (2.12)	3.49 (1.50)	1.99-4.99
Average user rating (iOS)	15 (39)	3.53 (0.90)	3.50 (1.00)	1.50-5.00
Average user rating (Android)	22 (58)	3.94 (0.51)	3.90 (0.50)	3.00-5.00
Number of ratings (iOS)	29 (76)	22.52 (58.26)	5 (16)	0-304
Number of ratings (Android)	23 (61)	47.35 (87.72)	17 (48.50)	0-419
Number of downloads (Android) [a]	23 (61)	5275.43 (8189.73)	3000 (4725)	30-30,000
Days since last update	38 (100)	498.63 (601.65)	177 (922)	2-2231

Note: [a] The Google Play store reports download numbers in ranges (e.g., "10-50"). These values were standardized by calculating the mean of the minimum and maximum (e.g., 10-50 downloads equals 30 downloads). SD: Standard deviation; IQR: Interquartile range.

3.3.2 Evaluating App Potential

3.3.2.1 App Functions (R1)

Tracking functions were the most common function category. Out of all 38 apps, 30 apps (79%) offered at least one of the following functions: peak flow tracking (23/38, 61%), medication tracking (22/38, 58%), symptom tracking (19/38, 50%), trigger tracking (18/38, 47%), notes (15/38, 39%), clinical asthma questionnaires (14/38, 37%), sleep tracking (11/38, 29%), health parameter tracking (9/38, 24%), medical

appointment tracking (8/38, 21%), location tracking (6/38, 16%), asthma attack tracking (4/38, 11%), accomplishment tracking (3/38, 8%), snapshots (3/38, 8%), score tracking of games and quizzes (2/38, 5%), tracking through Apple or Google Health (2/38, 5%), and medication package size tracking (1/38, 3%). Except for apps using Apple or Google Health for physical activity tracking and location tracking over the global positioning system (GPS), all parameters had to be entered manually. Additionally, 26 apps (68%, 26/38) provided functions to record the tracked values over time through diaries (e.g., calendars) and logs (e.g., lists and charts).

A total of 26 apps (68%, 26/38) incorporated at least one of the following information functions: therapeutic information or instruction (22/38, 58%), general asthma information (20/38, 53%), medication information or instruction (16/38, 42%), first aid information or instruction (10/38, 26%), inhaler technique guidance (10/38, 26%), app tutorial (9/38, 24%), peak expiratory flow information or instruction (9/38, 24%), news (8/38, 21%), air quality (7/38, 18%), information through doctor dashboard (4/38, 11%), information through games or quizzes (3/38, 8%), and clinic or pharmacy locator (2/38, 5%).

Assessment functions can be considered an extension of tracking functions by providing an interpretation or evaluation of recorded values. Twenty apps (53%, 20/38) offered one or more of these functions: decision support (14/38, 37%), peak flow classification (9/38, 24%), adjustable asthma action plan (5/38, 13%), standardized asthma action plan (4/38, 11%), and symptom forecast (1/38, 3%).

The least common category was notification functions. A total of 18 apps (47%, 18/38) notified the user in at least one of the following contexts or events: medication intake (12/38, 32%), asthma questionnaire reminder (7/38, 18%), peak flow reminder (7/38, 18%), alert notification to health care professionals (7/38, 18%), medical appointment reminder (6/38, 16%), news notification (4/38, 11%), adjustable task reminder (3/38, 8%), weather and pollen notification (1/38, 3%), and medication package depletion (1/38, 3%).

In summary, the most widespread functions in asthma apps were tracking and information functions. More specifically, providing therapeutic information or instruction, general asthma information, as well as tracking of peak flow values, medications and symptoms were implemented by at least half of all apps.

3.3.2.2 Potential to Change Behavior (R2)

On average, apps applied 7.12 (standard deviation (SD) = 4.46) of the 26 behavior change techniques (B1-B26). The amount of applied techniques ranged from 1 ("Asthma Treatment") to 19 ("Wizdy Pets").

The fraction of behavior change techniques rated as "partially applied" was negligible (27/988 ratings, 2.7%). For the sake of simplicity and interpretability, only behavior change techniques rated as "fully applied" are reported in this section and in Figure 3.2. The prevalence of behavior change techniques in asthma apps varied considerably between techniques. To aggregate findings, behavior change techniques were divided into four categories based on their application frequency: no application at all (i.e., technique not applied by any app resulting in an application frequency of 0%), seldom applied (i.e., technique applied by one to nine apps resulting in an application frequency between 0-25%), considerable application rates (i.e., technique applied by ten to 19 apps resulting in an application frequency between 25-50%), and frequent application (i.e., technique applied by 20 to 28 apps resulting in an application frequency between 50-75%).

Four behavior change techniques were not applied at all: provide general encouragement (B6), teach to use prompts or cues (B15), stress management (B24), and motivational interviewing (B25).

The nine seldom applied techniques were set graded tasks (B7; 3/38, 8%), provide contingent rewards (B14; 2/38, 5%), agree on behavioral contract (B16; 9/38, 24%), provide opportunities for social comparison (B19; 1/38, 3%), plan social support or social change (B20; 1/38, 3%), prompt identification as a role model (B21; 1/38, 3%), prompt self-talk (B22; 2/38, 5%), relapse prevention (B23; 6/38, 16%), and time management (B26; 8/38, 21%). Seven techniques were applied with considerable frequency: provide information about other's approval (B3; 11/38, 29%), prompt intention formation (B4; 13/38, 34%), prompt barrier identification (B5; 16/38, 42%), model or demonstrate the behavior (B9; 10/38, 26%), prompt specific goal setting (B10; 10/38, 26%), prompt practice (B17; 12/38, 32%), and use follow-up prompts (B18; 12/38, 32%).

The list of the most commonly applied behavior change techniques in mHealth asthma apps contained six techniques: provide information about behavior-health link (B1; 20/38, 53%), provide information on consequences (B2; 21/38, 55%), provide

instructions (B8; 21/38, 55%), prompt review of behavioral goals (B11; 28/38, 74%), prompt self-monitoring of behavior (B12; 28/38, 74%), and provide feedback on performance (B13; 22/38, 58%).

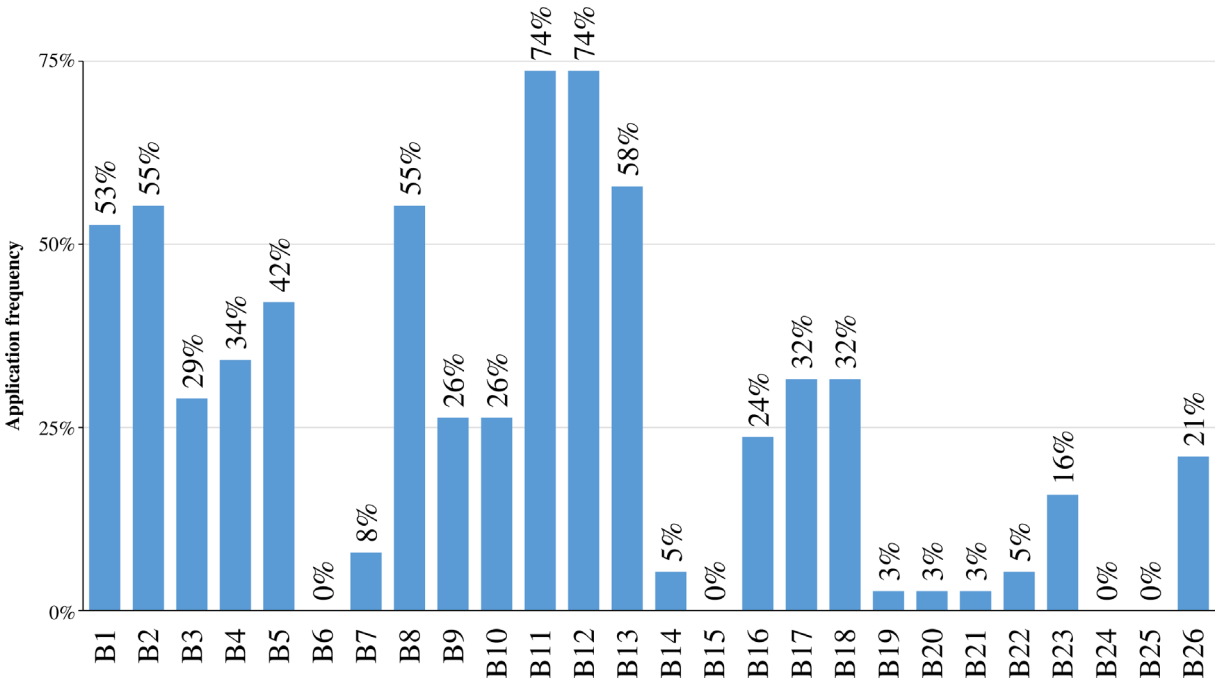


Figure 3.2. Application of behavior change techniques in asthma apps. Only fully applyied behavior change techniques (B1-B26; N=38) are considered.

3.3.2.3 Potential to Promote App Use (R3)

Asthma apps contained on average 4.89 gamification components (SD = 4.21) of a total of 31 components (G1-G31). The app with the most implemented gamification components was "WizdyPets" (n = 24.50), whereas "choO" integrated the fewest components (n = 0.50). Similar to the ratings of behavior change techniques, the amount of gamification components rated as "partially applied" can be considered insignificant (31/1178 ratings, 2.6%). Following the reporting logic from the previous section, only gamification components rated as "fully applied" are illustrated in Figure 3.3 and covered in this section.

Again, gamification components were grouped based on their prevalence into four categories: not implemented at all (i.e., component was not implemented by any app resulting in an implementation frequency of 0%), seldom implemented (i.e., component was implemented by one to nine apps resulting in an implementation frequency between 0-25%), considerably often implemented (i.e., component was implemented by ten to

19 apps resulting in an implementation frequency between 25-50%), and frequently implemented (i.e., component was implemented by 20 to 28 apps resulting in an implementation frequency between 50-75%).

In total, four gamification components were frequently implemented in the reviewed apps: feedback (G1; 22/38, 58%), meaning (G4; 20/38, 53%), shadowing (G22; 28/38, 74%), and ideological incentives (G29; 21/38, 55%). Two gamification components were considerably often implemented: reminder (G3; 12/38, 32%) and collaboration (G18; 11/38, 29%).

However, the vast majority of gamification components was seldom implemented: audible feedback (G2; 3/38, 8%), interaction concepts (G5; 9/38, 24%), visually resembling existing games (G6; 3/38, 8%), fantasy (G7; 2/38, 5%), goals (G8; 3/38, 8%), time pressure (G9; 1/38, 3%), progressive disclosure (G10; 2/38, 5%), ownership (G11; 2/38, 5%), achievement (G12; 2/38, 5%), point system (G13; 2/38, 5%), badges (G14; 2/38, 5%), bonus (G15; 1/38, 3%), loss aversion (G16; 1/38, 3%), status (G17; 1/38, 3%), reputation (G19; 1/38, 3%), social facilitation (G23; 4/38, 11%), conforming behavior (G24; 1/38, 3%), leaderboards (G25; 2/38, 5%), altruism (G26; 1/38, 3%), virtual goods (G27; 1/38,3%), user levels (G28; 1/38, 3%), virtual characters (G30; 1/38, 3%), and self-expression (G31; 1/38, 3%). Competition (G20) and envy (G21) were not implemented in the reviewed apps.

In addition to listing individual gamification components, the taxonomy groups individual gamification components into five categories: system design, challenges, rewards, social influences, and user specifics (Thiebes et al., 2014). Figure 3.4 illustrates how many apps implemented at least one component of the corresponding category.

In terms of gamification component category, system design components (e.g., feedback, reminder, and meaning) were implemented by almost every app (35/38, 92%). The majority of apps also made use of components from the categories social influences (28/38, 74%; e.g., leaderboards, competition, and reputation) and user specifics (21/38, 55%; e.g., user levels, virtual character, and self-expression). In contrast, challenges (i.e., goals, time pressure, and progressive disclosure) and rewards (e.g., achievements, point system, and badges) were applied very infrequently (each 3/38, 8%).

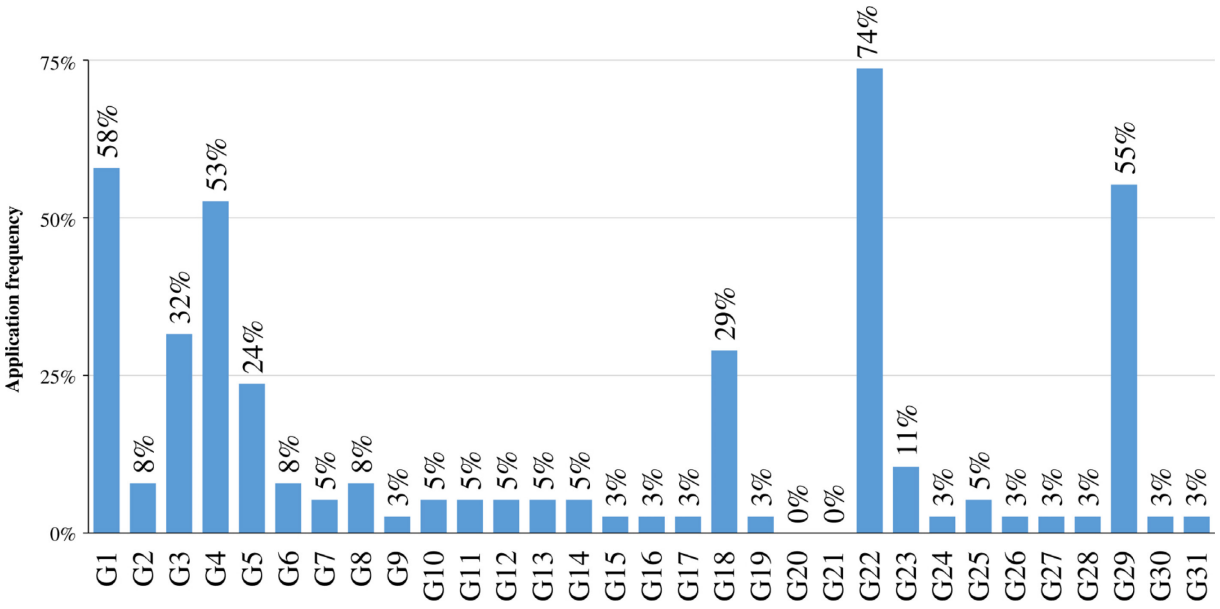


Figure 3.3. Application of gamification components in asthma apps. Only fully applied gamification components (G1-G31; N = 38) are considered.

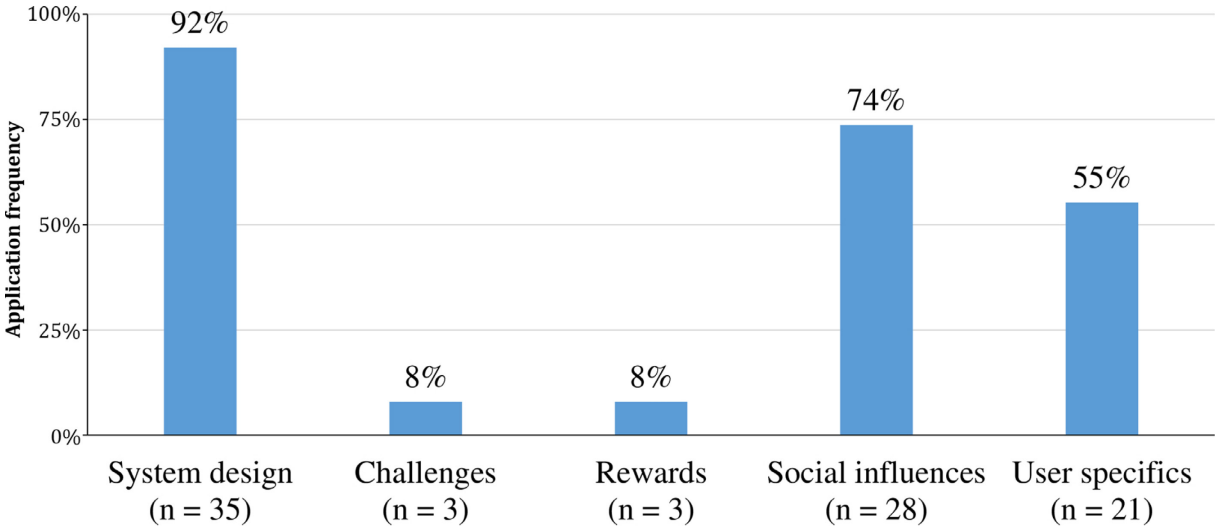


Figure 3.4. Application of gamification components by category. In order to count towards a category, at least one component of it had to be applied in the app (N = 38).

3.3.2.4 App Quality (R4)

The average quality of asthma apps can be considered marginally above acceptable (mean = 3.17), whereas average subjective app quality laid between poor and acceptable (mean = 2.65). In terms of MARS subscales, asthma apps performed worst in user engagement (mean = 2.77) and best in app functionality (mean = 3.55). Ratings for

aesthetics (mean = 3.12) and information quality (mean = 3.24) were rather mediocre (Table 3.2).

In the literature review, no study was identified that evaluated the efficacy of any of the included asthma apps. The only peer-reviewed papers to mention apps were app reviews or clinical communications (e.g., Wu, Carpenter, & Himes, 2015). Hence, the information quality mean was calculated from a maximum of 6 items. Additionally, eleven out of the 38 apps (29%) could not be assessed in some of the information quality items due to a lack of corresponding functions (e.g., no visualized information was provided that made it impossible to rate the visual information quality).

Considerable quality differences between apps emerged in the analysis. The range of app quality ratings and subjective app quality ratings reached from inadequate or poor (e.g., "Asthma" scored a 1.54 and a 1.00 in terms of app quality and subjective app quality) to almost excellent (e.g., "Wizdy Pets" scored a 4.55 and 4.50 in terms of app quality and subjective app quality).

Table 3.2. Descriptive results of Mobile Application Rating Scale scores (N=38).

MARS scales	**ICC [a,b]**	**Mean (SD)**	**Range**
Engagement	.92	2.77 (0.78)	1.00-4.73
Functionality	.72	3.55 (0.57)	1.75-4.42
Aesthetics	.72	3.12 (0.68)	2.00-4.78
Information quality	.88	3.24 (0.66)	1.40-4.33
Subjective quality	.85	2.65 (0.87)	1.00-4.50
App quality	.88	3.17 (0.58)	1.54-4.55

Note: [a] Intraclass correlations were calculated as a measure for interrater reliability in a two-way random model evaluating consistency among the three sets of ratings. [b] Interrater reliability was assessed based on the ratings of 37 apps. One app ("Asthma") was removed from the app store before it was rated by all raters. ICC: Intraclass correlation coefficient; SD: Standard deviation.

3.3.2.5 Summary of Requirements (R1 – R4)

Overall, the results demonstrate vast differences between apps in all of the investigated requirements of app potential (Table 3.3).

Table 3.3. Summary of all rated app potential requirements.

App potential requirements	Mean (SD)	Range	Scale
R1: functions			
Tracking functions	4.21 (3.39)	0-11.00	0-16.00
Information functions	3.21 (2.63)	0-8.00	0-12.00
Assessment functions	0.87 (0.98)	0-3.00	0-5.00
Notification functions	1.26 (1.65)	0-5.00	0-5.00
Functions (overall)	9.55 (5.73)	1.00-24.00	0-42.00
R2: behavior change techniques	7.12 (4.46)	1.00-19.00	0-26.00
R3: gamification components			
System design	2.20 (1.35)	0.50-4.00	0-7.00
Challenges	0.22 (0.60)	0-3.00	0-3.00
Rewards	0.26 (1.07)	0-6.00	0-6.00
Social influences	1.37 (1.24)	0-5.00	0-11.00
User specifics	0.84 (0.74)	0-4.00	0-4.00
Gamification components (overall)	4.89 (4.21)	0.50-24.50	0-31.00
R4: MARS scales			
Engagement	2.77 (0.78)	1.00-4.73	1.00-5.00
Functionality	3.55 (0.57)	1.75-4.42	1.00-5.00
Aesthetics	3.12 (0.68)	2.00-4.78	1.00-5.00
Information quality	3.24 (0.66)	1.40-4.33	1.00-5.00
Subjective quality	2.65 (0.87)	1.00-4.50	1.00-5.00
App quality	3.17 (0.58)	1.54-4.55	1.00-5.00

Note: Behavior change techniques or gamification components rated as "fully applied" and "partially applied" were included in the analysis. SD: Standard deviation; MARS: Mobile Application Rating Scale.

To synthesize the findings, associations between the different review frameworks were considered by calculating the corresponding correlation coefficients between the aggregated scores (Table 3.4). All correlations between review frameworks were significant. This pattern of correlations implies consistency of ratings between different review frameworks. In other words, apps that scored well in one review framework tended to also score well in all the other frameworks.

Table 3.4. Pearson correlations between aggregated review frameworks (N=38).

Aggregated review frameworks	Number of functions (R1)	Number of behavior change techniques (R2)	Number of gamification components (R3)
Number of behavior change techniques (R2)	.73**		
Number of gamification components (R3)	.33*	.80**	
MARS app quality (R4)	.38*	.56**	.62**

Note: All ratings of behavior change techniques and gamification components were included in the analysis (including techniques and components rated as "partially applied or implemented"). MARS: Mobile Application Rating Scale; * $p < .05$; ** $p < .001$

3.4 Discussion

3.4.1 Principal Findings

This review analyzed whether asthma apps have the potential to improve a patient's asthma self-management. For this purpose, different requirements of app potential were considered, namely available functions (R1), applied behavior change techniques (R2), implemented gamification components (R3), and general app quality (R4).

In terms of available functions (R1), asthma apps offered functions associated with active ingredients of effective self-management to a considerable extent (i.e., asthma education, self-monitoring of symptoms or peak flow values, regular review of treatment, and an action plan; Gibson et al., 2003). However, with regard to self-monitoring of symptoms and peak flow values, none of the apps offered options to track asthma-related parameters through mobile phone sensors. Without exploiting the full potential of today's technology (e.g., through automated tracking functions; Barata, Kowatsch, Tinschert, & Filler, 2016), therapeutic advantages of mobile phones cannot be fully realized (e.g., delivery of just in time adaptive interventions; Tinschert, Barata, & Kowatsch, 2017).

The investigated apps applied a number of behavior change techniques (R2). This finding implies that the apps could in principle enable behavior change relevant for asthma self-management. However, techniques related to stress management and motivational interviewing were not implemented at all. This is particularly striking because stress management is recommended by asthma guidelines (Global Initiative for

Asthma, 2018), and asthmatics tend to trivialize their disease symptoms (Rabe et al., 2000), which might result in a lack of long-term motivation for disease management.

In general, asthma apps also seemed to be able to motivate users through gamification components (R3) but with considerable differences between apps: the relatively high standard deviation of gamification components relative to its mean and its wide range imply that only a few apps have implemented gamification features to a significant extent. For example, the category "rewards" was rarely implemented: only three out of all 38 apps (8%) implemented at least one gamification component of this category. This is somewhat surprising as rewards usually belong to the most commonly implemented gamification components (Thiebes et al., 2014). Point systems, badges, and achievements can be implemented comparatively easy, and their effectiveness is backed by operant conditioning theory, one of psychology's most recognized theories (Staddon & Cerutti, 2003).

Furthermore, app quality varied widely (R4). In terms of MARS subscales, engagement scored worst. This may call into question the long-term engagement with asthma apps, a crucial factor for determining their value (Wu, 2016). In other domains like diabetes self-management, researchers have observed that long-term engagement of app users is generally limited (Tatara, Arsand, Skrovseth, & Hartvigsen, 2013). However, chronic diseases like asthma require long-term self-management (Global Initiative for Asthma, 2018). One potential way to improve long-term engagement, which has been successfully applied to physical activity, are interactions with digital coaches (Watson, Bickmore, Cange, Kulshreshtha, & Kvedar, 2012). Thus, developers of upcoming asthma apps might consider the implementation of digital coaches (e.g., chat bots) to enhance long-term engagement.

In summary, great variation in all of the investigated requirements of app potential was found. Therefore, an unequivocal conclusion whether currently available asthma apps have the potential to improve asthma self-management is neither reasonable nor possible. However, due to the high correlations between review frameworks, this review has shown that ratings are consistent across the four requirements of app potential. This implies that high quality apps tend to score well in all requirements for app potential. For example, "Asthma Health by Mount Sinai" which was ranked second best out of all 38 apps in terms of MARS app quality, performed also very well in terms of behavior change techniques (rank 2/38), gamification components (rank 4/38), and available functions (rank 3/38). On the other hand, one of the apps with the lowest MARS app

quality ratings ("Asthma Treatment"; rank 36/38) also scored extremely poorly in terms of behavior change techniques (rank 38/38), gamification components (rank 37/38), and available functions (rank 38/38). The consistency between frameworks facilitates the decision which asthma apps to recommend to patients: a promising decision strategy might be to pick one of the best rated apps; no trade-off between app potential requirements is necessary.

3.4.2 Limitations

In the definition of app potential used in this paper, no measure of long-term engagement was included. As mentioned before, long-term engagement is highly relevant for asthma apps in particular and mHealth apps in general. To the best of the authors' knowledge, there is no valid proxy that predicts long-term use reliably. App reviews and developers would highly benefit from the identification of such proxies, making it a promising field for future research.

Furthermore, apps that are not publicly available were excluded. This limits the generalizability of the results. For example, three apps, which were restricted to study participants and thus were not publicly available, have indicated promising results regarding efficacy (Cook et al., 2016; Merchant et al., 2016; Nkoy et al., 2019). Excluding not publicly available apps might have led to a systematic selection bias against apps with a greater potential for improving asthma self-management. The likely existence of such a bias is supported through the review of Farzandipour et al. (2017) who have shown that publicly not-available smartphone apps improved asthma control and quality of life in the majority of the reviewed studies (cf. Sub-section 2.3.1.3).

Another limitation of this review is that it did not contain a content analysis. It only assessed whether a function was implemented, but conclusions regarding its medical value are beyond the scope of this review. However, such an analysis was already conducted in prior reviews (Huckvale et al., 2012; Huckvale et al., 2015).

Finally, it should be noted that the app search for this review was conducted in April 2016. In the meantime, new apps might have been published in or the reviewed apps have been updated. Therefore, the results of this review do not necessarily reflect today's asthma app landscape. Nevertheless, the general patterns identified in this review provide valuable insights for understanding the potentials and shortcomings of

smartphone-based digital medicine interventions and can be used to inform the development of new apps.

3.4.3 Comparison to Prior Work

In general, this review extends the findings of previous reviews by focusing on the potential of apps for asthma self-management. Some of the findings are in line with prior research (Al-Durra, Torio, & Cafazzo, 2015; Huckvale et al., 2012; Huckvale et al., 2015; Marcano Belisario et al., 2013): the biggest concern regarding currently available apps is the lack of clinical validation. Not a single study demonstrating efficacy for any of the investigated apps could be identified. However, as argued above, this constraint might be limited to apps that are publicly available. Nevertheless, this review suggests that even without scientific proof for efficacy, at least some of the investigated apps still have the potential to improve asthma self-management. Therefore, a somewhat more positive conclusion regarding the value of asthma apps can be cautiously drawn in comparison with prior reviews (e.g., Huckvale et al. (2012) and Huckvale et al. (2015)). Among other factors, this may be due to the bottom-up research perspective focusing on app potential instead of an app's evidence base and the development that asthma apps have undergone since the last reviews have been conducted.

3.4.4 Contributions to Research

This review has analyzed the asthma app landscape based on recognized review frameworks. Thus, it can inform future research on asthma apps and digital interventions by providing a reference frame for the status quo in practice. Furthermore, all review frameworks were found to be highly intercorrelated (e.g., number of behavior change techniques and number of gamification strategies were correlated with .80). Correlations above .70 suggest convergent validity (Carlson & Herdman, 2012). This may have implications for the operationalization of behavior change techniques and gamification strategies. For example, it could be argued that merging both review frameworks into one novel joint framework could facilitate future reviews in this field. Furthermore, the app review has identified an implementation gap in terms of mobile sensing, which could be addressed by future research.

3.5 Conclusion and Implications

This review has found that the potential of apps to improve asthma self-management varies considerably between apps. It seems likely that at least some of the publicly available asthma apps have the potential to improve asthma self-management, even though the lack of clinical studies makes it impossible to assess whether these apps actually do improve asthma outcomes. However, one critical limitation of asthma apps was identified: the asthma apps that are currently available do not take full advantage of today's technology, especially with regard to mobile sensing. This finding is particularly striking considering the potential of passive monitoring enabled by mobile sensing to create patient value and medical value (cf. Sub-section 2.3.3). It further illustrates that the investigated digital biomarkers in RQ3 are not only relevant from a research perspective, but that passive nocturnal monitoring by means of mobile sensing constitutes a novel and innovative approach in the practice of digital medicine for asthma.

Chapter 4

Unmet Patient Needs

4.1 Introduction and Related Work

In this chapter, RQ2a and RQ2b will be addressed. More specifically, the unmet needs of Swiss patients will be identified and the patients' attitudes towards digital self-management interventions will be examined. In contrast to the preceding chapter, the results of this chapter are hitherto unpublished.

Addressing patient needs is not only relevant for patient satisfaction, but it is also associated with better treatment outcomes (Schreitmüller, Apfelbacher, Sheikh, & Loerbroks, 2019). The Global Initiative for Asthma guideline (2018), for example, emphasizes the importance of adapting medication according to patient preferences. Additionally, the guideline urges physicians to establish a trustful partnership with their patients: research has found that involving patients in the disease-related decision-making process, for example by addressing patients' needs, results in improved treatment adherence and outcomes in asthma (Wilson et al., 2010). Wilson and colleagues (2010) refer to this treatment approach as "shared treatment decision making" (p. 566). Two related treatment approaches, which also emphasize the importance of addressing patient needs, are patient centeredness (i.e., putting patients and their needs at the center of a patient-physician consultation), and patient empowerment, which is based on the notion that patients who are self-determined and perceive themselves to be in charge of their disease and their patient journey have superior treatment outcomes (Holmström & Röing, 2010). Aujoulat, d'Hoore, and Deccache (2007), for example, point out in their review on patient empowerment that treatment goals and objectives should be negotiated with every patient individually, so

that patients' personal situations, priorities, and needs are reflected in the treatment decisions.

Prior research on unmet needs of asthma patients has focused primarily on specific clinical needs of patients, for example with regard to medication (Hyland, 2004), self-management programs (Worstell, 2000), non-adherence (Canonica et al., 2007), and education (Thoonen et al., 2002). A notable exception is the Patient Needs in Asthma Treatment questionnaire developed by Loerbroks et al. (2016a), which is a validated tool for assessing unmet asthma needs systematically and more comprehensively than prior research. Of the 13 identified asthma needs, two needs were reported as unmet by the majority of patients[18], nine needs were reported by a quarter to half of the patients[19], and two needs were reported by less than a quarter of the patients[20] (Loerbroks et al., 2016b, p. 2).

A separate literature stream focuses further on unmet needs and attitudes of patients towards digital self-management interventions. In a meta-ethnography review, Morton et al. (2017) found that patients using digital self-management interventions felt that they received better treatment. The availability and visualization of disease monitoring data was perceived to be particularly useful: it was reported to raise disease awareness and to motivate patients to improve their health behavior. Anderson et al. (2016) and Dennison et al. (2013) found converging evidence in their qualitative studies for patients' openness to using digital self-management interventions and a particular interest in the visualization of disease monitoring data. In their focus groups, Dennison et al. (2013) were further able to identify antecedents for the use of such interventions, namely credibility, measurement accuracy, data security, effort, and instant gratification.

In their interview study focusing specifically on asthma, Pinnock, Slack, Pagliari, Price, and Sheikh (2007) found that although patients were generally open to using digital self-

[18] These two needs are: "information about interactions of asthma drugs with other medication" and "information from physician about side-effects".
[19] These are: "information on how asthma drugs operate", "information about whether asthma inhaler may be taken more often than prescribed", "information about what to do during an asthma attack", "family members/friends know how to help during an asthma attack", "practice under professional guidance breathing techniques", "would like physician to ask about individual asthma triggers during diagnosis", "would like physician to consider personal circumstances to a larger extent in asthma treatment", "would like physician to consider patient's asthma knowledge to a larger extent", and "would like physician to make more time in case of special requests".
[20] These are: "information about how to take asthma medications" and "practice under professional guidance how to handle your inhaler".

management interventions, the expected utility of these interventions depended on the treatment phase: while patients suspected that these interventions would be useful directly after diagnosis, they were concerned about becoming too dependent on the technology in the long-term. Similar patient concerns regarding technology dependence were raised in a review by Miles et al. (2017). On the other hand, as has already been discussed in Sub-section 2.3.1.3, support for the openness toward and interest in continued use of digital self-management intervention was found in a study by Merchant et al. (2018a): 64 of 89 participants were interested in continuing to use the evaluated digital intervention after the study was completed.

One of the most comprehensive studies investigating patients' unmet needs and attitudes with regard to digital self-management interventions was published by Simpson et al. (2017). In a survey of 186 patients, features were rated with regard to their desirability in a digital self-management intervention. The top three features were asthma monitoring support (72%), generating status reports for upcoming physician visits (70%), and an early deterioration warning system (69%). In contrast, the three least desirable components were asthma education materials (22%), replacement of regular physician visits (25%), and medication response assessment (36%). Interestingly, the same survey was also administered to 63 health care professionals. Yet the two groups seem to assess unmet needs differently. For example, while educational materials were the least desired feature for patients, 73% of health care professionals identified them as desirable features. Significant differences between patients and health care professionals were also observed for early deterioration warning systems (69% and 86%, respectively), recommendation systems for medical attention (49% and 87%, respectively), inclusion of asthma action plans (46% and 79%, respectively), emergency instructions (45% and 81%, respectively), and asthma control improvement detection (36% and 76%, respectively).

Simpson and colleagues (2017) also evaluated attitudes towards disease monitoring: patients most commonly wanted lung function (71%), environmental (70%), and respiratory symptom (64%) measurements. Diet (32%), self-reported symptoms (34%), and inhaler technique (42%) measurements were least popular with patients. Differences between patients and health care professionals emerged for measurements of stress levels (53% and 37%, respectively), medication adherence (48% and 89%, respectively), inhaler techniques (42% and 87%, respectively), and self-reported symptoms (34% and 57%, respectively). Based on these differences, it seems that health

care professionals are more aware of patients' clinical needs than patients (e.g., asthma education, action plans, and measurements of inhaler technique and adherence are associated with treatment outcomes as discussed in Sub-section 2.3.1.2). The authors explain these differences by stating that many of the features and measurements that are least popular with patients do not provide them with additional value as they are often things that they can easily assess themselves (e.g., self-reports and diet tracking). The authors further argue that other measurements that are less popular for patients but important for treatment success (e.g., adherence and inhaler technique measurements) may be perceived as disempowering by patients as a result of supervision that is too close-mashed.

In summary, unmet patient needs in general, and digital self-management interventions in particular, have been subject to a considerable amount of research. However, in addition to the unclear generalizability of the aforementioned results to Switzerland, where the research for this dissertation was conducted, a few questions remain unanswered or had mixed results. For example, it is unclear how general unmet needs transfer to the digital sphere, or, in other words, whether patients perceive digital interventions as a solution to experienced unmet needs. In a similar vein, mixed results were found regarding patients' openness towards and interest in digital self-management interventions: while a few studies found evidence for an open-minded attitude, other qualitative studies reported concerns and unwillingness to use these interventions.

Therefore, this chapter aims to address the aforementioned gaps and mixed results to understand unmet patient needs, both with regard to asthma in general and for digital self-management interventions in particular. Additionally, this chapter is an expression of the increasingly important notion of explicitly considering patients' perspectives in medical research, an approach also known as participatory research (Andersson, 2018).

4.2 Methods

4.2.1 Overview

To answer RQ2a and RQ2b, an exploratory sequential mixed methods approach comparable to Finucane and Mercer (2006) was employed. The rationale behind selecting this approach is that patients' needs and the reasons for their behavior can be openly explored in the first qualitative stage. To this end, two focus groups were

conducted. As argued by Kitzinger (1995) and Krueger and Casey (2014), focus groups allow researchers to gain a deeper understanding of patients, because the interactions between patients serve as an additional stimulus for discussion, and also tend to reveal otherwise obscured insights into patients' cognition and behavior. In the second stage, a quantitative survey – informed by the results from the focus groups – was administered to collect more generalizable data.

4.2.2 First Stage: Focus Groups

4.2.2.1 Disclaimer

The focus groups were conducted in collaboration with CSS Insurance, a health insurance company from Switzerland, and Link Marketing Services AG, an independent market research company. The discussed topics were defined primarily by the author of this dissertation and were refined in several iterations with all involved parties. Other parts of the focus groups, which were related to the validation of services offered by CSS Insurance, are subject to confidentiality and will thus not be covered in this chapter.

4.2.2.2 Participant Selection

Participants were recruited through an internal recruitment panel by Link Marketing Services AG. The inclusion criterion was physician-diagnosed asthma, while participants not fluent in Swiss German or who suffer from COPD were excluded. Furthermore, criteria for the composition of each focus group were defined as follows: the majority of participants should own a smartphone, heterogeneity in terms of occupation, family status, and housing should be ensured, and at least two participants should suffer from uncontrolled asthma. Participants were awarded CHF 150 for taking part in the focus groups.

4.2.2.3 Execution and Discussion Guide

The two focus groups were conducted in Lucerne, Switzerland, in September 2016. Each focus group lasted for two and a half hours. In the first focus group, participants were between 18 and 40 years old, while in the second group participants ranged in age from 41 to 70 years. Participants were divided by age segment to increase homogeneity of attitudes towards technology, thereby fostering an environment for productive discussions.

Both focus groups were moderated on the basis of a structured topic guide (Table 4.1). In addition to the guide, stimulus material was prepared for the last topic. More specifically, participants were shown screenshots of a smartphone app concept for asthma self-management to facilitate discussion.

Table 4.1. Focus group topic guide.

Topic (duration) and exemplary discussion prompts
Topic 1: Patient journey (20 minutes)
What were the first signs of your disease? Who gave you your diagnosis? Are you treated for your asthma by your family physician or by a specialist? Have you used the internet to research your condition?
Topic 2: Everyday life with asthma (20 minutes)
Which impairments due to asthma do you perceive in your everyday life? How are you coping with your symptoms in everyday life? What are your strategies to improve your asthma?
Topic 3: Attitudes towards health care service providers (30 minutes)
What are your opinions on the different services providers in health care, namely family physicians, specialists, health insurance companies, patient organizations, or pharmacies?
Topic 4: Digital self-management interventions (50 minutes)
Can you imagine using digital self-management for asthma in your everyday life? How should an app be designed to provide you with additional value for your disease management?

4.2.2.4 Analysis

Both focus groups were recorded on video. The recordings were analyzed by means of thematic analysis as described by Braun and Clarke (2006), who recommend this method for the analysis of qualitative data due to its flexibility and suitability for participatory research. In short, thematic analysis condenses complex qualitative data by identifying emerging patterns, which are also referred to as themes. Link Marketing Services AG performed the initial analysis on the raw data and proposed a first set of themes. The initial findings were discussed with all involved parties and subsequently refined. While the results presented in this dissertation are based on this joint analysis, they were translated, streamlined, and adapted for this chapter to develop a consistent narrative with regard to RQ2a and RQ2b. This narrative-driven analysis approach constitutes best practice in thematic analysis and is recommended by Braun and Clarke (2006).

4.2.3 Second Stage: Survey

4.2.3.1 Disclaimer

The survey reported in this chapter is one of three surveys from the MAC study (Tinschert et al., 2019b). In this study, participants were recorded at night for one month and had to engage with a digital coaching-based app on a daily basis to investigate the potential of nocturnal cough and sleep quality as markers for asthma control. For more details, please refer to Chapter 5.

4.2.3.2 Sample

The inclusion and exclusion criteria described in Sub-section 5.2.3 apply to this survey. In short, participants had to have physician-diagnosed asthma, had to be 18 years or older, and had to be capable of using a smartphone to participate in the MAC study. Study participation was not reimbursed. Furthermore, as this survey was administered on the last study day, no data is available for participants who withdrew prematurely from the study.

4.2.3.3 Execution and Survey Items

Participants filled out the pen-and-pencil survey at the end of the MAC study. Insights gathered in the focus groups and the mixed results presented in the introduction of this chapter informed the design of the survey. More specifically, the survey was designed to examine whether participants feel that they need support managing their asthma, whether such help is desired by participants, and whether participants think that digital self-management interventions can deliver this support (see Table 4.2 for the translated items). Similar to Simpson et al. (2017), participants' attitudes towards specific components of a digital self-management intervention were queried. Furthermore, asthma control was assessed with the ACT (Nathan et al., 2004).

Table 4.2. Survey items.

Theme	Item
Attitudes towards specific features	• How important do you consider the following features of a potential asthma digital self-management app? [a] – An overview screen, in which you can see the current status of your symptoms – Visualization of the course of your symptoms over the last days/weeks – An early warning system that warns you in time if your asthma is likely to worsen – A digital coach, who will contact you when needed – General asthma knowledge (e.g., with instruction videos for correct use of an inhaler) – Allergy information (e.g., pollen count) – Asthma action plan
General attitudes	• Do you feel you need help managing your asthma? [b] • In general, do you want support in managing your asthma? [b]
Attitudes towards asthma apps	• I am open to the idea of using an asthma app for improving my disease management. [b,c] • I am interested in trying out asthma apps. [b,c] • I would be willing to spend time learning how to use an asthma app. [b,c] • I would be willing to pay for an asthma app. [b,c]

Note: [a] On a scale from 1 (not important at all) to 5 (very important). [b] On a scale from 1 (strongly disagree) to 7 (strongly agree). [c] Item adapted from Fiore, Lee, Kunz, and Campbell (2001).

4.2.3.4 Analysis

The survey was analyzed visually and descriptively. To obtain statistically significant differences between items, non-parametric Friedman tests for repeated measures and pairwise comparisons with paired t-tests, corrected for multiple comparisons using the Benjamini-Hochberg method, were calculated. Group comparisons were analyzed by means of two pair t-tests. Pearson correlations quantify the strength of associations between variables.

4.3 Results

4.3.1 Focus Group Results

4.3.1.1 Participants

In total, 15 participants were recruited for the focus groups (n = 8 and n = 7 for the group with the age range 18 to 39 and 40 to 70, respectively). Participant descriptions are provided in Table 4.3.

Table 4.3. Focus group participants.

Focus group	Sex	Age	Year of diagnosis	Asthma control [a]	Housing situation	Smartphone user
1	Female	21	2008	Controlled	Alone	Yes
	Male	27	1999	Controlled	Partner	Yes
	Female	27	2000	Uncontrolled	Shared flat	Yes
	Male	29	2015	Partially controlled	Partner & children	Yes
	Female	31	2002	Controlled	Partner	Yes
	Male	34	1987	Controlled	Alone	Yes
	Female	37	1989	Controlled	Partner & children	Yes
	Male	37	2009	Uncontrolled	Partner & children	Yes
2	Female	42	2014	Uncontrolled	Partner & children	Yes
	Male	42	2009	Uncontrolled	Alone	Yes
	Male	53	1985	Controlled	Partner & children	Yes
	Female	57	2006	Controlled	Children	Yes
	Female	58	1988	Uncontrolled	Children	Yes
	Male	59	1963	Partially controlled	Alone	Yes
	Female	66	2012	Controlled	Partner	No

Note: [a] Classified by means of the Asthma Control Test (cf. Sub-section 2.2.2.1 and Appendix 7.1.4).

4.3.1.2 Exploration of Patient Needs

In the following, insights for each of the topics listed in Table 4.1 will be presented. In order to make the findings more tangible, quotations from participants are occasionally included.

Patient Journey A common theme which emerged, especially in the first focus group, is that participants were unsatisfied with the initial diagnosis of their asthma. Participants reported that, in their perception, the diagnostic process took too long and

was characterized by uncertainty. For example, some participants reported that after consulting the physician with their first asthma symptoms the diagnostic process took months. Even after receiving their diagnosis, participants often felt unsupported by physicians as they felt like they hadn't received all of the information they needed.

> *"Well, I would have liked to know where it came from. It [asthma] just appeared two years ago. I would have liked to know where it suddenly came from. ... In my case, I have just got the medicine."* (Female, 42 years old, uncontrolled asthma)

> *"The family doctor just gave me the asthma spray. He just said you don't breathe well. I asked myself, what about any clarifications? You just get [the asthma spray] and that's that."* (Female, 31 years old, controlled asthma)

Participants often tried to treat their first symptoms on their own without consulting with the physician, for example by using cold medication.

> *"I tried home remedies first. I boiled candied sugar with onions and made syrup. I have taken such things. It loosened a little slime, but the wheezing didn't go away."* (Female, 66 years old, controlled asthma)

Around the time of their diagnosis, participants also struggled to find credible and reliable sources for respiratory-health-related information. For example, some participants stopped using the internet to search for health information because they were overwhelmed and lacked the skills to filter out information that did not apply to their situation.

> *"[Using Google] my first search result was cancer, so I stopped using Google."* (Male, 29 years old, partially controlled asthma)

However, once the diagnosis was confirmed and participants felt that they had received the right treatment and the necessary information to manage their disease, participants were largely satisfied with the treatment. They reported having visited the specialist at the time of the initial diagnosis, after which they mainly continued their treatment with the general practitioner.

Participants also emphasized the importance of medication, which constituted the most important treatment strategy for them by far. However, some participants felt that due to permanent prescriptions they lacked the supervision of a physician and might therefore have missed out on newer, better treatment options that became available.

> *"Then I had the same asthma medication for decades, I was not aware of other options, until I went to the new doctor because I had no [medication] left. And he said it was outdated, I shouldn't take this kind of medication anymore."* (Male, 53 years old, controlled asthma)

Everyday Life with Asthma The most prominent theme in this topic was that participants did not perceive themselves to be chronically ill and therefore did not want to be constantly reminded of their disease.

> *"If I don't have any attacks, I'm healthy, and I don't want to be constantly reminded [of asthma]."* (Female, 21 years old, controlled asthma)

> *"I just don't think asthma should be put in the foreground of everyday life."* (Female, 42 years old, uncontrolled asthma)

There was a tendency among participants – especially for those who have suffered from asthma for a long time – to ignore and trivialize asthma symptoms, and an unwillingness to try out new treatment options to improve quality of life was observed.

> *"I have the spray and I've come to terms with it. As long as it doesn't get worse, I just accept it. I haven't tried out all treatment options."* (Male, 37 years old, uncontrolled asthma)

Furthermore, seemingly causeless fluctuations in symptoms and asthma control were considered a significant stressor in everyday life. Participants often attributed these fluctuations to external factors, such as weather and stress.

> *"It depends on the weather and what I have to do. Then sometimes I have more control when everything is going well and when things aren't going so well, [my asthma control] goes haywire."* (Female, 58 years old, uncontrolled asthma)

> *"I have the feeling it also depends on the circumstances of life, the situational stress. So that's how it is with me. When I'm on holiday, I have practically nothing."* (Female, 42 years old, uncontrolled asthma)

The fear of asthma attacks was also reported to be a significant stressor in everyday life. Participants perceived asthma medication to be crucial for the prevention of attacks and reported few adverse effects from the medication. Nevertheless, even if adverse effects did occur, participants were willing to accept them to prevent attacks.

> *"You almost suffocate, that's the feeling. You have the feeling of dying. You have enough air, but there's also the panic."* (Male, 53 years old, controlled asthma)

> *"If I have to take the [asthma spray] six, seven, or ten times a night, then I won't be able to sleep. But I'd rather not have to wheeze and be able to breathe than be nervous."* (Female, 58 years old, uncontrolled asthma)

Attitudes towards Health Care Service Providers Despite the aforementioned issues with regard to the initial asthma diagnosis, the family physician remained the participants' first contact point for asthma care. Even though specialists were perceived to be more competent, participants were skeptical whether treatment by a specialist was necessary, especially with regard to time and financial expenditure associated with specialist treatment.

> *"So I went to a specialist and I had to give it up, it just got too much for me. He kept calling me in every two or three weeks and I had to do that lung function test again and I had to go back to the cabin. And I don't know, suddenly I just said, 'I'm going back to the family physician'."* (Female, 58 years old, uncontrolled asthma)

Participants were particularly skeptical about the involvement of health insurance companies in treatment. In general, participants suspected a profit motive behind services offered by insurers.

> *"I'm not sure if the [health insurance companies] have the same goal as me. So I trust my physician more than my health insurance company. They have the objective to make profit. Sure, they don't want me to get sick, but when I'm sick, I'm not sure they support every therapy and everything."* (Male, 37 years old, uncontrolled asthma)

Participants did not consider pharmacies to be a relevant service provider for asthma due to limited expertise and training of the staff, their inability to prescribe medication, and a potential profit motive.

> *"I don't think I have confidence [in the pharmacy]. It's about life or death, it's too serious for me. That's why I go to the physician. The physician is my specialist."* (Female, 57 years old, controlled asthma)

In contrast, participants assessed patient organizations like the Swiss Lung League as highly credible and perceived their personal interests to be in line with these organizations.

Digital Self-Management Interventions Initially, participants were highly critical of the presented exemplary app concept, which consisted of two main components: a digital asthma coach and symptom monitoring by means of mobile sensing. Reasons for the critical mindset emerged in the discussions. The most important theme was the effort required to use the app. Participants emphasized that if an app requires too much effort, which participants perceived to be the case when a digital coach is implemented, they were not interested in using it in everyday life. In a similar vein, participants felt very uncomfortable with the notion of being continuously reminded of their disease through regular interactions with a digital coach. Another critical theme was that a playful app was perceived as trivializing the disease.

> *"Every day he tells you that you have asthma. You have the app every day. It always says asthma. You already know that you have asthma. And you see the disease every day."* (Female, 37 years old, controlled asthma)

> *"It puts the disease in the foreground all day long."* (Female, 45 years old, uncontrolled asthma)

> *"It's just so playful. It's just playful to me, I don't have time for this."* (Female, 58 years old, uncontrolled asthma)

> *"I don't need it. I'm usually so busy, and then I would have to feed someone [with information] who tells me how I'm doing, no."* (Female, 31 years old, controlled asthma)

Furthermore, participants were afraid that a self-management app might patronize and disempower them by taking away their responsibility for managing the disease themselves. Also, a fear of technology-dependence in the long-term was voiced.

> *"Well, I personally wouldn't really need an [app] because I've actually had this disease since I was young. I know exactly how to deal with it. I have my medication."* (Female, 27 years old, uncontrolled asthma)

In contrast to the negative attitude towards the interactive component of the app, participants generally had a positive attitude towards mobile sensing. The participants considered the notion of having objective measurements of their symptoms or lung functions at their disposal, which are accessible on an as-needed basis to improve asthma control, a valuable addition to the current standard of care in asthma. However, participants made clear that they would be willing to use an intervention with such a

functionality only if the monitoring worked automatically, so that little to no extra effort is required from the patient's side.

In addition to expectations of low to no additional effort, the following desired characteristics of asthma apps emerged during the discussions: the app should be developed or endorsed by a credible, ideally non-profit, patient organization like the Swiss Lung League; a free test version should be available; it should also be designed for temporary use (e.g., during allergy season); the layout and design should look professional; the main functionalities should also be available in airplane mode to reduce electromagnetic radiation; and the opportunity to directly contact health care professionals through the app would foster interest in using such an app in everyday life.

4.3.2 Survey Results

4.3.2.1 Sample

In total, 94 participants (56% female, average age of 44.6 years) participated in the MAC study, in which this survey was administered. At baseline, the majority of participants had controlled asthma (70%) followed by partially controlled asthma (19%). Nine participants had uncontrolled asthma (10%) and for one participant measurement was incomplete (1%). On average, participants suffered for 18.09 years from asthma (SD = 14.66). The comprehensive baseline characteristics can be found in Appendix 7.2.2. After accounting for dropouts and premature withdrawals, survey data for 88 of the 94 participants was available.

In the MAC study, participants were equipped with a Samsung smartphone running the Android operating system. Privately, 51 participants owned an Apple iPhone (58%), 34 participants owned an Android-powered smartphone (39%), two participants owned a smartphone from a different manufacturer (2%), and one participant did not own a smartphone (1%). Most participants used their smartphone several times a day (n = 70; 80%), seven participants reported using it once-a-day and an additional seven participants reported using it multiple times per week (both 8%), one participant communicated once a week by means of the smartphone (1%), and three participants reported not communicating via their smartphones at all (3%). Three participants further reported using smartphone asthma apps, of which one participant used a self-management support app ("Asthma MD") and the two others used allergy apps developed by the Swiss Allergy Center (e.g., "Pollen-News").

4.3.2.2 Patient Attitudes

General Attitudes Overall, 50% of participants wanted support managing their asthma and 41% of participants reported needing support in their asthma management (Figure 4.1). In contrast, 21% and 30% of participants reported not wanting or needing support, respectively. Interestingly, two sample t-tests revealed that participants with uncontrolled or partially controlled asthma and participants with controlled asthma did not differ significantly in terms of their self-reported desire (mean = 4.48, SD = 1.42 and mean = 3.95, SD = 1.65, respectively; $t(85) = 1.40$, $p = 0.16$) and need (mean = 4.72, SD = 1.43 and mean = 4.40, SD = 1.68, respectively; $t(85) = 0.83$, $p = .41$) for support in asthma management. Furthermore, desire and need for support were not associated with the years a participant had lived with the disease ($r = -0.03$, $p = .81$ and $r = -0.02$, $p = .89$).

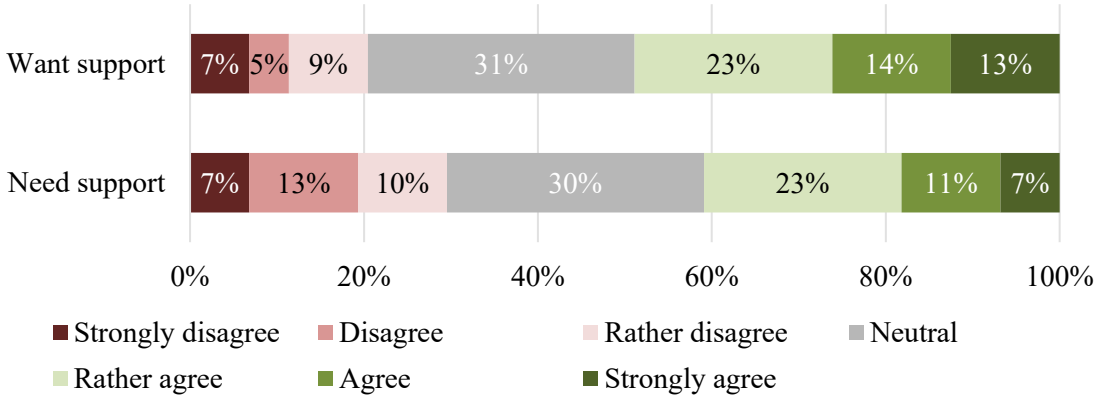


Figure 4.1. Self-reported desire and need for support in asthma management (n = 88). Differences from 100% due to rounding.

Attitudes towards Specific Features All of the six evaluated features were rated as important by the majority of participants (Figure 4.2). Yet differences between some of the features emerged in terms of their importance. The feature that was considered most important by participants was an early warning system for asthma deteriorations (mean = 4.27, SD = .99). Participants identified a status overview of the current symptom level as the second most important feature (mean = 4.25, SD = .93) and a visualization of symptoms over time as the third most important feature as (mean = 4.09, SD = .90). The availability of an asthma action plan was in fourth place in terms of importance (mean = 3.85, SD = 1.12). Allergy information (e.g., pollen count; mean = 3.76, SD = 1.23), a

digital coach (mean = 3.66, SD = 1.03), and availability of education materials (mean = 3.55, SD = 1.22) were perceived as the three least important features. Please note that all features that are comprised of or rely on monitoring of symptoms (i.e., deterioration early warning system, symptom monitoring overview, and symptom visualization over time) were introduced in the survey as being based on passive monitoring.

The differences in feature importance were found to be statistically significant by means of a non-parametric Friedman test for repeated measures, $\chi^2(6, n = 86) = 58.83$, $p < .001$. Pairwise comparisons with paired t-tests, corrected for multiple comparisons using the Benjamini-Hochberg method, provided further insights: the early warning system and symptom status overview were found to be significantly more important than the action plan, allergy information (both $p < .01$), a digital coach, and educational material (both $p < .001$). Symptom visualizations were also considered more important than allergy information ($p < .05$), a digital coach, and educational material (both $p < .001$). Lastly, the action plan was considered more important than educational materials ($p < .05$).

Furthermore, no statistically significant associations were observed between attitudes towards specific features and asthma control (all p's > 0.1), implying that participants assessed the importance of each feature independent of their level of asthma control. Additionally, no statistically significant correlations were found with years lived with the disease (all p's > 0.1).

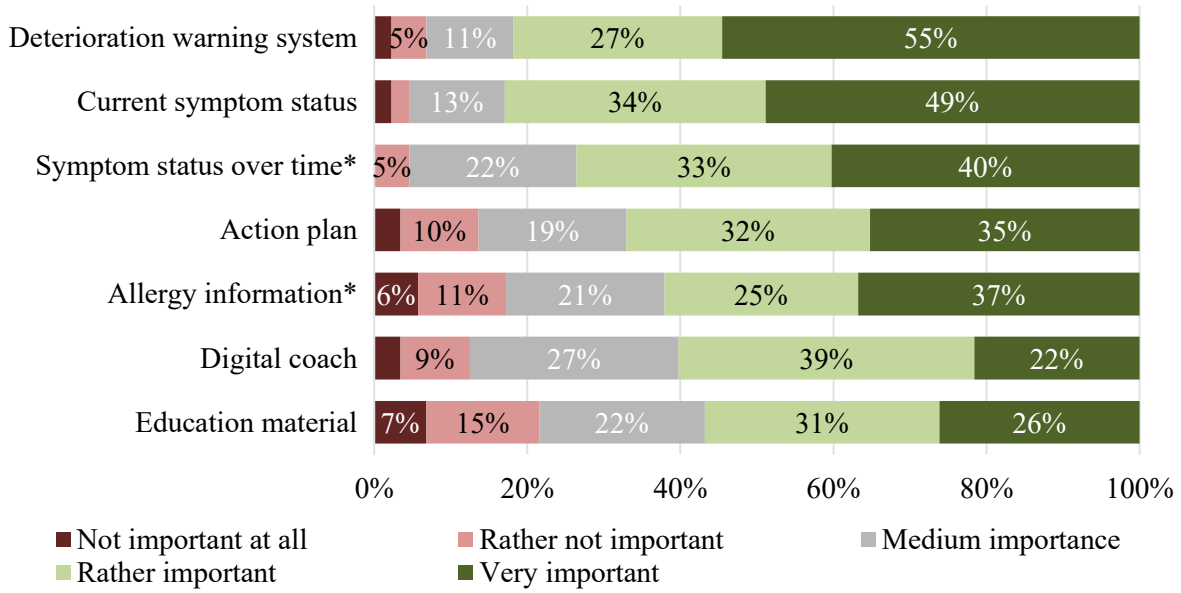


*Figure 4.2. Importance of app features. Data labels were suppressed for frequencies below 5%. * n = 87, otherwise n = 88.*

Attitudes towards Asthma Apps As indicated in Figure 4.3, most participants were open to the idea of using apps for asthma self-management, were interested in trying out asthma apps, and were willing to invest time to learn how to operate an asthma app (89%, 69%, and 69% of participants, respectively). However, only a minority of participants would be willing to pay for an app (39%). Differences between willingness to pay for an app and the three other indicators of attitude towards self-management apps were statistically significant (all p's < .001 in pairwise comparisons with paired t-test using the Benjamini-Hochberg correction).

Interestingly, all measures of attitudes towards digital self-management apps were positively correlated with the desire and need for asthma management support (Table 4.4). All correlations were highly statically significant and their association strength can be considered intermediate to large based on Cohen's rule of thumb (1988), which was presented in Sub-section 2.3.3. This finding implies that participants who report wanting or needing support in asthma self-management have more positive attitudes towards asthma apps. However, except for the willingness to pay, app attitudes were independent of asthma control. For willingness to pay, the counterintuitive finding that participants with higher levels of asthma control tend to be more willing to pay for asthma apps was observed. No significant correlations were found between attitudes towards apps and years lived with the disease.

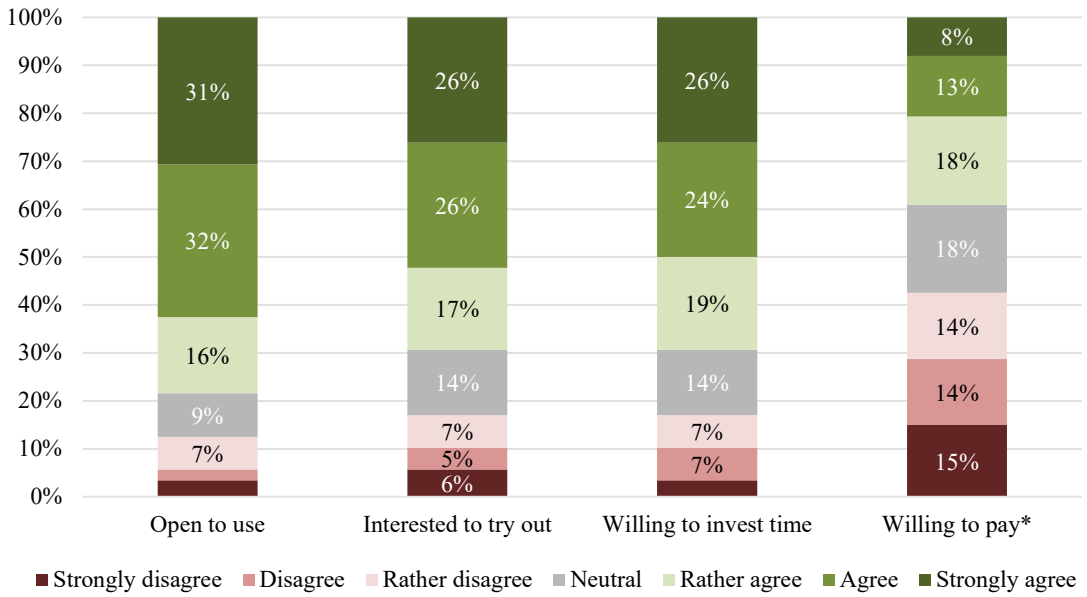


*Figure 4.3. Attitudes towards self-management apps for asthma. Data labels were suppressed for frequencies below 5%. * n = 87, otherwise n = 88.*

Table 4.4. Pearson correlations for attitudes towards self-management apps.

	Desire for self-management support (n = 87)	**Need for self-management support (n = 87)**	**Asthma Control Test Score (n = 86)**	**Years lived with the disease (n = 82)**
Openness to use apps for asthma self-management	.43*	.44*	-.07	.04
Interest in trying asthma apps	.38*	.47*	.04	-.02
Willingness to invest time to learn app handling	.35*	.38*	.04	.05
Willingness to pay for an app	.32*	.38*	.20†	.05

Note: † $p < 0.1$; * $p < .001$.

4.4 Discussion

4.4.1 Principal Findings

This chapter has explored patients' unmet needs and their attitudes towards digital asthma self-management apps by means of an explorative and sequential mixed-methods approach. To explore patient needs, two focus groups were conducted. The insights gathered informed the subsequent survey.

In discussions about their patient journey, participants reported two main unmet needs: first, the initial diagnosis of asthma was often accompanied by uncertainty and considerable time expenditure, and, second, there was a perceived lack of credible and reliable information. In this early stage of their asthma-related patient journey, participants did not feel cared for properly by their physicians. Not educating patients properly about their diagnosis is particularly troublesome as this is in stark contrast to patient empowerment (Aujoulat et al., 2007) and to the guideline recommendations for establishing a patient-physician partnership (Global Initiative for Asthma, 2018). This finding also seems paradoxical in the context of Simpson and colleagues' survey (2017), which found that the vast majority of physicians considers asthma education to be important. Due to the limited generalizability of focus groups, the discrepancy between physicians' attitudes and participants' experiences should not be overinterpreted, but it may suggest that while physicians are aware of the importance of asthma education,

physician-related interventions could focus more on physicians' abilities and resources to convey knowledge to patients.

Participants reported coping with asthma in their everyday lives, at least to a certain extent, by ignoring and hiding it. It seemed that if it is not absolutely necessary, they are not interested in dealing with their disease on a daily basis and do not perceive themselves to be chronically ill. Participants' fear of asthma attacks was also clearly observed. Interestingly, their attitudes towards asthma medication were overwhelmingly positive, and any adverse side-effects were accepted as the necessary consequences of preventing deteriorations. In addition to attack anxiety, participants also reported struggling with symptom fluctuations. Not being able to comprehend why symptoms change constitutes a major daily stressor. Thus, understanding asthma better in everyday life emerged as an important unmet need for participants, in particular with regard to day-to-day symptom fluctuations. Furthermore, the experience of being constantly confronted with situations beyond one's influence (in this case, unpredictable symptom fluctuations) can lead to learned helplessness (i.e., the belief that a negative situation is inevitable and not changeable; Peterson, 2010). When learned helplessness occurs in conjunction with an internal locus of control (i.e., the tendency to attribute reasons for experiences to internal forces) it may lead to depression (Seligman & Peterson, 2001). This argumentation is in line with the finding that depression is a common comorbidity in asthma (Goldney, Ruffin, Wilson, & Fisher, 2003).

On a related note, Vergara and colleagues (2017) demonstrated that patients with active rheumatoid arthritis experience more learned helplessness and have lower levels of self-efficacy (i.e., the sense of having control over one's own actions or events so that desired outcomes can be generated) in comparison to patients in remission. For asthma, this finding could imply that patients who experience more (seemingly) uncontrollable symptom fluctuations may exhibit lower levels of self-efficacy, predisposing them to suboptimal coping styles as they might doubt that they are able to control their asthma with their actions (e.g., through proper self-management and regular medication adherence). Poor self-management and medication non-adherence, in turn, increase symptom fluctuations, resulting in a downward spiral of decreasing self-efficacy and increasing symptom fluctuations. Therefore, it can be argued that insufficient comprehensibility of symptom fluctuations might contribute to patient disempowerment, puts patients at risk for affective disorders, and fosters suboptimal coping styles characterized by poor self-management and lower medication adherence.

In discussions of health care service providers, the extent to which a provider was perceived to be driven by the profit motive has been identified as the main determinant for credibility and trust. Participants perceived patient organizations such as the Swiss Lung League to be highly credible and trustworthy, while they were highly skeptical of health insurers and the presumably profit-oriented intentions behind offering health services. Furthermore, the family physician constitutes the primary point of contact for all asthma-related matters, even though specialists are believed to be more competent. This belief is in line with research confirming that specialists deliver better asthma outcomes in comparison with general physicians (Harmsen et al., 2010; Schatz et al., 2005). However, participants suspected specialists of being more profit-oriented and were therefore doubtful about whether their treatment recommendations were driven by medical or financial considerations.

The attitudes of focus group participants towards digital asthma self-management through a smartphone app varied depending on the app's functionalities. Participants stated clearly that the most important design requirement was little to no effort required on the user side. Furthermore, an app should not increase the role of asthma in everyday life. For example, participants were not interested in using a digital coach-based app, because the interaction with a digital coach was perceived as being too time-consuming and increasing the prominence of asthma in their lives. Considering the promising research results on digital coaches, which were shown to improve clinical outcomes (e.g., Fitzpatrick, Darcy, & Vierhile, 2017; Laranjo et al., 2018; Ma, Sharifi, & Chattopadhyay, 2019), participants' negative attitudes towards a potentially supportive technology is rather unfortunate. However, the concept of passive and automatic symptom monitoring was positively assessed by participants. Under the assumption that the app would have a free test phase and would be developed or supported by institutions considered credible, participants could envision using a passive monitoring app in their everyday lives.

The survey largely supports the sentiments observed in the focus group about the individual app features: participants found passive monitoring features (e.g., deterioration warning system, symptom status overview, and symptom visualizations over time) to be significantly more appealing than other features, such as a digital coach, educational material, and allergy information. However, all features investigated in the survey were rated as rather important or very important by the majority of participants,

thereby putting the very critical attitudes of focus group participants towards some of the features into perspective.

A further theme that emerged in the focus group was that participants do not perceive a need for additional support in their asthma management as they consider themselves to be experts in managing their own disease. For this reason, the survey explicitly posed questions regarding the desire and need for support in asthma self-management: 50% of participants want and 41% of participants need support in managing their asthma to some extent. Furthermore, at least half of the participants reported being open to the notion of using digital self-management apps, being interested in trying asthma apps, and being willing to invest time to learn how to operate the app. These results are somewhat contrary to the focus group insights.

When considering their willingness to pay for an asthma app, participants were more reserved in their attitudes: only 39% would consider paying for it. Different explanations for this change in attitudes are conceivable: participants might have the expectation that effective treatment options, analogue or digital, are reimbursed or that the expected benefit of using asthma apps for self-management is assumed to be too low to be worth paying for. Interestingly, participants with better asthma control tended to be more willing to spend money on asthma apps, thus indicating that the willingness to pay does not seem to be driven by an actual clinical need.

However, apart from this tendentious association, participants' attitudes towards asthma apps in general, as well as towards specific features, was independent of their level of asthma control. This also applies to participants' reported desire and need for support in asthma self-management. Similar to asthma control, attitudes were independent of the years lived with the disease. Considering the difficulty of assessing symptom severity correctly with increasing duration of illness (Von Leupoldt et al., 2011) and the higher objective need for support in patients with poorly or partially controlled asthma (Global Initiative for Asthma, 2018), it seems that patient-reported needs are not particularly well aligned with their actual clinical needs. With regard to practice implications, it can be argued that asthma patients have, independent of the state and duration of their disease, mostly homogenous attitudes on the topics covered in the survey, implying that an all-purpose approach towards the development, sale, and marketing of asthma apps may be justified.

Finally, the positive correlations between the desire and need for support in self-management and all indicators of attitudes towards digital self-management indicate that survey participants perceive smartphone apps as valid options to satisfy their self-management needs.

4.4.2 Limitations

Due to the exploratory character of the research presented in this chapter, limitations apply with regard to the generalizability of findings. While in the first and qualitative stage generalizability is not an objective, the survey sample of the second stage is biased, so that the insights have to be interpreted cautiously. More specifically, the survey was administered on the last study day of the MAC study, which means that all participant selection biases from the study directly apply to the survey. Additionally, participants who withdrew from the study prematurely were not included in the survey.

Before completing the survey, participants voluntarily took part in a study on digital biomarkers for asthma, which required them to use a digital coaching app. Thus, it is plausible to assume that participants who are fundamentally opposed to the concepts of digital self-management interventions, passive monitoring, and digital coaching are most likely excluded from the survey due to self-selection. Additionally, because the study lasted for one month and required daily participant engagement, the sample is biased towards patients who were at least somewhat motivated to deal with their asthma. However, it can also be argued that MAC study participants were able to gain insights into digital coaching and passive monitoring during their participation, so they were at least somewhat knowledgeable in their assessments. In contrast, focus group participants had no prior understanding of or experience with asthma self-management apps, which makes it hard to assess, for example, whether they were skeptical at times due to genuine dislike of a proposed concept or due to a general resistance to novel ideas (i.e., a status quo bias; Kahneman, Knetsch, & Thaler, 1991).

However, the heterogeneity of participants in both stages, which is further illustrated by the fact that focus group participants were well paid for a two-and-a-half hour afternoon session while study participants did not receive reimbursement despite the study duration of one month, suggests that converging evidence between both stages (e.g., a general preference for passive monitoring over digital coaching) are all the more meaningful. This also applies to convergence of insights with other literature.

4.4.3 Comparison to Prior Work

The predominant coping styles observed in the focus groups, namely ignoring and hiding asthma symptoms, are in line with prior research on asthma coping styles (Aalto et al., 2002). This also holds for disease-related attitudes identified in the focus groups, such as trivialization of symptoms and the desire not to be labelled as chronically ill (Price et al., 2014). However, focus group participants showed more positive attitudes towards medication than would have been expected based on prior research. For example, while many patients have mixed attitudes towards asthma medication due to, inter alia, possible negative side-effects (Miles et al., 2017; Partridge et al., 2006; Price et al., 2014), focus group participants were fully convinced of the necessity and importance of asthma medication. However, this divergence might be explained by the fact that prior research differentiated between controller and reliever medication and primarily found negative attitudes towards the former (Partridge et al., 2006), while in the focus group medication was discussed in general terms. It could be possible that focus group participants would have also reported more negative attitudes towards corticosteroid-based controller medication if they were asked to differentiate between both medication options.

One of the most prominent pain points for patients suffering from asthma – the fear of asthma attacks (Ten Thoren & Petermann, 2000) – was also observed in the focus groups. Participants also reported the lack of comprehensibility of their symptom fluctuations as a key unmet need. This unmet need may be related to patients' difficulty assessing the severity of their symptoms properly, which is well established in literature (e.g., Gillissen, 2015).

Further convergence also emerged in participants' attitudes towards specific app features and the results published by Simpson et al. (2017): early warning features for deteriorations and (passive) monitoring features were desired by patients in an asthma app, while features providing general information (e.g., educational materials) were perceived to be less desirable. However, the focus group additionally highlighted that feature assessments were driven by effort expectations and expected salience of asthma due to app use in everyday life. These explanations are somewhat contrary to Simpson et al. (2017, p. 8), who argue that patients rated self-reported symptom measurements as one of the least desirable measurements because they "may be inherently aware of [them] and therefore see no need for mHealth feedback".

4.4.4 Contributions to Research

The two focus groups have revealed a stressor for asthma patients, which has not been extensively discussed in literature thus far: unpredictable daily symptom fluctuations. In the discussion of the principal findings, it was argued that this may be a contributing factor to the increased prevalence of depression in asthma – a hypothesis which has, to the best knowledge of the author, not yet been investigated. Furthermore, evidence was found in the survey that asthma patients perceive digital pills to be valid options to satisfy their need and desire for support in their asthma self-management. This finding enables future research to drive research on digital asthma pills, based not only on clinical necessity and technological opportunity, but also based on patient needs.

4.5 Conclusion and Implications

The research presented in this chapter suggests that patients consider digital self-management apps a valuable addition to asthma care if they are designed according to their needs. Patients were very open towards the concept of digital self-management apps and were willing to try them out. While they were willing to invest time to get used to them, spending money on asthma apps seemed to be a higher barrier. Nevertheless, digital self-management apps were perceived as valid options to address the need for support in asthma self-management, which was present in a substantial share of patients.

For patients to consider the daily use of an app, it should generate very little to no additional effort for the patient. This finding is highly relevant for the digital pill foundation proposed in this dissertation. In conjunction with a general preference for monitoring features identified in the survey and in prior research, these findings clearly advocate for passive symptom monitoring. Symptom self-reports, on the contrary, are not perceived to be a desirable feature by patients. Considering that the publicly available asthma apps reviewed in Chapter 3 rely exclusively on symptom self-reports and none of the apps offered any passive symptom monitoring features, a substantial mismatch between patients' needs and the status quo in asthma apps can be ascertained. In contrast, passive monitoring of symptoms, as proposed in this dissertation, offers a promising foundation to address patients' needs, thereby creating patient value.

Chapter 5

Clinical Utility of Nocturnal Cough and Sleep Quality as Biomarkers

5.1 Introduction and Related Work

Based on the insights gathered so far, passive monitoring of asthma symptoms has the potential to create patient value for asthma care. As argued in Sub-section 2.3.3, nocturnal cough and sleep quality are two CDBs that could enable passive asthma monitoring. Sleep quality, for example, is statistically associated with asthma control[21] (Luyster et al., 2012). This association is in line with the fact that asthma symptoms tend to get worse at night and often cause awakenings (Global Initiative for Asthma, 2018). For nocturnal cough, a first cross-sectional study has indicated that nocturnal cough frequency might be a valid marker for asthma control (Marsden et al., 2016). A second cross-sectional study has found more support for the potential of nocturnal cough as a monitoring biomarker for asthma: patients with asthma not only cough considerably more at night than healthy people do, but their nocturnal cough also decreases after receiving appropriate treatment (Fukuhara et al., 2019). In addition to the criteria introduced in Sub-section 2.3.3.4, a positive response to drugs can be regarded as a further criterion for the clinical utility of a biomarker (Institute of Medicine, 2010).

Even though the above-mentioned studies suggest potential medical value of sleep quality and nocturnal cough as digital biomarkers for asthma, their actual clinical utility. While statistical significance has been established on a between-patient level, patient

[21] Asthma control was introduced in detail in Sub-section 2.2.1.2. It is considered a key outcome in research and clinical practice alike. Poor asthma control is a risk factor for asthma attacks and deaths due to asthma, negatively affects quality of life, and drives cost-of-illness.

acceptance, persistence, statistical significance on a within-patient level, and biomarker performance for monitoring and prognostic purposes has not, to the best knowledge of the author, been investigated yet. This chapter addresses this research gap by assessing the clinical utility criteria for biomarkers outlined in Sub-section 2.3.3.4 and summarized in Table 5.1.

Table 5.1. Clinical utility criteria and their research questions.

Criteria	Research question
C1: Patient acceptance	Are patients open to using a digital pill based on nocturnal passive monitoring? *(RQ3a)*
C2: Persistence	Are the two CDBs temporally persistent? *(RQ3b)*
C3: Statistical significance	Are the two CDBs statistically associated with asthma control on a within-patient level? *(RQ3c)*
C4: Monitoring performance	To what extent do the two CDBs enable useful assessments of asthma control? *(RQ3d)*
C5: Prognostic performance	To what extent do the two CDBs enable early detection of asthma attacks? *(RQ3e)*

Note: CDBs: Candidate digital biomarkers.

5.2 Methods

5.2.1 Overview and Disclaimer

To answer the research questions, a longitudinal observational study with two stages was conducted. The study stages were identical in terms of included participants and data collection procedure. This section focuses on the study aspects relevant to the research questions outlined in Table 5.1; irrelevant aspects are omitted (e.g., the division into two stages, participant recruitment strategies, and unrelated study measures are not discussed). For a comprehensive description of the study design, please refer to the published study protocol (Tinschert et al., 2019b). The study presented in this chapter was reviewed and approved by the ethics commission responsible for research involving humans in eastern Switzerland (BASEC ID: 2017–01872).

5.2.2 Study Setting

Two study centers in Switzerland participated: The Clinic for Pulmonology and Sleep Medicine of the Cantonal Hospital St. Gallen and the mediX Group practice Zurich in

cooperation with the University of Zurich. The study lasted from February 2018 until May 2019. The study duration per participant was 29 days. On the first and last days of the study, participants had an in-person appointment at one of the study centers. In the time between appointments, patient-reported outcomes and nocturnal sensor data were collected by means of a smartphone.

5.2.3 Eligibility Criteria

The population investigated in this study were adults with asthma. Inclusion criteria were not restrictive to ensure that findings are generalizable to the target population of adults with asthma: participants had self-reported physician-diagnosed asthma, were 18 years or older, provided written informed consent, and knew how to operate a smartphone (self-reported in a yes–no question).

Participants with the following criteria were excluded from participation: those who were unlikely to successfully complete the daily study tasks on a regular basis (i.e., participants with cognitive impairments due to diseases such as severe depression, dementia, and Alzheimer's disease); participants for whom obtaining reliable nocturnal measurements was not feasible due to the study's rule-based smartphone recording system (i.e., participants with severe insomnia and workers with varying day and night shifts); and participants for whom a solely acoustic-based allocation of nocturnal coughs would have been highly error prone (i.e., participants who share their bedroom with a person of the same sex).

5.2.4 Outcomes and Endpoints

Overviews of the relevant study measures are presented in Table 5.2 and Table 5.3 in the data collection section (cf. Sub-section 5.2.7). Four primary endpoints were measured: coughs per night (c/n), sleep quality, asthma control, and asthma attacks. A cough is defined through its distinctive sound, which is created as a result of a "forced expulsive manoeuvre or manoeuvres against a closed glottis" (Morice et al., 2007, p. 1256). Sleep quality and asthma control were collected through questionnaires, namely the Pittsburgh Sleep Quality Index (PSQI; Buysse, Reynolds, Monk, Berman, & Kupfer, 1989) and the ACT (Nathan et al., 2004), respectively. Days with asthma attacks were self-reported by participants at the end of each study week.

5.2.5 Participant Recruitment and Timeline

Multiple recruitment channels (personal or impersonal) were employed to recruit study participants. Participants did not receive monetary incentives for study participation. Travel costs were reimbursed up to CHF 50, and, at the end of the study, a lottery was held with 10 prizes worth CHF 300 each.

The study flow chart from a participant's perspective is illustrated in Figure 5.1. Participants had to adhere fully to the protocol of the smartphone-based remote data collection phase (d_1–d_{28}) on at least 23 days. Otherwise, they were withdrawn from the study. More specifically, participants were instructed to complete the daily questionnaire, keep the study smartphone in their bedroom at night, and ensure that the smartphone either had a battery level of at least 80% or was recharged at night.

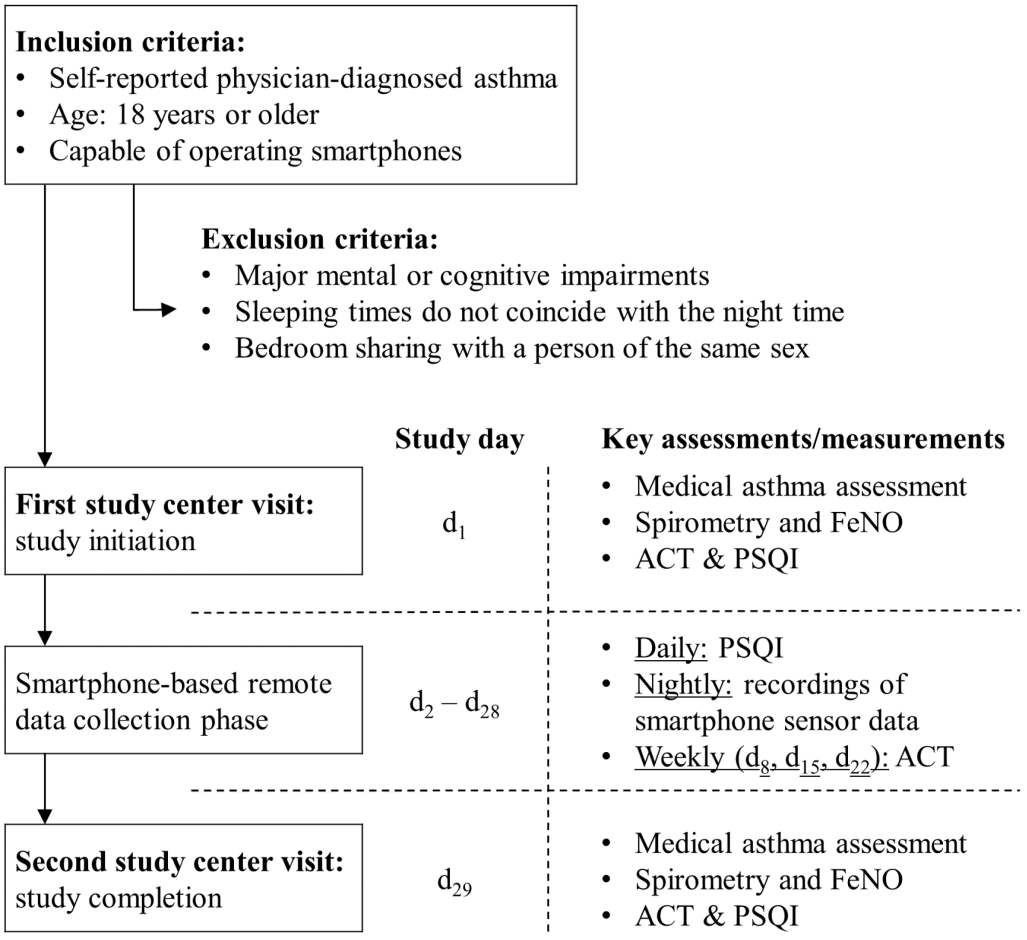


Figure 5.1. Study flow chart from the participant's perspective. ACT: Asthma Control Test; FeNO: Fractionated exhaled nitric oxide; PSQI: Pittsburgh Sleep Quality Index.

5.2.6 Sample Size

The study was powered to detect a statistically significant relationship between c/n and asthma control. The required sample size was calculated based on the results of Marsden et al. (2016). That is, a correlation of r = 0.30 between nocturnal cough frequency and asthma control was set as the expected strength of correlation. A comparable strength of association was also reported for sleep quality and asthma control (r = 0.31–0.36; Luyster et al., 2012).

In order to ensure a power (1-ß) of 80% with a two-tailed type 1-error probability (α) of 5% for rejecting a zero bivariate correlation (Hulley et al., 2013), 85 participants were required. In terms of parameter accuracy estimation (Bonett, 2002), this sample size results in a 95% CI for the above-mentioned correlation of [0.09, 0.48]. A dropout rate of 10% was assumed, thus 94 participants were recruited.

5.2.7 Data Collection

5.2.7.1 Methods

Health professionals performed medical assessments in the study centers on the first and last days of the study. For the time between physician appointments, participants were equipped with a smartphone (Samsung Galaxy A3 2017, SM-A320FL) on which "Clara", the chat-based study app, was installed. This app was a study-specific adaption of the mobile app (Kowatsch et al., 2017) for the open source behavioral intervention platform MobileCoach (www.mobile-coach.eu; Filler et al., 2015). It recorded a participant's sensor data in the night (e.g., audio data via a smartphone's microphone; cf. Appendix 7.1.1 for more information on the nocturnal recording settings) and delivered daily questionnaires to participants. Figure 5.2 illustrates the app's user experience. More information on the app is provided in the retention section (cf. Sub-section 5.2.7.3).

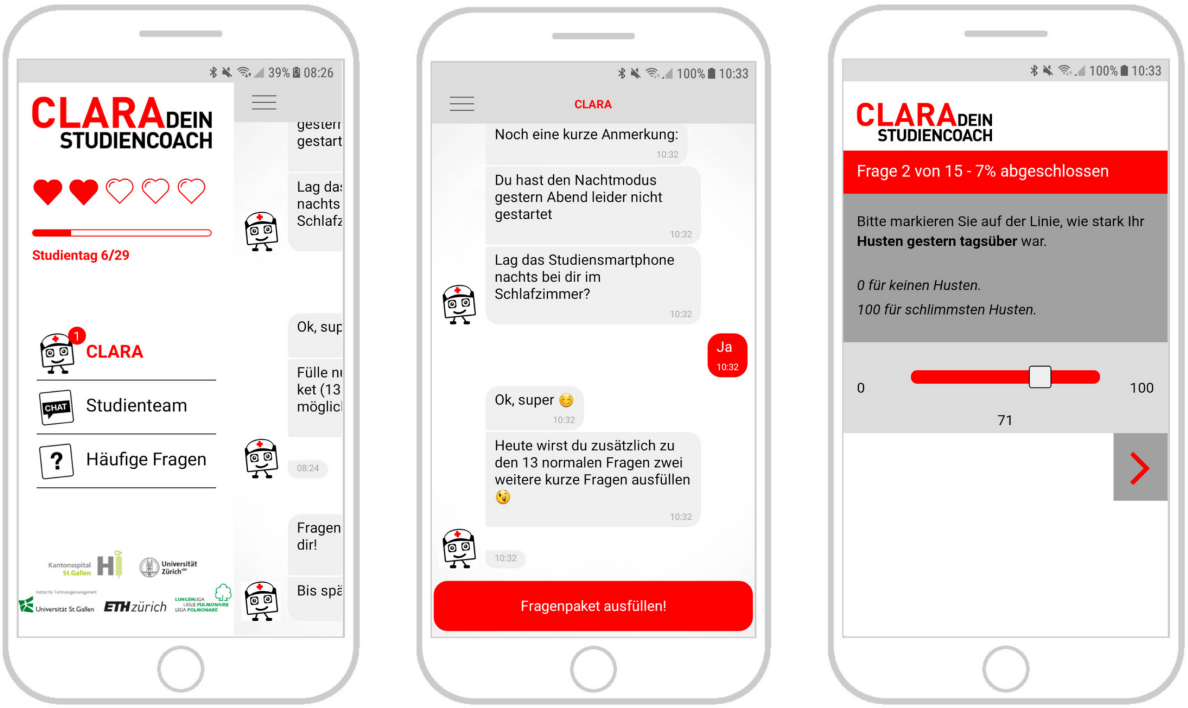


Figure 5.2. Screenshots of the "Clara" study app. Sidebar for navigation (left), chat-based interface with predefined answer options (middle), and questionnaire module for patient-reported outcomes (right).

5.2.7.2 Measures

Table 5.2 and Table 5.3 summarize the relevant measures, including their temporal frame of reference for patient-reported outcomes, time of measurement, and means by which they were obtained (e.g., medical personnel or the mobile app). All smartphone measures were collected on the study smartphone handed out to participants on the first study day. Measures can be divided into patient-reported outcomes (Table 5.2: e.g., medical questionnaires) and objective measures (Table 5.3; i.e., lung function assessments and nocturnal smartphone sensor data).

In addition to the relevant measures in Table 5.2, Table 5.3, and further measures specified in the published study protocol (Tinschert et al., 2019b), a comprehensive medical assessment of a participant's asthma was performed on the first study day.

Table 5.2. Overview of relevant patient-reported measures.

	Frame of reference	Time of measurement	Obtained by/in
Medical questionnaires			
ACT	Last 4 weeks	d_1, d_{29}	Physician
ACT	Last week [a]	d_8, d_{15}, d_{22}, d_{29}	Smartphone app
PSQI	Last 4 weeks	d_{29}	Study nurse
PSQI	Last night	Daily (d_1 – d_{29})	Smartphone app
Other questionnaires			
Measures of patient acceptance [b]	Last 4 weeks	d_{29}	Study nurse
Medical control questions			
Occurrence of cold/rhinitis	Last week	d_8, d_{15}, d_{22}, d_{29}	Smartphone app
Asthma attacks	Last week	d_8, d_{15}, d_{22}, d_{29}	Smartphone app

Note: [a] The questionnaire was adapted from originally one month to one week. [b] The following constructs were measured: spontaneous attitude towards the app concept, openness to trying the app out (adapted from Hartmann & Apaolaza-Ibáñez, 2012; Spears & Singh, 2004), and performance expectancy (Venkatesh, Thong, & Xu, 2012). ACT: Asthma Control Test; PSQI: Pittsburgh Sleep Quality Index.

Table 5.3. Overview of relevant objective measures.

	Time of measurement	Obtained by
Lung function assessments		
FEV_1, FVC, FEV_1/FVC	d_1, d_{29}	Spirometry
FeNO	d_1, d_{29}	NIOX handheld device
Smartphone data		
Microphone	Every night (n_1 – n_{28}[a])	Smartphone app

Note: [a] n1 is the night between day 1 (d1) and day 2 (d2) and so forth; for a detailed explanation of the nocturnal recording settings please refer to Appendix 7.1.1. FEV_1: Forced expiratory volume in one second; FVC: Forced vital capacity; FeNO: Fractionated exhaled nitric oxide.

5.2.7.3 Retention

Adherence to the data collection protocol was promoted through multiple strategies. First, participants met with the study nurse during their first study center visit to discuss how they could implement the instructions into their daily lives and overcome possible barriers. Second, the study app contained a reminder system. If a participant did not interact with the study app (and thus failed to comply with their study tasks), they received an SMS reminder on their private smartphone. If non-adherence occurred for two consecutive days, the participant received a reminder phone call from the study nurse. Third, the study app was specifically designed to promote participant retention.

Participants were guided through the remote data collection phase of the study by a text-based healthcare chatbot (Kowatsch et al., 2018). More specifically, all study information, instructions, and tasks were conveyed in a daily conversation with "Clara", a virtual study nurse designed to establish a working alliance with the participants (Bickmore, Gruber, & Picard, 2005). This interactive approach is known to increase adherence in clinical settings (Bickmore, Puskar, Schlenk, Pfeifer, & Sereika, 2010b). Furthermore, several nudging techniques (Thaler & Sunstein, 2008) were incorporated in the app. Figure 5.2 shows how the study made use of loss aversion in participants to increase engagement, i.e., by symbolizing non-adherence as lost hearts.

5.2.8 Analysis

5.2.8.1 Data Preparation

Labeling of Coughs per Night In order to obtain c/n, the raw audio data had to be annotated for coughs by human annotators. To quantify labeling quality, two approaches were employed. Firstly, human annotators were instructed to tag an acoustic event if they were uncertain whether it was a cough. Out of a total of 704,697 acoustic events, 30,260 were classified unambiguously as coughs. In 0.11% of all acoustic events, annotators were uncertain (i.e., 767 cases). These events were not considered in the analysis. Secondly, interrater reliability was estimated for two annotators[22] based on 65 nights using a zero-inflated generalized mixed effects model with a Poisson response distribution. The two labelers had an ICC of 95.8% (mean absolute error = 0.44 c/n) and 85.4% (mean absolute error = 0.76 c/n) for cough in general and coughs correctly assigned to the participant's sex, respectively. These ICCs can be interpreted as excellent and good reliability, respectively (Koo & Li, 2016).

Missing Data For nocturnal cough, sleep quality, and weekly asthma control, 3.03% (67 nights), 1.79% (41 questionnaires), and 3% (8 questionnaires) of observations were missing, respectively. Missing data were imputed for nocturnal cough and sleep quality. Different imputation methods were benchmarked by comparing imputations to deleted observations. For nocturnal cough, imputation was performed by means of Kalman Filtering (based on an auto-regressive moving average model fitted

[22] In total, five annotators labelled the data. However, the two annotators for whom interrater reliability was estimated together labelled 90.2% of all nights.

across all participants; Durbin & Koopman, 2012), while for sleep quality the participant mean was imputed. Imputations with negative values were set to zero.

Transformation of Predictor Variables For c/n, the raw counts were used. For 182 PSQI questionnaires (8.23%), data for six out of the seven components were available. To ensure consistent scaling, the PSQI score (for participant *j* on day *i*) was standardized using formula 1 so that a score of 0% represents the worst possible sleep quality and 100% the best possible sleep quality. In predictive modelling, the PSQI score was inverted to facilitate comparability with nocturnal cough.

$$Standardized\ PSQI\ score_{ij} = \frac{Obtained\ PSQI\ score_{ij}}{Maximum\ score\ possible_{ij}} * 100 \quad (1)$$

To investigate the associations between predictors[23] and outcomes in regression models on between- and within-patient levels, variance is decomposed through centering predictors around the grand and participant mean, respectively (Enders, 2013)[24]. Additionally, predictors were aggregated over one week for the investigation of statistical significance and monitoring performance. In this way, temporal symmetry between predictors and outcome was ensured. For the aggregation of predictor variables for investigating prognostic performance, a sliding window approach was employed (cf. Sub-section 5.3.6 for a detailed explanation).

Furthermore, the R package *tsfeatures* (Hyndman et al., 2019) was used to calculate additional predictors quantifying the time series characteristics of c/n and sleep quality for predictive modelling. More specifically, predictors based on trend decomposition (e.g., linearity, curvature, and spikes) and the autocorrelation function (e.g., the first autocorrelation coefficient of the regular, differenced, and twice-differenced time series) were estimated.

Transformation of Endpoints The weekly version of the ACT served as the main outcome in data modelling (cf. Appendix 7.1.3 for a brief validation of the weekly adaptation of the ACT). In this way, repeated measurements of asthma control are available so that within-patient variance can be modelled explicitly.

[23] To ensure consistency, the term *predictor* is used throughout this chapter instead of modelling-paradigm-specific terms (i.e., *independent variable* in explanatory modelling and *feature* in predictive modelling).
[24] For a formal explanation of variable centering, please refer to Appendix 7.1.2.

Due to the importance of the within-patient level in asthma monitoring (cf. Sub-section 2.3.3.3), clinically significant deteriorations of asthma control were selected as the outcome for modelling monitoring performance. Therefore, changes in the weekly ACT score were coded based on the minimally important difference, which is "the smallest difference in score on the instrument that represents a clinically significant change" (Schatz et al., 2009, p. 719). For the ACT, a minimally important difference of 3 points was reported (Schatz et al., 2009). The ACT score was dummy-coded accordingly: "1" for a decrease of ≥ 3 points, otherwise "0" [25].

Self-reported asthma attack days were also dummy-coded. To prevent spill-over effects, only the first attack day per participant was considered. Furthermore, attacks occurring in the first study week were excluded from the analysis due to a lack of preceding observations.

Cross-Validation Biomarker performance was estimated by means of predictive modelling. Therefore, k-fold cross-validation was employed. As suggested by Zhang (1993) and in line with best practices in data science (Ozdemir, 2016), between five and ten folds were generated. To prevent data leakage due to repeated measurements, each fold contained all observations from randomly selected participants. In this way, models were tested not only on unseen observations, but also on unseen participants. To deal with unbalanced data, the distribution of the outcome was taken into account when generating the folds. More specifically, each fold contained approximately the same number of observations from the less prevalent class.

5.2.8.2 Statistical Analyses

All analyses were performed in R 3.5.1 (R Core Team, 2018). Visualizations were created with the *ggplot2* R package (Wickham, 2016). The following additional packages were employed: for the analysis of persistence, (partial-)autocorrelation functions were estimated by means of the *Hmisc* (Harrell, 2019) and *ppcor* package (Seongho, 2015). To investigate the statistical significance, mixed effects regression models were estimated with the *lme4* package (Bates, Mächler, Bolker, & Walker, 2015). Machine learning models were set up using the *caret* package (Kuhn, 2015).

[25] While ACT scores can also be coded to categorize asthma control into uncontrolled, partially controlled, and controlled asthma (cf. Appendix 7.1.4), such a classification is particularly useful to investigate between-patient variance (e.g., for diagnostic and stratification purposes) and therefore less relevant for this chapter.

Formulas two to five formalize the performance metrics considered in predictive modelling (formulas according to Bossuyt, 2010):

$$Sensitivity = \frac{True\ Positives}{True\ Positives + False\ Negatives} \quad (2)$$

$$Specificity = \frac{True\ Negatives}{True\ Negatives + False\ Positives} \quad (3)$$

$$Positive\ predictive\ value = \frac{True\ Positives}{True\ Positives + False\ Positives} \quad (4)$$

$$Negative\ predictive\ value = \frac{True\ Negatives}{True\ Negatives + False\ Negatives} \quad (5)$$

Additionally, to quantify marker performance in unbalanced data, balanced accuracy (BAC; Guyon et al., 2008)[26,27], Youden's J Index (Bossuyt, 2010)[28], and Cohen's kappa[29] were estimated:

$$Balanced\ Accuracy\ (BAC) = \frac{Sensitivity + Specificity}{2} \quad (6)$$

$$Youden's\ J\ Index = Sensitivity + Specificity - 1 \quad (7)$$

$$Cohen's\ kappa = 1 - \frac{1 - Relative\ Correct\ Classifications}{1 - Probability\ of\ Correct\ Classifications\ by\ Chance} \quad (8)$$

5.3 Results

In the next sub-section, adherence, dropouts, sample characteristics, and descriptive statistics of both CDBs (i.e., c/n and PSQI score) and endpoints (i.e., weekly ACT score and asthma attacks) will be described.

[26] Formula 6 only applies for binary predictions and outcomes.

[27] When quantifying biomarker performance, the area under the receiver operating characteristic curve is often taken into account (Bossuyt, 2010). Since this chapter focusses on the performance of models with threshold-specific classifications, the area under the curve would be misleading (estimation based on only one set of sensitivity and specificity). However, for the binary classifications and outcomes presented in this chapter, BAC is equivalent to the area under the curve (Pedregosa et al., 2019). Swets (1988) suggested the following classification of area under the curve: rather low accuracy (< .70), useful accuracy for certain purposes (.70 – .90), and rather high accuracy (>.90).

[28] For binary predictions and outcomes, Youden's J Index is conceptionally identical to BAC and is only used for illustration purposes in graphs.

[29] Landis and Koch (1977) suggested the following classification of Kappa: poor agreement (< 0), slight agreement (0 – .20), fair agreement (.21 – .40), moderate agreement (.41 – .60), substantial agreement (.61 – .80), and almost perfect agreement (.81 – 1).

Afterwards, sub-sections are structured based on the clinical utility criteria for CDBs postulated in Sub-section 2.3.3.4, namely patient acceptance (C1), persistence (C2), statistical significance (C3), monitoring performance (C4), and prognostic performance (C5).

5.3.1 Overview

5.3.1.1 Adherence and Dropouts

The 94 recruited participants successfully completed 2,487 of the 2,557 daily questionnaires (97.26%) in the study app. To enhance adherence, the app reminder system sent out 170 SMS and triggered 41 calls by health professionals. A descriptive evaluation of Clara, the app's digital study coach, is provided in Appendix 7.2.1.

In total, 15 participants had to be excluded from analysis (=dropouts). Dropout reasons were the following: two participants withdrew by themselves, three participants were non-adherent to the study protocol, and in 10 participants, audio recordings were missing for more than five nights.

The 79 remaining participants were non-adherent to the protocol on a total of 53 days (i.e., mean = 0.67 non-adherent days per participant; SD = 1.06). The majority of the 79 remaining participants (n = 51; 72.2%) was fully adherent on all study days.

5.3.1.2 Sample Characteristics

The baseline characteristics of the sample are summarized in Table 5.4. The complete table can be found in Appendix 7.2.2.

Table 5.4. Sample characteristics at baseline.

Measure and unit (if not a count variable)	**Median (Q_1 – Q_3) or count (%)** [a]
Participant characteristics	
Age, years	45 (30–59)
Female; count (%)	53 (56%)
Body mass index, kg/m^2	25 (22–28)
Smoking status; count (%)	
Current	3 (3%)
Former	27 (29%)
Never	64 (68%)
Lung functions	
FEV_1, % predicted	88 (77–101)
FeNO, ppb	20 (12–34)
Asthma severity; count (%)	
Intermittent	13 (14%)
Mild	42 (45%)
Moderate	35 (37%)
Severe	4 (4%)
Asthma control test at baseline, points	21 (19–23)
Asthma control at baseline; count (%)	
Controlled	66 (70%)
Partially controlled	18 (19%)
Uncontrolled	9 (10%)
Incomplete measurements	1 (1%)
Type of asthma (multiple choices possible); count (%) [b]	
Intrinsic	64 (68%)
Allergic	61 (65%)
Exercise induced	44 (47%)
Attacks in the last 12 months; count (%)	
No	34 (36%)
Yes	60 (64%)
If yes, median number of attacks	2
Hospitalizations due to asthma (last 12 months)	4 (4%)
ED visits due to asthma (last 12 months)	11 (13%)

Note: [a] Median (Q_1–Q_3) by default, count (%) only if explicitly stated. [b] Answer options with frequencies below 10% are not shown. Q_1: First quartile (25th percentile); Q_3: Third quartile (75th percentile); FEV_1: Forced expiratory volume in 1 second; FeNO: Fractionated exhaled nitric oxide; ppb: Parts per billion; GINA: Global Initiative for Asthma; ED: Emergency department; ACE: Angiotensin-converting enzyme.

5.3.1.3 Descriptive Statistics

For histograms illustrating the distributions of sleep quality, nocturnal cough, and asthma control, please refer to Appendix 7.2.3.

Sleep Quality In 2,291 nights, the 79 participants slept rather well with an average sleep quality of 77.45% (SD = 15.17%).

Nocturnal Cough The distribution of c/n was heavily right-skewed. On average, participants coughed 9.86 times per night (SD = 27.06) with a median of 1 c/n (first quartile = 0 c/n, third quartile = 8 c/n). Of the 2,145 nights for which c/n was available, participants did not cough in 964 nights (44.94%). Furthermore, the distribution was characterized by outliers: in 60 nights participants coughed 75 or more times with a maximum of 345 c/n. Additionally, the average c/n varied considerably between participants. For example, while one participant did not cough at all throughout the study duration, another participant coughed almost 100 times per night on average (mean = 97.25, SD = 65.91). Figure 5.3 illustrates the between-patient differences in c/n.

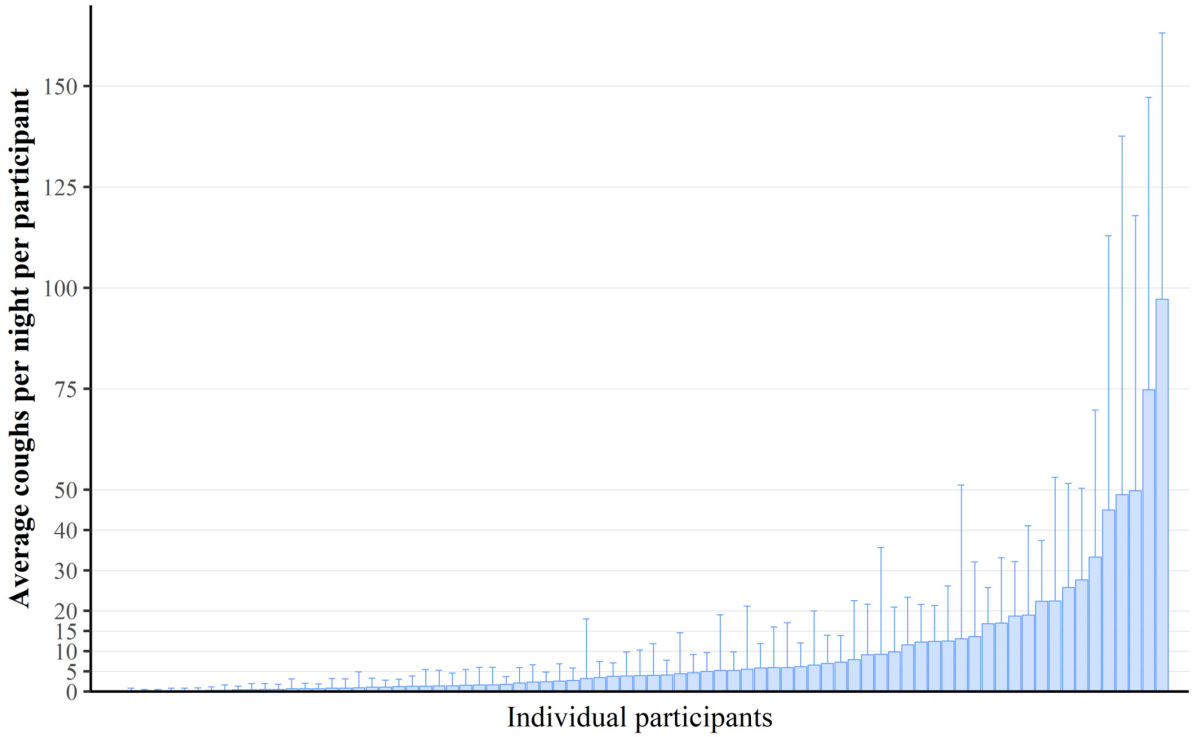


Figure 5.3. Average nocturnal coughs by participant. Each bar represents one participant. Error bars depict the standard deviation. Based on data from 2,145 nights (n = 79 participants). One patient has not coughed at all.

Weekly Asthma Control In the 316 weekly ACT measurements, participants had an average score of 20.50 points (SD = 3.54), which corresponds to controlled asthma. Changes in weekly asthma control could be calculated for 227 weeks. In the majority of weeks, no clinically significant changes occurred (166 weeks; 73.13%). Clinically significant improvements and deteriorations occurred in 32 weeks (14.10%) and 29 weeks (12.78%), respectively.

Asthma Attacks 12 participants reported suffering at least one day from an acute asthma attack during the study duration (mean = 2.92 days, SD = 2.50). In total, 35 days with attacks were registered.

5.3.2 Patient Acceptance (C1)

On the last study day, participants were presented with an abstract app concept based on passive nocturnal monitoring of the two CDBs. Participants were asked to give their spontaneous opinion of this concept on an anchored scale from 1 ("I don't like this app concept at all") to 10 ("I like this app concept very much"). The vast majority of participants (96%) liked the proposed concept (i.e., rated it six or more points), with 70% of participants selecting the second-highest (9 points; 24%) or highest (10 points; 46%) answering option. Appendix 7.3.1 contains a visualization of the distribution of participants' spontaneous opinions.

More evidence for patient acceptance was found in two additional questions. Firstly, participants were open to trying the app concept out: 70 of the 89 participants (78%) would likely (39%) or definitely (39%) try the app out, while only 7 participants (8%) were not interested in trying it out (i.e., likely not try: 6%, definitely not try: 2%). The remaining 12 participants (13%) stated they would maybe consider using such an app. Secondly, most participants believed that such an app would be helpful in managing their disease (i.e., performance expectancy): 56 participants (69%) expected such an app to improve their asthma management, 14 participants (17%) were undecided, and 11 participants did not expect a positive effect (14%). Appendix 7.3.2 further contains a correlation table between measures of patient acceptance and participant characteristics.

5.3.3 Persistence (C2)

Figure 5.4 illustrates the persistence of nocturnal cough and sleep quality by depicting the (partial) autocorrelation function. For both CDBs, statistically significant autocorrelations (i.e., correlations with preceding measurements of the same variable) throughout the entire study duration were observed. Associations with immediately preceding nights were considerably weaker for sleep quality in comparison to nocturnal cough (e.g., the first-order autocorrelation, which is the correlation of a measurement with its direct predecessor from the night before, is .66 for nocturnal cough and .44 for sleep quality). The autocorrelation pattern of sleep quality, however, appeared more stable as values fluctuated mostly between .30 and .40.

Another difference between nocturnal cough and sleep quality was observed in the partial autocorrelation function, which controls statistically for the autocorrelations of earlier lags, thereby describing the unique explanatory power of each lag. In comparison to sleep quality, the partial autocorrelation function of nocturnal cough decreased more rapidly within the first lags. Therefore, while lags beyond the second-order offered limited additional explanatory power for cough in the current night (cf. Figure 5.4, bottom-left graph), the third and fourth lags still seemed to provide explanatory power for sleep quality (cf. Figure 5.4, bottom-right graph).

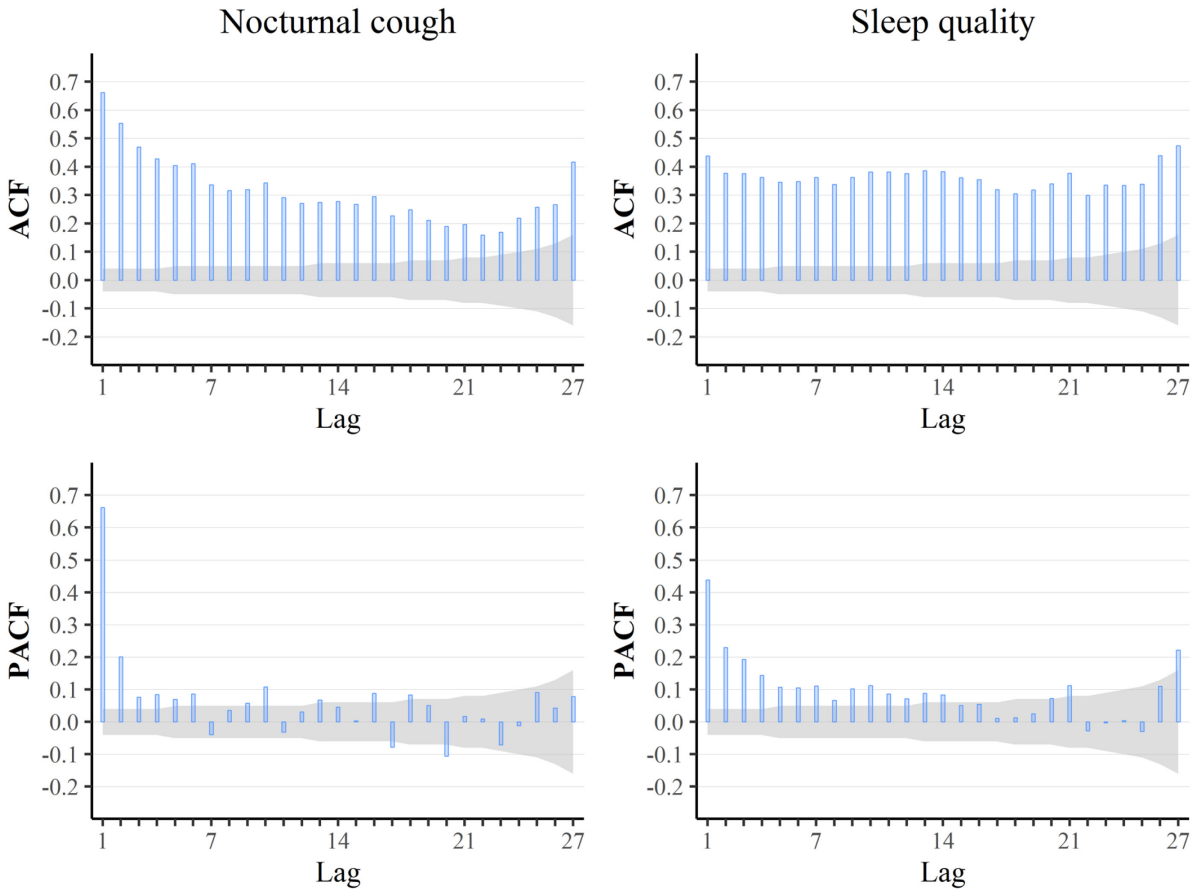


Figure 5.4. (Partial) autocorrelation functions of nocturnal cough and sleep quality. Grey colored areas depict white noise bands. ACF: Autocorrelation function; PACF: Partial autocorrelation function.

5.3.4 Statistical Significance (C3)

The mixed-effects models described in Table 5.5 demonstrate that weekly aggregated measurements of nocturnal cough and sleep quality were statistically significantly

associated with asthma control in the same week. In contrast to sleep quality, weekly aggregated nocturnal cough was also statistically significantly associated with asthma control in the subsequent week. Furthermore, the interaction between nocturnal cough and sleep quality has not reached statistical significance, suggesting that both CDBs explained asthma control independently.

Table 5.5. Summarized mixed-effects regression models for the candidate biomarkers.

	Dependent variable: Asthma Control Test score					
Lag	**Estimate**	**df**	**t**	**p**	**Marginal R^2 [a]**	**Conditional R^2 [b]**
Nocturnal cough						
l_0	-.56 [c]	287.05	-5.07	≤ .001	.06	.72
l_1	-.25 [c]	197.54	-2.28	.02	.01	.79
Sleep quality						
l_0	1.08 [d]	296.34	5.67	≤ .001	.11	.70
l_1	-.00 [d]	228.74	-1.13	.26	> .01	.73
Interaction of nocturnal cough and sleep quality [e]						
l_0	-0.14	271.34	-1.06	.29	.15	.71
l_1	-0.94	183.11	-0.21	.83	.04	.76

Note: Each line represents one mixed-effects model with a random intercept for every participant. In each model, one fixed effect was estimated, except for the interaction models, where two main effects and one interaction effect was calculated. For nocturnal cough and sleep quality, predictors are the summed raw values of the corresponding variable of the current (l_0) and the preceding (l_1) week. [a] R^2 attributable to the fixed effect(s). [b] R^2 of the whole model. [c] Rescaled estimate: An increase of 100 coughs per week reduces the ACT score by .56 (.25) points [d] Rescaled estimate: An average daily increase in sleep quality of 10% throughout the week increases the ACT score by 1.08 (0) points. [e] Estimates and parameters (df, t, p) refer to the interaction effect, main effects are not shown; predictor variables were z-standardized prior to modelling to enable model convergence.

However, the models in Table 5.5 only considered the pooled variance of each predictor. To investigate C3 properly, within-patient associations between each predictor and asthma control are relevant. Table 5.6 therefore differentiates between the explanatory power of the between- and within-patient variance of nocturnal cough and sleep quality. It reveals that both nocturnal cough and sleep quality were statistically significantly associated with asthma control on both a between-patient level and a within-patient level. It was therefore not only the case that participants with more c/n (or less sleep quality) tended to have worse asthma control, but also that an increase of c/n (or a decrease in sleep quality) was associated with a decrease in asthma control in individual participants, and vice versa.

Furthermore, as indicated by the general model fit indices listed in Table 5.6 (e.g., AIC and BIC), sleep quality explained asthma control's variance better than nocturnal cough. However, model 3, which contains both sets of predictors, explained the data statistically

significantly better than both model 1 (nocturnal cough; $\chi^2(2) = 26.28$, $p \leq .001$) and model 2 (sleep quality; $\chi^2(2) = 16.32$, $p \leq .001$). Therefore, it can be argued that both predictors had an additive relationship in explaining the variance of asthma control: while both predictors were explaining asthma control independently of each other (cf. Table 5.5), a model based on both predictors delivered more explanatory power than models based on each predictor separately (cf. Table 5.6).

Table 5.6. Comparison of mixed-effects models analyzing the explanatory power of the between- and within-patient variance of each predictor.

	Dependent variable: Asthma Control Test score		
	Model 1: Nocturnal cough	**Model 2: Sleep quality**	**Model 3: Both**
Nocturnal cough (between-patient [a])	-.87*** (.22) t = -3.99		-.51** (.21) t = -2.46
Nocturnal cough (within-patient [b])	-.46*** (.13) t = -3.60		-.41*** (.13) t = -3.23
Sleep quality (between-patient [a])		2.71*** (.48) t = 5.68	2.26*** (.50) t = 4.56
Sleep quality (within-patient [b])		1.01*** (.33) t = 3.04	.85*** (.33) t = 2.60
Intercept	20.52	22.40	22.11
Observations	308	308	308
Log Likelihood	-712.31	-705.67	-699.41
Marginal R^2 [c]	.14	.25	.29
Conditional R^2 [d]	.74	.74	.75
AIC	1,434.63	1,421.35	1,412.83
BIC	1,453.28	1,440.00	1,438.94

Note: First row contains the estimate of the predictor, second row the standard error. [a] Predictor is centered around the grand mean. [b] Predictor is centered around the participant mean. [c] R^2 attributable to the fixed effects. [d] R^2 of the whole model. AIC: Akaike information criterion; BIC: Bayesian information criterion; * $p < 0.1$; ** $p < 0.05$; *** $p < 0.01$;

Finally, to investigate the CDBs' applicability in different subgroups, an exploratory analysis was conducted. In short, only one moderator for the association of both CDBs with asthma control was found out of a total of 42 considered participant characteristics: participants with higher standard deviations of their repeated ACT measurements had a statistically significantly higher chance that nocturnal cough ($p = .001$) and sleep quality ($p = .01$) were statistically significantly associated with asthma control in the expected direction (i.e., more cough/lower sleep quality was associated with lower levels of asthma control with statistical significance, and vice versa). Furthermore, for

participants reporting to usually not cough at night (p = .03), the likelihood was statistically significantly higher that nocturnal cough is associated with asthma control in the expected direction (albeit without statistical significance). For the full analysis, please refer to Appendix 0.

5.3.5 Monitoring Performance (C4)

To investigate the monitoring performance of both CDBs, clinically meaningful deteriorations in asthma control were classified using predictor data from the week of the deterioration. In contrast to the preceding sub-section, predictive modelling was employed. More specifically, data were modelled using 5-fold cross-validation.

Two analysis approaches were employed: machine learning algorithms and threshold-based decision boundaries. For machine learning algorithms, predictors and time series characteristics were used as input variables. Appendix 7.3.5 provides a comprehensive description of the machine learning model training settings. The application of threshold-based classifiers seemed promising due to the visible differences in the distributions of nocturnal cough and sleep quality between weeks with and without clinically meaningful deteriorations (cf. Appendix 7.3.4). A threshold-based classifier derives its predictions as follows: if, for example, a certain amount of c/n (i.e., the optimal threshold in the train data set, which consists of data from four of the five cross-validation folds) was reached or surpassed in a week from the test data set (i.e., the remaining fifth fold), a deterioration in this week is predicted – otherwise the model classifies the week as being without deterioration. For threshold-based models, only the predictors (i.e., nocturnal cough and sleep quality aggregated over the same week as the asthma control measurement) were considered.

Figure 5.5 shows the Cohen's kappa of the models grouped by algorithm and predictor set (i.e., models based exclusively on nocturnal cough or sleep quality, or both sets of predictors combined). In general, sleep quality (including its time series predictors) seemed to perform better in algorithms designed for modelling linear relationships (i.e., logistic regression and support vector machines), while cough achieved better results in tree-based methods. The Cohen's kappa of the most performant models ranged between .2 and .3, which can be interpreted as a "fair" agreement[29]. The best overall model in terms of Cohen's kappa values was a random forest based on nocturnal cough predictors with a sensitivity of 39% (SD = 26%), a specificity of 91% (SD = 3%), a positive

predictive value of 39% (SD = 16%), a negative predictive value of 91% (SD = 4%), a BAC of 66% (SD = 13%), and a Cohen's kappa of 30% (SD = 22%).

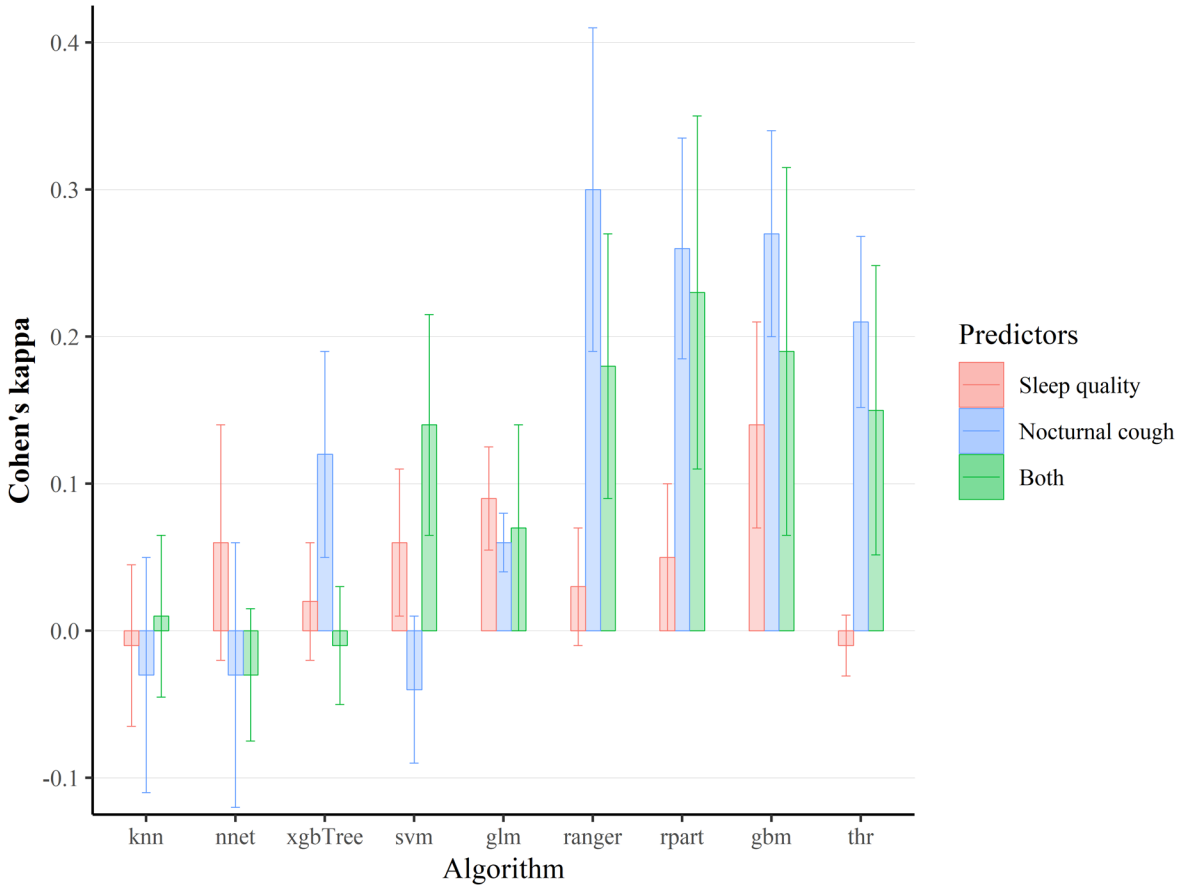


Figure 5.5. Cohen's kappa of models examining monitoring performance. Error bars indicate the standard deviation across test folds (+/- 0.5 SD). Knn: K-nearest neighbors; nnet: Neural net; xgbTree: Extreme gradient boosting; svm: Support vector machines; glm: Logistic regression; ranger: Random forest; rpart: Decision tree; gbm: Gradient boosting machine; thr: Threshold-based model. For details on model training and a result table please refer to Appendix 7.3.5 and Appendix 7.3.6, respectively.

Figure 5.5 further indicates that the best classifiers were models based on nocturnal cough. From the models listed in Figure 5.5, random forest ("ranger"), decision tree ("rpart"), logistic regression ("glm"), gradient boosting machine ("gbm"), neural nets ("nnet"), and extreme gradient boosting ("xgbTree") provided estimates for predictor importance. As depicted in Figure 5.6, weekly aggregated nocturnal cough emerged as the most important predictor for classifying clinically significant deteriorations in asthma control. Weekly aggregated sleep quality, in contrast, placed ninth in terms of importance from a total of 24 predictors.

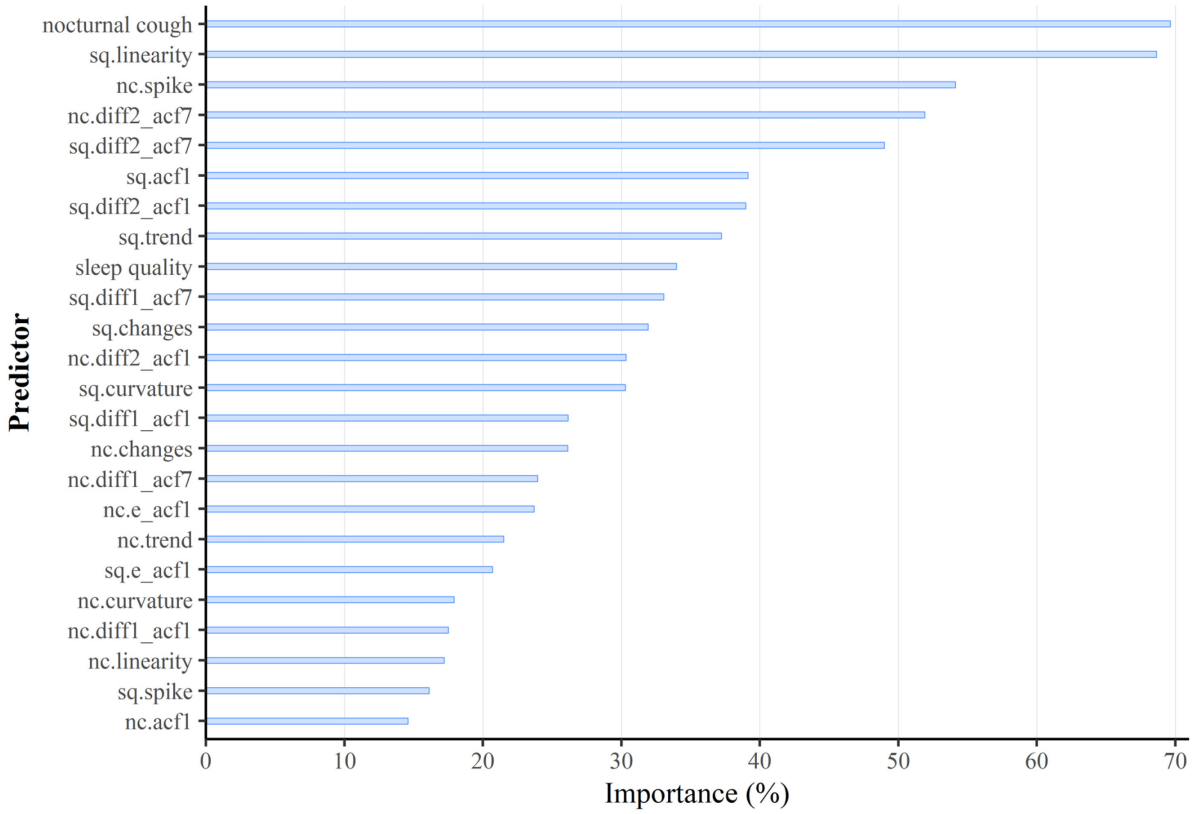


Figure 5.6. Predictor importance of all models from Figure 5.5, which are based on both predictors and output predictor importance. Prefixes "sq" (sleep quality) and "nc" (nocturnal cough) specify the referenced time series/predictor. Figure contains weekly aggregated predictors (i.e., "nocturnal cough", "sleep quality", and their "changes" over time) and time series predictors (i.e., all remaining predictors, further specified through the following suffixes: acf7: Sum of squares of the autocorrelation function of the last seven days; acf1: First coefficient of the autocorrelation function; e_acf1: First coefficient of the error term of the decomposed autocorrelation function). Diff1/diff2 indicates whether a predictor refers to the first/second-order differenced series.

Considering the high interpretability of threshold-based models, their classification performance is of particular interest and will be investigated in the remainder of this sub-section. Due to the exploratory character of this analysis and to enhance interpretability, the decision boundary threshold was directly applied to the entire sample, so that no internal validation was performed[30] (in contrast to Figure 5.5, where thresholds were internally validated).

[30] Please note that despite the lack of internal validation, the standard deviation across test folds will be reported in the subsequent paragraphs and will be depicted in the corresponding figures (i.e., Figure 5.7 – Figure 5.9) as an indicator of the variance in performance of threshold-based classifiers.

Figure 5.7 shows the classification performance of a threshold in weekly aggregated nocturnal cough. The model with the best classification performance (i.e., highest Cohen's kappa) had a threshold of 55 nocturnal coughs per week. More specifically, it had a sensitivity of 62% (SD = 27%), a specificity of 75% (SD = 8%), a positive predictive value of 27% (SD = 10%), a negative predictive value of 93% (SD = 5%), a Cohen's kappa of 24% (SD = 17%), and a BAC of 69% (SD = 13%).

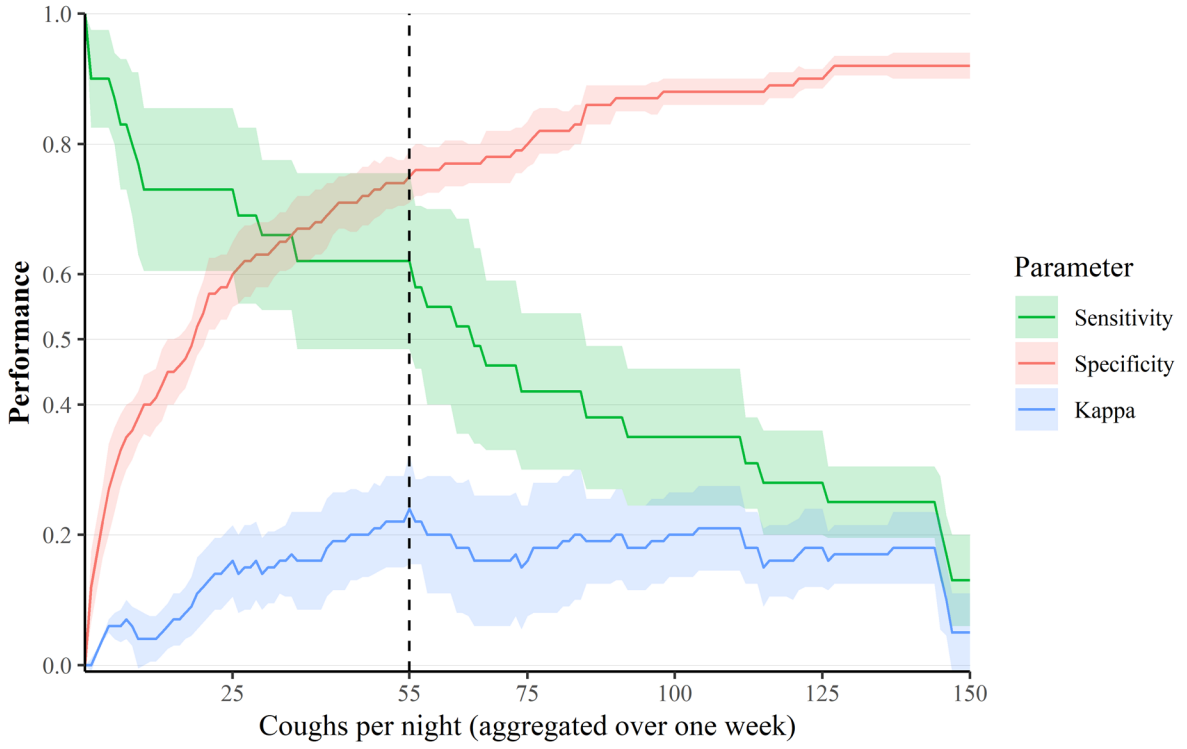


Figure 5.7. Performance of threshold-based models of nocturnal cough. Colored areas indicate the standard deviation across test folds (+/- 0.5 SD). The dashed line specifies the threshold with the highest kappa (Cohen's kappa).

Figure 5.8 replicates Figure 5.7 for weekly aggregated sleep quality (scaled to daily values). As evident by the consistently low Cohen's kappa values, classification of weeks with clinically significant deteriorations in asthma control based on a sleep quality threshold does not appear feasible. The best model based on Cohen's kappa, which used an average daily sleep quality of 88% as the decision threshold, achieved a Cohen's kappa of merely 4% (SD = 18%) and a BAC of 52% (SD = 9%), with a sensitivity of 18% (SD = 18%), a specificity of 87% (SD = 5%), a positive predictive value of 15% (SD = 17%), and a negative predictive value of 88% (SD = 3%).

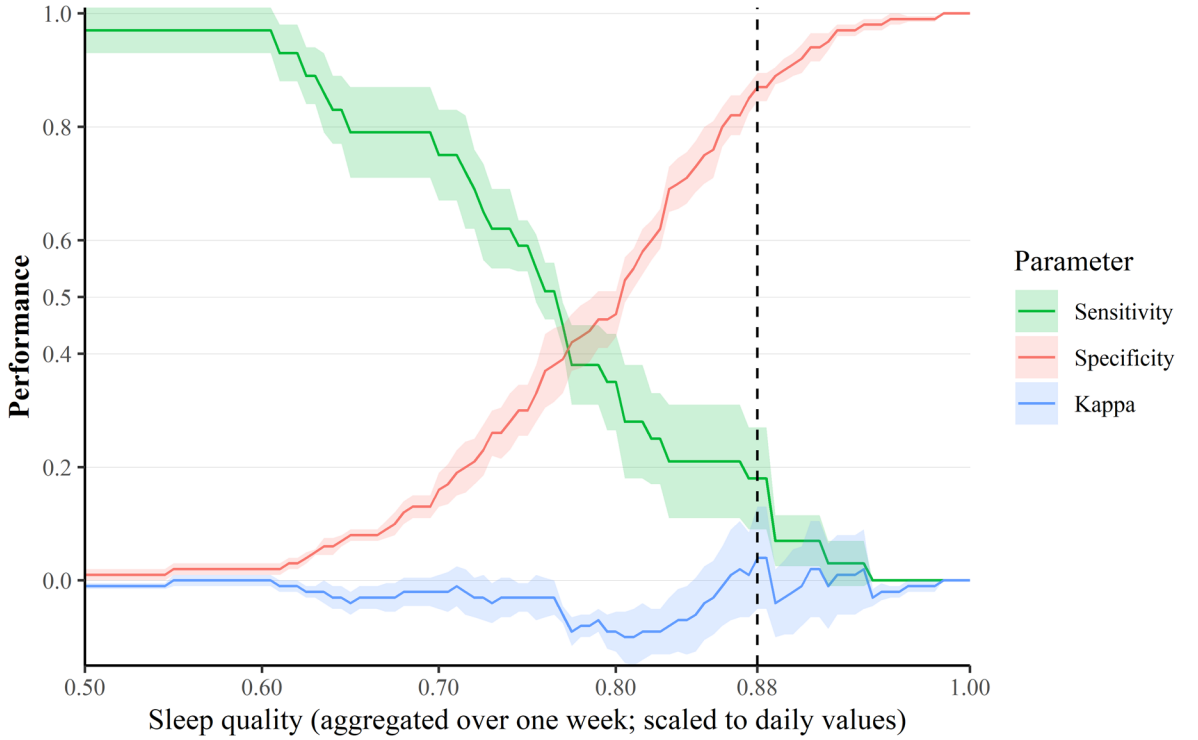


Figure 5.8. Performance of threshold-based models of sleep quality. Colored areas indicate the standard deviation across test folds (+/- 0.5 SD). The dashed line specifies the threshold with the highest kappa (Cohen's kappa).

By scaling nocturnal cough and sleep quality around their means, the performance of a threshold-based model for the sum of both predictors could be estimated. Therefore, Figure 5.9 provides insights into whether combining both parameters leads to better threshold-based models. While combining both parameters clearly outperformed models based on sleep quality alone, nocturnal cough alone enabled the best classifications: the best model with both parameters (i.e., threshold at the 87th percentile of the complete sample) had a lower Cohen's kappa (κ = 21%, SD = 18%) than the best nocturnal cough model (i.e., $\Delta\ \kappa$ = 3%). The best combined model further had a BAC of 62% (SD = 10%), a sensitivity of 35% (SD = 19%), a specificity of 88% (SD = 1%), a positive predictive value of 29% (SD = 13%), and a negative predictive value of 90% (SD = 3%).

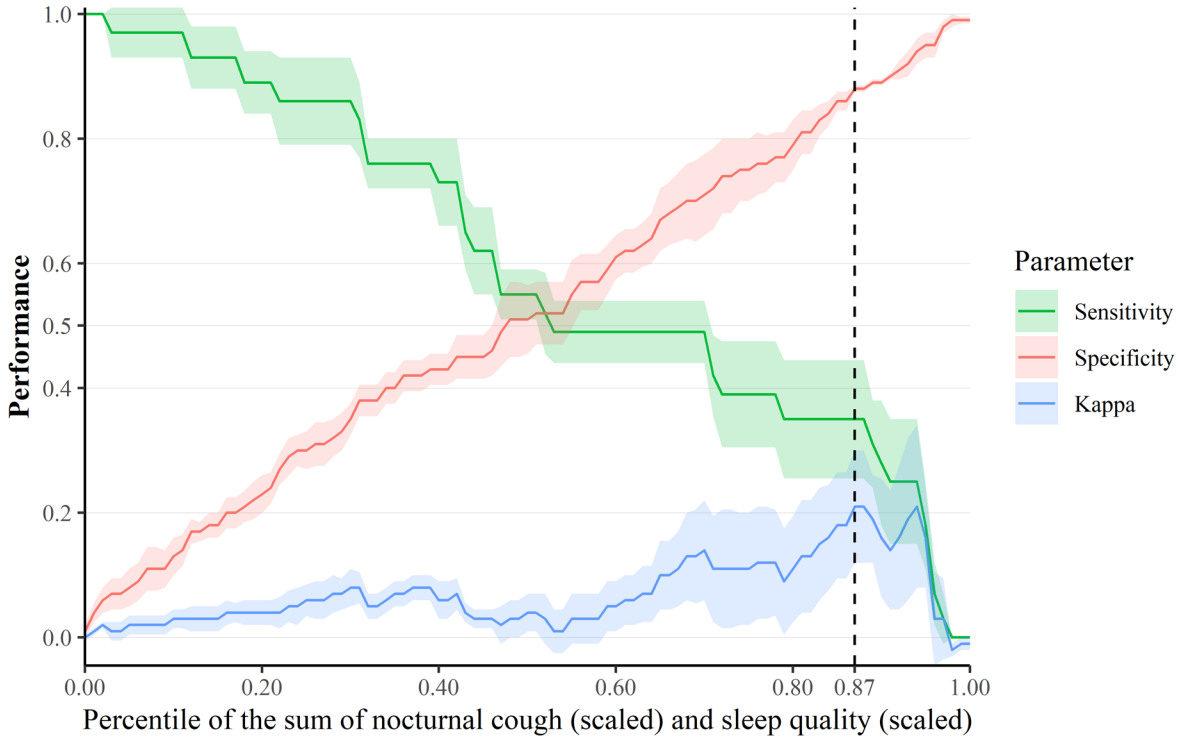


Figure 5.9. Performance of combined threshold-based models. Colored areas indicate the standard deviation across test folds (+/- 0.5 SD). The dashed line specifies the threshold with the highest kappa (Cohen's kappa).

5.3.6 Prognostic Performance (C5)

As pointed out in Sub-section 5.3.1.3, participants reported few attacks during the study duration. After applying the criteria specified in Sub-section 5.2.8.1, eight self-reported asthma attacks remained in a total of 2,004 study days.

Data were modelled using leave-one-out cross-validation, which in this case corresponds to an 8-fold cross-validation. A sliding window modelling approach was employed to evaluate the prognostic performance of nocturnal cough, sleep quality, and both CDBs in combination. Two parameters of the sliding window were varied: the length of the sliding window (i.e., 1 – 7 days) and the start of the sliding window (i.e., 0 – 7 days in advance, which corresponds to the lag of the predictors). For prognostic performance, the latter parameter is of interest since it answers the question of how many days in advance an asthma attack can be detected. The former parameter will not be explicitly considered in the analyses, but is provided in Appendix 7.3.6. As the first attack occurred on the ninth study day, the sliding window was restricted to encompass

a maximum of eight preceding days. Predictors were aggregated over the sliding window[31].

Machine learning models based on the most performant algorithms from Figure 5.5, trained with different re-sampling methods, cross-validation strategies, and predictor combinations (i.e., with and without time series predictors), failed to detect any attacks in the test data sets (i.e., sensitivities of 0%).

Therefore, threshold-based models were employed. Contrary to the preceding chapter, their performance was assessed based on a different parameter: due to the extreme imbalance of outcome classes, Cohen's kappa would inherently favor specificity over sensitivity in model selection. However, for the early detection of attacks, the latter parameter is decisive. Therefore, model selection was done based on the BAC and Youden's J Index, which weigh both parameters equally[28].

Figure 5.10 illustrates the predictive performance of nocturnal cough, sleep quality, and their combination by depicting the BAC for each lag. In contrast to monitoring performance, for which nocturnal cough outperformed sleep quality, sleep quality predicted asthma attacks more accurately. While nocturnal cough achieved a higher BAC than sleep quality only in the first lag (i.e., 69% vs. 65%), sleep quality delivered more accurate predictions in all remaining lags. However, the best prediction performance was observed for the combination of both parameters: together, both predictors consistently achieved a BAC of .70 or higher in the first four lags. In particular, for the sixth lag, the combination of both predictors resulted in a considerable increase in prediction performance in comparison to both predictors separately (i.e., a BAC of 67% (combination) vs. 53% and 57% for nocturnal cough and sleep quality, respectively). The complete model result table is provided in Appendix 7.3.6.

Figure 5.11 examines the prediction performance of nocturnal cough, sleep quality, and their combination in more detail by depicting the model with the highest Youden's J Index for each predictor and lag. Up until the third lag (nocturnal cough) and fourth lag (sleep quality and both predictors combined), prediction performance fluctuated around a stable level (i.e., increases in sensitivity between lags were offset by similar decreases in specificity, and vice versa). In these lags, the Youden's J Index ranged between .2 and .4 for nocturnal cough, between .3 and .4 for sleep quality, and between .4 and .5

[31] For example, a sliding window that started on the second day (i.e., a lag of two days) and had a length of four days aggregated the values of the corresponding predictor from the second to the fifth day before the attack.

for the combination of both predictors. In later lags, prediction performance decreased considerably and continuously, at least if predictors were considered separately (a slight increase in prediction performance from the fifth to the sixth lag was observed if both predictors are combined). However, all Youden's J Indices dropped below 0 in the last lag, which implies a worse prediction performance than a classifier that would always predict the dominant class (i.e., no attack).

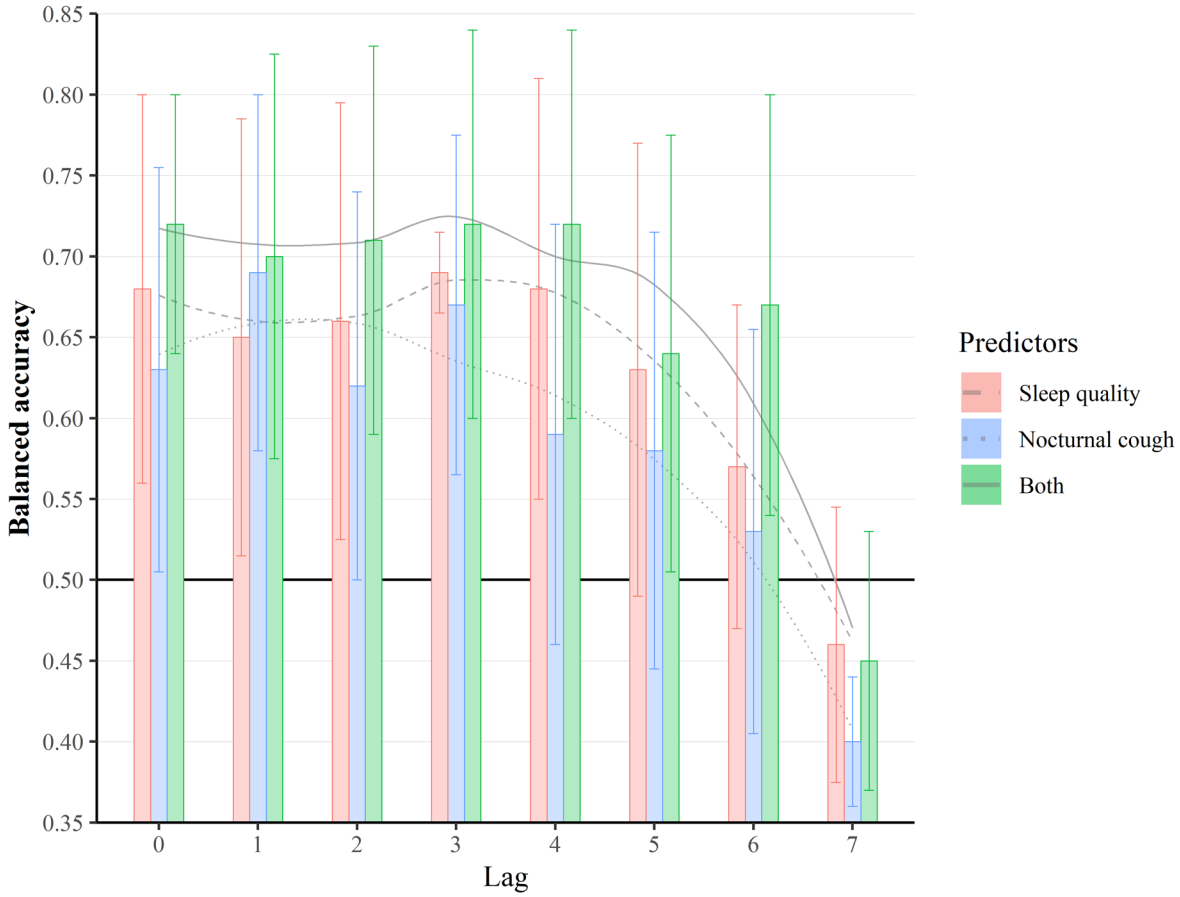


Figure 5.10. Balanced accuracy of threshold-based prognostic models of nocturnal cough, sleep quality, and both predictors combined for asthma attack detection. Trend lines are estimated through local polynomial regression. Lag refers to the predictor variables. The black line indicates the balanced accuracy of a model which always predicts the dominant class (i.e., no attack will occur at all).

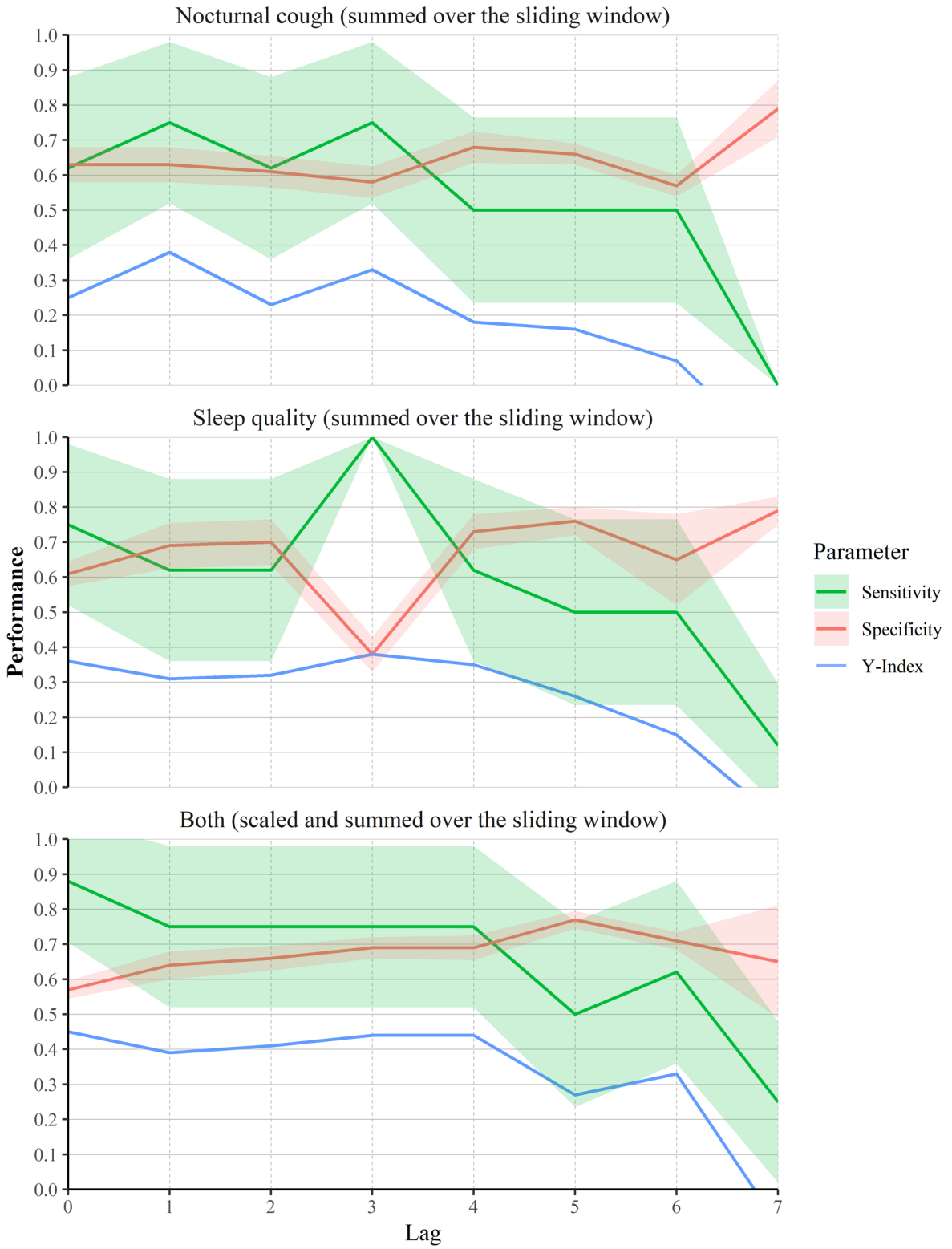


Figure 5.11. Prognostic performance of threshold-based models of nocturnal cough, sleep quality, and both predictors combined for asthma attack detection. Colored areas indicate the standard deviation across test folds (+/- 0.5 SD). Lags refer to the predictor variables. A Y-Index of 0 indicates the performance of a model that always predicts the dominant class. Y-Indices below 0 are not depicted. Y-Index: Youden's J Index.

5.4 Discussion

5.4.1 Principal Findings

The objective of this chapter was to assess the clinical utility of nocturnal cough and sleep quality as digital biomarkers for asthma. Clinical utility was defined by virtue of five criteria: patient acceptance (C1), persistence (C2), statistical significance (C3), monitoring performance (C4), and prognostic performance (C5). To investigate these criteria, an analysis of 2,212 nights of 79 participants suffering from asthma was conducted. In the following, the results for each criterion will be summarized.

The results demonstrate patient acceptance (C1) despite the inherent privacy-invasiveness of passive nocturnal monitoring. On a more critical note, the participants gave their informed consent to participate in a study on nocturnal asthma monitoring. It can be argued that the observed acceptance could be due to a self-selection bias (Heckman, 2010), meaning that patients who had greater privacy concerns have chosen not to participate in the study. However, an alternative explanation is that participants perceived the proposed app concept as creating considerable value for them, so that the expected benefits outweighed their privacy concerns. The weighing of benefits against privacy concerns is referred to as the *privacy calculus* in literature (e.g., Kehr, Kowatsch, Wentzel, & Fleisch, 2015). The latter explanation is also supported by the survey data, since participants' spontaneous opinions of the app concept and their openness to trying it out depended on the benefit they expected to receive through the app (cf. Appendix 7.3.2). This explanation is in line with the findings reported in Chapter 4, which indicate that participants in two focus groups, who were otherwise skeptical of digital interventions, also believed that passive nocturnal monitoring could support them in managing their asthma.

Both CDBs can be considered to be highly persistent (C2) as their autocorrelations throughout the entire study duration were positive and statistically significant. For sleep quality, this finding is in line with previous research that has found long-term persistency of impaired sleep quality in different subgroups (e.g., Belleville, Guay, & Marchand, 2011; Quan et al., 2005). Less research is available with regard to nocturnal cough. In general, humans have an increased threshold of the cough reflex at night (Wang, Nakagawa, Sekizawa, Kamanaka, & Sasaki, 1998). In addition to the inhibitory effects on cough at night, which are believed to be controlled by the cerebral cortex,

many proximate causes of cough are also less prevalent at night (e.g., exposure to cough-inducing stimuli). Both factors lead to almost complete suppression of nocturnal cough in healthy people and to a reduced nocturnal cough frequency in patients suffering from chronic cough (Lee & Birring, 2010). The results for this criterion provide initial insights into how nocturnal cough behaves in asthma when it occurs. More specifically, its occurrence followed an underlying pattern over many nights and was not driven by a random process.

In terms of statistical significance (C3), this chapter replicated the associations between both CDBs and asthma control reported by Marsden et al. (2016) and Luyster et al. (2012). In addition to the correlations on a between-patient level found by prior research, it demonstrated that the associations also hold on a within-patient level. Not only did participants with better asthma control tend to cough less at night and to sleep better, but changes in nocturnal cough and sleep quality were also indicative of changes in asthma control for individual participants. This finding supports the utility of both CDBs for asthma monitoring – prior research, which was based on cross-sectional association, only warranted the usage of both CDBs for stratification purposes. Interestingly, statistical significance was observed despite a comparatively homogenous sample in terms of asthma control: large scale surveys have found shares of patients with controlled asthma between 20% and 30% and a prevalence of uncontrolled asthma between 40% and 50% (Murphy et al., 2012; Price et al., 2014). In the present study, the majority of participants had controlled asthma (70%) and only a small fraction suffered from uncontrolled asthma (10%). Furthermore, in the majority of participant study weeks (73%), no clinically meaningful changes in asthma control occurred. Therefore, only limited variance in asthma control was available for modelling. Interestingly, the subgroup analysis in Appendix 0 shows that for participants with higher variances in their repeated asthma control measurements, an association of both CDBs with asthma control was more likely. Furthermore, it can be argued that in a sample with worse asthma control, stronger and more frequent symptoms would likely have been observed, which could also improve the explanatory power of statistical models. In summary, the association between both CDBs and asthma control might be stronger in a more clinically relevant sample.

For monitoring performance (C4), nocturnal cough delivered a higher biomarker performance than sleep quality. One plausible explanation for the lower monitoring performance of sleep quality could be that it is less indicative of respiratory functions

than cough. Sleep quality is considered a general marker for physical health and mental health (Reid et al., 2006). It seems reasonable that the monitoring of an inherently unspecific marker would provide less precise insights about a patient's asthma control than a respiratory system-specific parameter such as nocturnal cough.

In terms of Cohen's kappa, the best monitoring models ranged between .2 and .3, which can be interpreted as a fair agreement between model predictions and actual observations. Interestingly, threshold-based models performed quite well on the data set despite the bias induced by their simplicity: the best threshold-based model for nocturnal cough achieved a lower Cohen's kappa of 9% in comparison to the best machine learning model (i.e., 21% versus 30%). Considering that machine learning models had access to additional predictors (i.e., time-series characteristics) and the well-recognized problems of transparency and interpretability for many of the employed algorithms (Došilović, Brčić, & Hlupić, 2018), one could argue for a higher utility of threshold-based models based on the presented analyses. However, due to the fact that machine learning models only play to their full algorithmic potential in large data sets (Jordan & Mitchell, 2015; Suthaharan, 2014), it may well be the case that machine learning models would outperform threshold-based models more clearly in a larger sample with more data per participant. Nevertheless, in the medical domain, where critical treatment decisions need to be based on the output of predictive models (Chen & Asch, 2017), interpretability and transparency of these models seem particularly important. Therefore, based on the analyses of C4, a decision rule of 55 or more nocturnal coughs per week can be recommended to indicate deteriorations in asthma control with a BAC of almost 70%.

For prognostic performance (C5), a diverging conclusion can be reached with regard to the importance of both CDBs: sleep quality predicted asthma attacks more accurately than nocturnal cough in almost all predictor lags. Interestingly, prediction performance drops after the third (nocturnal cough) and fourth lag (sleep quality), which could be explained through less signal and/or less available predictor data (i.e., for later lags, the length of the sliding window is inherently limited). However, the complete model results presented in Appendix 7.3.6 illustrate that while usually models based on a longer sliding window were selected, this is not always the case (e.g., the well-performing unlagged sleep quality model considered only the preceding night, even though sliding window lengths of up to eight days were available). Therefore, it seems more likely that the worse prediction performance was due to less signal in the data as opposed to shorter

sliding window lengths. This explanation would also be in line with prior research describing the course of an asthma attack, which will be discussed Sub-section 5.4.3.

In contrast to C4, where combining both CDBs has not delivered an additional benefit in biomarker performance, asthma attack detection improved considerably when both CDBs were combined: up to the fourth lag, six of the eight asthma attacks were correctly detected. To contextualize these results, the GINA guideline recommendations for the treatment of asthma attacks can be considered: after noticing worsening asthma symptoms, patients should at least double their controller medication dose and increase the frequency of reliever medication usage. If no improvement occurs after two days, a physician should be consulted so that, depending on the attack severity, a course of oral corticosteroids (up to 50mg of prednisolone) can be initiated for 5 to 7 days (Global Initiative for Asthma, 2018). Therefore, early warnings of four days before an attack would give patients a window of opportunity to initiate pharmaceutical treatment early enough to conclude the first stage of treatment escalation (i.e., increase of controller and reliever medication for 48h) and to decide whether a physician visit would still be necessary. Furthermore, oral corticosteroids take effect within 12h to 24h (Honkoop et al., 2013). Therefore, early warnings more than three days before an attack could theoretically allow patients to have already visited their physician, receive a prescription of oral corticosteroids if needed, and be under their effect before symptom deteriorations have developed into a life-threatening attack.

5.4.2 Limitations

In the following, three limitations will be highlighted. Further limitations due to the study design are discussed in the published study protocol (Tinschert et al., 2019b).

The first limitation refers to interpretations of the predictive modelling results (i.e., C4 and C5). In both predictive modelling tasks, outcome classes (weeks with/without deterioration for C4 and attack/no attack for C5) were unbalanced (i.e., roughly 1:10 for C4 and 1:250 for C5). Since biomarker performance is contingent upon the class distributions in the sample (Bossuyt, 2010), the reported figures must be interpreted with caution. Thus, C4 and C5 should be viewed as exploratory research.

A second limitation was that only 29 days of data were available per participant. All threshold-based models presented in the analysis of C4 and C5 rely on a general threshold, which was identical for all participants. However, taking into account the

differences in nocturnal cough between participants and the considerable explanatory power of the random intercept (i.e., the difference between the marginal and conditional R^2 in Table 5.5 and Table 5.6), it seems likely that personalized models (e.g., a different threshold for each participant) would result in a higher biomarker performance. Furthermore, having more data available per participant would enable more complex prediction models as more predictors could be considered. For monitoring performance, for example, predictors had to be aggregated weekly as stipulated by the ACT, which reduced sample size from 2,291 days to 227 weeks. As recommended by Hua, Xiong, Lowey, Suh, and Dougherty (2004), the rule of thumb for selecting the number of (correlated) predictors in predictive modelling is the square root of the sample size, which would correspond to 15 predictors for C4. Therefore, the limited sample size prohibited the inclusion of more predictors in the models (e.g., more than 40 participant characteristics were considered in the subgroup analysis presented in Appendix 0)[32].

The third limitation is concerned with the generalizability of marker performance. In the analyses on statistical significance, monitoring performance, and prognostic performance, only one active smoker was included in the sample. However, prior research has found that smokers have a significantly higher cough reflex threshold (Dicpinigaitis, 2003). Smoking is also considered to be one of the most common causes for persistent cough (Morice, McGarvey, & Pavord, 2006). Due to the established relationship between smoking and cough, biomarker performance of nocturnal cough might be different in a sample with a higher share of smokers. However, this limitation may be addressed by personalized prediction models and thresholds that future research should strive towards (cf. discussion in the preceding paragraph).

5.4.3 Comparison to Prior Work

Two streams of prior work are considered in this section: research on nocturnal cough in asthma and research on early prediction of asthma attacks[33].

Marsden et al. (2016) found a cross-sectional correlation between nocturnal cough and asthma control of .30. If the same correlation ought to be replicated in the present study,

[32] However, please note that the objective of this chapter was to evaluate biomarker performance and not to develop a prediction model for asthma control and/or asthma attacks. Even though both tasks require a similar analysis approach, they are different tasks with diverging priorities (e.g., interpretability of models).

[33] Due to the transformation of the PSQI from a monthly to a daily measurement, and the fact that sleep quality estimates vary considerably by measure (Matthews et al., 2018), sleep quality results will not be explicitly compared to prior work.

it would not have reached statistical significance: the absolute value (abs) of the correlation between the monthly ACT score at day 29 and c/n of the directly preceding night was .16 (p = .17). Yet statistical significance was reached if c/n is aggregated over the week prior to the ACT measurement or over the entire four study weeks (i.e., abs(r) = .24, p < .05 and abs(r) = .27, p = .01, respectively). However, due to the different operationalizations of asthma control in both studies (i.e., ACQ in Marsden et al. (2016) and ACT in the present study), direct comparisons of two correlation coefficients have to be interpreted carefully.

Cough frequency, in contrast, can be compared directly between studies: Marsden et al. (2016) have reported a geometric mean of .50 coughs per hour. In the present study, the geometric was almost identical, with .49 coughs per hour. Patients with asthma coughed more frequently at night in a study by Fukuhara et al. (2019): they reported a median of 4.7 c/n (interquartile range = [1.7,13.7]), whereas the median in the present study was 1 c/n (interquartile range = [0,8]). A possible explanation might be that patients included in the Fukuhara et al. (2019) study had a considerably lower level of asthma control on average (i.e., a mean ACT score of 15.9 (SD = 4.6) versus a mean ACT score of 20.5 (SD = 2.8) on the first study day of the present study).

Interestingly, while in the present sample FeNO was not associated with nocturnal cough, which is in line with the findings of Marsden et al. (2016) and Fukuhara et al. (2019), different results emerged in terms of nocturnal cough's relationship with FEV_1%. The two above-mentioned studies report that nocturnal cough frequency is not statistically significantly associated with FEV_1%. This was also true for the present study, if only c/n from the night before the FEV_1% measurement was considered (r = -.13, p = .25). However, there was a statistically significant correlation between FEV_1% and nocturnal cough on a between-patient level if cough was aggregated (e.g., r = -.22, p = .05 and r = -.28, p = .01 for the week before the FEV_1% measurement and for the entire study duration, respectively). Together with the preceding paragraph, it seems that the consideration of past values in nocturnal cough provides additional information for understanding its role in asthma. It may, for example, reflect memory effects in the respiratory system as discussed by Frey and Suki (2008).

The second literature stream is concerned with asthma attacks and their early detection. Tattersfield et al. (1999) have descriptively investigated 425 severe attacks with regard to changes in symptoms and PEF in the two weeks prior to the attack. They have found that the decline in PEF and symptoms "occurred gradually between day -10 and day -3

and then more rapidly" (Tattersfield et al., 1999, p. 595). Similar courses of asthma attacks were described by Honkoop et al. (2013). While the analysis of prognostic performance in this chapter only considered lags up until the seventh order, the results presented in Figure 5.10 seem to converge with the aforementioned descriptions: after the third or fourth lag (for nocturnal cough and sleep quality, respectively), asthma attack detection performance also decreased gradually.

Honkoop et al. (2013) evaluated action points (e.g., increase of symptom scores by more than two standard deviations and a PEF of < 70% pb) for asthma early attack detection. For that purpose, two data sets based on diary data from a total of 259 patients were analyzed over the span of 12 to 18 months. In the validation data set, they achieved an average BAC for attack prediction of .77 for symptom-based action points (on average 3.70 days ahead of the attack) and .82 for peak-flow-based action points (on average 2.98 days ahead of the attack). In the present study, models with a comparable predictor lag (i.e., three and four days ahead of the attack) achieved an average BAC of .68. One possible explanation for the lower BACs in the present study might be the different study durations: Honkoop et al. (2013) had access to more data per patient (12–18 months versus 29 days), which allowed them to estimate a person-specific symptom baseline level using periods in which patients' asthma was under control. Having a valid baseline available per patient may particularly enhance a model's specificity, as it provides additional information, for example, on whether a cough frequency that would be considered clinically relevant for most patients is in fact normal for a given patient and thus must not be mistakenly classified as an early attack sign. Indeed, the classification models published by Honkoop et al. (2013) outperform the models presented in this chapter mainly due to a better specificity: while models in this chapter have a similar sensitivity (both 68%), their specificity was considerably lower (65% versus 92%)[34,35].

5.4.4 Contributions to Research

While prior research on nocturnal cough and sleep quality in asthma relied mainly on cross-sectional study designs (e.g., Fukuhara et al., 2019; Luyster et al., 2012; Marsden

[34] Symptom score and PEF models from the validation data set as reported by Honkoop et al. (2013) have been compared against models with a comparable predictor lag (up to 5 days) from this chapter.

[35] An action-point-inspired approach has also been evaluated in the present study (i.e., predictors were within-patient scaled, so that their daily values represent deviations from the patient mean), but resulted in a worse early attack detection (unscaled predictors achieved an average Youden's J Index of .16 across all threshold-based models, while the same models with scaled predictors had a mean Youden's J Index of .03).

et al., 2016), the study presented in this chapter was, to the best knowledge of the author, the first longitudinal study in this area. Novel insights for nocturnal cough and sleep quality with regard to persistence, within-patient associations with asthma control, monitoring performance, and prognostic performance were generated. While cough was found to be a useful diagnostic biomarker for respiratory diseases by prior research (Porter et al., 2019), the research presented in this chapter is, to the best knowledge of the author, the first systematic attempt to investigate its clinical utility as monitoring and prognostic biomarkers. This also applies to sleep quality. Furthermore, discrepancies with prior research have been found: while nocturnal cough was not related to lung functions in research by the Marsden and Fukuhara research groups, the present study has shown that there seems to be a relationship if repeated measurements of nocturnal cough (rather than one signal measurement) have been considered. Finally, the statistical analyses in this chapter suggest that both CDBs explain asthma control statistically independent of each other. The increase in prognostic biomarker performance when combining both markers further suggests that the performance of the CDBs behaves, at least to some extent, additively. This provides a starting point for future research to clarify the relationships of both CDBs and asthma outcomes.

5.5 Conclusion and Implications

The present chapter provides insights into the clinical utility of nocturnal cough and sleep quality as digital biomarkers for asthma. The clear majority of participants approved of the notion of nocturnal passive monitoring, which suggests the creation of value for patients. The analyses of C2 to C5 indicated the CDBs' potential for creating medical value: while nocturnal cough seemed to be more useful for asthma monitoring, sleep quality enabled better results for the early detection of asthma attacks. However, combining both CDBs delivered the highest prognostic performance, which was defined in Sub-section 2.3.3.4 as the most important criterion for clinical utility. In conclusion, the analyses presented in this chapter suggest that the proposed digital pill foundation, namely passive monitoring of nocturnal cough and sleep quality, has the potential to create patient value and medical value.

Chapter 6

General Discussion

The objective of this dissertation is to investigate whether digital medicine can create patient value and medical value in asthma care. For this purpose, a foundation for future digital pills, namely smartphone-based passive asthma monitoring enabled by the two CDBs nocturnal cough and sleep quality, was proposed and evaluated.

While the last three chapters derived insights empirically, the general discussion aims to connect the chapters with the overarching research objective of this dissertation. First, each chapter will be summarized and key findings will be extracted. Second, answers to research questions will be provided. Third, practical implications will be derived. Fourth, the contributions of this dissertation will be highlighted, and promising avenues for future research will be explored.

6.1 Summary of Key Findings

In the introductory chapter, outcomes for asthma and other chronic diseases were argued to be suboptimal, which puts a considerable burden on patients' lives and health care systems alike. While continuous interventions to manage chronic NCDs like asthma are required to improve outcomes, today's health care systems are ill-equipped to provide this type of intervention to patients. This is in part due to the fact that health care systems were originally set up for the treatment of acute diseases that do not require long-term continuous disease management interventions, but rather short-term curative interventions. However, due to constantly rising health care costs and an increasing share of patients suffering from NCDs, health care systems are in dire need of novel and innovative approaches to mitigate this shortcoming. Fortunately, the internet of things, more specifically in the form of digital medicine, provides opportunities to enable

scalable, long-term continuous disease management interventions in a highly cost-efficient manner. This dissertation set out to make the potential of digital medicine for improving asthma outcomes more tangible by proposing and evaluating a foundation for digital pills that fulfills unmet patient needs and creates medical value.

The second chapter summarized the status quo in asthma care. Shortcomings in asthma care were identified and served as the rationale for a digital pill foundation. It was shown that, despite the availability of effective treatment options, a substantial share of patients suffers from uncontrolled asthma and partially controlled asthma, which are risk factors for potentially life-threatening asthma attacks. Unfortunately, patients seem to systematically overestimate their level of asthma control in their subjective self-assessments, thereby compromising their window of opportunity to abort developing asthma attacks. While monitoring solutions are available for objective assessments of asthma control, they are only used by a small fraction of patients. In part, this is due to patients' attitudes towards their asthma: despite their pronounced fear of recognizing attacks too late, many patients do not want to deal with their disease in everyday life. They seem to lack the motivation to manage their disease properly, even though asthma self-management is known to improve asthma outcomes and constitutes an important pillar of asthma care. In summary, asthma control is suboptimal, patients struggle to assess their asthma properly, and the vast majority of patients lacks the motivation to regularly use the available objective disease monitoring methods. To address these issues, the following digital pill foundation was proposed: a smartphone-based system to monitor nocturnal asthma symptoms passively without any patient involvement. This dissertation has argued that in order to create medical value, the digital pill would need to go beyond the mere quantification of symptoms. It would also need to allow for inferences with regard to asthma control and enable early attack detection. Two CDBs were identified that were believed to be useful for this purpose: nocturnal cough and sleep quality. Despite first positive results in terms of technological feasibility and between-patient associations of both CDBs with asthma control, it was unclear whether these two CDBs are sufficiently clinically useful for the intended use.

After having derived a foundation for digital asthma pills, the objective of the third chapter was to obtain insights into current practice of digital medicine for asthma, namely publicly available asthma self-management apps. Out of a total of 523 identified apps, 38 apps were reviewed by multiple raters in terms of available functions, potential to change behavior, potential to promote app use, and app quality. A key finding was

that apps varied considerably in terms of their potential to improve and promote asthma self-management. Interestingly, it was found that currently available apps for asthma management do not exploit the technological potential of smartphones: since none of the apps employed mobile sensing, all apps offering monitoring functions relied exclusively on user input. Except for a few dynamic functionalities like pollen counts, currently available asthma apps seem to deliver limited additional value in comparison to traditional asthma self-management. In summary, Chapter 3 highlights the innovativeness of the digital pill foundation proposed in this dissertation by showing that no comparable functionality has been implemented in asthma apps yet.

Chapter 4 explored patient attitudes towards asthma in general and towards digital asthma interventions in particular. For this purpose, a mixed methods approach was employed. Firstly, two focus groups were conducted, in which 15 participants suffering from asthma discussed multiple topics with regard to their disease and smartphone apps. Secondly, the insights from these focus groups informed a survey, in which 88 people with asthma participated. The focus group demonstrated, in line with prior research, that patients do indeed have limited motivation to deal with their disease in everyday life. This also applied to patients who suffer considerably from their asthma symptoms. Thus, to have a chance of adoption in this difficult patient population, a digital asthma pill must function with only a minimal amount of patient effort. In the survey, attitudes towards digital pills were more positive: almost half of the participants wished for support in their asthma self-management and asthma apps were perceived as valid options to address this need. In conclusion, Chapter 4 provides support for the proposed digital pill foundation by clarifying patient needs and indicating that passive, smartphone-based symptom monitoring seems to fulfill them.

While Chapters 3 and 4 have shown that the proposed digital pill foundation is innovative and would create patient value, Chapter 5 was mainly concerned with demonstrating its potential medical value. More specifically, the clinical utility of the two CDBs was evaluated in a longitudinal study of 94 participants with a duration of 29 days. For 79 participants, sufficient data was available for statistical analyses. Clinical utility was operationalized by virtue of five criteria, namely patient acceptance, persistence, statistical significance (on a within-patient level), monitoring performance, and prognostic performance. Participants were highly accepting of smartphone-based passive nocturnal monitoring. Both CDBs were further shown to be highly persistent and statistically significantly associated with asthma control on a between-patient and

within-patient level. For monitoring performance, it was found that highly transparent and explainable threshold-based models using nocturnal cough as the predictor provide a fair classification performance of clinically meaningful deteriorations in asthma control. In terms of prognostic performance, threshold-based models achieved an average BAC of 68% three to four days ahead of an attack with average sensitivities of 73%. Interestingly, while sleep quality did not appear to be clinically useful for asthma monitoring (i.e., poor performance detecting clinically meaningful deteriorations in asthma control), it outperformed nocturnal cough-based models in terms of prognostic performance (i.e., prediction of upcoming asthma attacks). However, it was found that combining both CDBs resulted in the highest prognostic performance. Therefore, Chapter 5 presents mixed evidence with regard to the clinical utility of both CDBs, suggesting that each CDB has the potential to create medical value in asthma care, in particular if both CDBs are combined, but neither of the CDBs seems to be a highly accurate all-purpose biomarker for asthma.

6.2 Answers to Research Questions

In the following, the concrete research questions will be addressed first. The overarching research question will be discussed at the end of this section.

6.2.1 Review of Asthma Apps

> ***RQ1:*** *"What is the potential of publicly available asthma apps for improving asthma self-management?"*

Mixed results were found with regard to the potential of publicly available asthma apps for improving asthma self-management. While some high-quality apps include functionalities associated with effective asthma self-management (e.g., written asthma action plans, self-monitoring diaries, and educational material) and employ behavior change and gamification strategies known to be effective, these apps only constitute a minority of the reviewed apps. Furthermore, all apps suffered from two important limitations. Firstly, clinical validation studies were missing. Secondly, currently available apps do not exploit the technological capabilities of smartphones, in particular with regard to mobile sensing. In summary, the smartphone's potential for improving asthma outcomes has not yet been fully exploited.

6.2.2 Unmet Patient Needs

RQ2a: *"What unmet needs do patients perceive in asthma care?"*

Patients described the process from recognizing their first symptoms of asthma until their confirmed asthma diagnosis as very burdensome. They would have liked a faster diagnostic process. Around the time of diagnosis, patients reported a lack of credible and available information. They would have liked their general physician to take more time to inform them about their disease and about available treatment options. In the time after diagnosis, two main stressors were reported: attack anxiety and seemingly unpredictable symptom fluctuations. Patients would appreciate more peace of mind with regard to asthma attacks and a better understanding of their symptom fluctuations in everyday life.

RQ2b: *"What are the patients' attitudes towards digital self-management interventions for asthma?"*

In the survey, the vast majority of patients was open to using digital self-management interventions (79%). The majority of patients was also interested in trying these interventions out (69%) and willing to invest time to get accustomed (69%). However, only a minority (39%) expressed willingness to pay for digital asthma pills. Furthermore, digital self-management interventions were considered to be valid options to satisfy currently unmet needs in self-management. In conclusion, patients' attitudes towards digital self-management interventions in general can be interpreted as positive.

6.2.3 Clinical Utility of Nocturnal Cough and Sleep Quality as Digital Biomarkers for Asthma

RQ3a / Patient acceptance (C1): *"Are patients open to using a digital pill based on nocturnal passive monitoring?"*

Patient acceptance of nocturnal passive monitoring was found to be high: almost all patients had a positive attitude towards an abstract app concept based on nocturnal passive monitoring, and more than three-quarters of patients reported being interested in trying such an app out. However, since the survey was part of a study in which participants were monitored at night, it may be the case that patients more skeptical of nocturnal passive monitoring were less likely to participate in the survey. Thus, it seems likely that the results were influenced by a selection bias.

RQ3b / Persistence (C2): *"Are the two CDBs temporally persistent?"*

Both CDBs were temporally persistent: their positive autocorrelations across the entire study duration were statistically significantly greater than zero.

RQ3c / Statistical significance (C3): *"Are the two CDBs associated with asthma control on a within-patient level?"*

Both CDBs were statistically significantly associated with asthma control on a within-patient level. The direction of the association was as expected (i.e., an increase in nocturnal cough/a decrease in sleep quality is associated with a decrease in asthma control, and vice versa).

RQ3d / Monitoring performance (C4): *"To what extent do the two CDBs enable useful assessments of asthma control?"*

Based on the interpretation guidelines for Cohen's kappa by Landis and Koch (1977), the agreement of actual clinically meaningful deteriorations in asthma control and classifications made by nocturnal cough and sleep quality can be considered fair (κ = 21%) and poor (κ = -.01), respectively. If the rules of thumb for the interpretation of the area under the receiver operating characteristic curve proposed by Swets (1988) are applied to the (in this case identical) BAC, nocturnal cough's monitoring performance was at the boundary between low and useful accuracy (BAC of 65% and 69% with and without internal cross-validation, respectively), while sleep quality's accuracy was clearly low (BAC of 49% and 52% with and without internal cross-validation, respectively). Therefore, nocturnal cough seems to have some potential to serve as a monitoring biomarker, while sleep quality does not.

RQ3e / Prognostic performance (C5): *"To what extent do the two CDBs enable early detection of asthma attacks?"*

Considered separately, nocturnal cough reached a BAC of almost 70% up to three days ahead of an attack (e.g., BAC = 67%, sensitivity = 75%, specificity = 58% on the third lag) and sleep quality up to four days ahead of an attack (BAC = 68%, sensitivity = 62%, specificity = 73%). BACs over .70 were achieved up to four days ahead of an asthma attack if both CDBs were combined (e.g., BAC = 72%, sensitivity = 75%, specificity = 69% on the fourth lag). Based on the above-mentioned BAC interpretation, a BAC larger than 70% indicates predictions "useful for some purposes" (Swets, 1988, p. 1292).

Therefore, both CDBs seem to be useful prognostic biomarkers if combined, but are restricted in their field of application.

> ***RQ3:*** *"To what extent are nocturnal cough and sleep quality clinically useful digital biomarkers for asthma control?"*

Overall, nocturnal cough and sleep quality have clinical utility as digital biomarkers for asthma, at least for certain applications. While nocturnal cough appears to have potential for disease monitoring, the combination of both CDBs seems to enable useful prognoses of asthma attacks up to four days ahead of the attack.

6.2.4 Overarching Research Question

> *"How can the potential of digital medicine be leveraged to cost-effectively create patient value and medical value in asthma care?"*

This dissertation argues that digital medicine can create patient value and medical value in asthma care through smartphone-based passive monitoring of nocturnal cough and sleep quality. Considering that the only technological requirement for implementation is ownership of a smartphone, a technology that is already widely adopted, a digital pill based on nocturnal monitoring of the two CDBs can have a virtually unlimited reach while being highly cost-effective due to its scalability. Thus, it can enable continuous self-management interventions for asthma.

As demonstrated in a sample of rather well-controlled asthma patients, nocturnal cough and sleep quality have, depending on their application, potential as biomarkers for asthma. In addition, the high interpretability of the threshold-based models can enhance medical decision making: asthma control classifications or asthma attack predictions made by the threshold-based models can be easily explained, even to medical laymen. Furthermore, thresholds can be adjusted depending on the intended application. These arguments provide support for the notion that the proposed digital pill foundation has the potential to create medical value.

Patient value is created due to multiple factors. First, effortless peace of mind can be enabled through automatic early attack detection, which, in the present sample, missed only two of the eight attacks four days ahead of the attack (i.e., 25% false negatives if both CDBs are used). Furthermore, it may be the case that through the combination of the CDBs and a patient's subjective risk assessment, the percentage of missed attacks

could even be substantially lower in practice. Second, by longitudinally tracking and passively monitoring patients' symptoms, day-to-day fluctuations may become more comprehensible to patients. In this way, patients would have additional data at their disposal to interpret the course of their disease without any additional effort required to obtain these measurements. Third, patients can share the objective biomarker measurements with their physicians, so that treatment decisions would not only be supported by the information obtained in a physician consultation at a given day, but also through objective and longitudinal measurements of clinically useful biomarkers. This applies to nocturnal cough frequency in particular, since neither physicians nor patients currently have access to measurements of this CDB.

However, one factor can limit the created patient value considerably, namely the comparatively low specificity in early asthma attack detection. This is due to the fact that asthma attacks are a very rare event (cf. Sub-section 2.2.1.1). For example, in the present study, attacks occurred on 35 out of 2,291 days. Thus, a specificity of 75%, for example, implies that patients would have been incorrectly warned of a developing attack on 573 days. Consequences could negate the created patient value (e.g., increase in stress instead of peace of mind) and result in a financial burden on health care systems when patients unnecessarily visit their physicians. In fact, the example of Babylon Health's triage app, which supports patients in deciding whether to consult a physician, has shown that the introduction of digital pills to health care systems may at first lead to higher costs due to an increase in medical service utilization (Iacobucci, 2018). Nevertheless, it is important to consider that excessive nocturnal cough in particular is likely to be a clinically significant symptom and an indication of a serious treatment need even if it results in a false positive attack prediction. For example, one patient who coughed almost 100 times per night on average did not suffer from a single attack in the study and was thus always classified as a false positive. Incidentally, this patient had to postpone their final study visit due to a diagnosis of pneumonia.

Finally, it is important to consider that the clinical utility of both CDBs, as has been pointed out in the preceding sub-section, is restricted to certain applications. Thus, digital pills based on the CDBs must be designed to mitigate the relatively low specificity. At the end of the next section, an example of a viable digital pill will be presented.

6.3 Practical Implications

Based on the exploratory character of many of the analyses and the discussed limitations of each chapter, drawing extensive implications for clinical practice would be premature. The main implication for clinical practice, however, is that current operationalizations of asthma control may fall short of encompassing all relevant dimensions. Refined longitudinal symptom measurements may provide additional benefits for disease monitoring.

However, eight key implications for the design of digital asthma pills can be derived from the research presented in this dissertation.

First, there is a need for digital asthma pills. Research has shown that asthma self-management is crucial for improving outcomes, but effective self-management is associated with an increase in health expenditure (cf. Sub-section 2.3.1.1). Considering the ever-increasing cost pressure in health care systems, in part due to the increase in NCD prevalence (cf. Sub-section 1.1.1), the time has come for a new paradigm of cost-efficient, scalable and continuous interventions enabled by mobile technology.

Second, there is an opportunity for digital asthma pills. Many requirements for potentially successful interventions are already in place, namely written asthma action plans, patients' willingness to adjust their own medication dosage, and the widespread adoption of smartphones (cf. Sub-section 2.3.3.1). Furthermore, asthma is a disease that affects patients of all ages. As a contrasting example, COPD disproportionally affects older patients (cf. Sub-section 2.1.3.3). Age is relevant due to the literature on the *digital divide*, which suggests that older patients are less likely to benefit from digital pills due to poorer adoption of technology (Choi & DiNitto, 2013). Therefore, asthma seems to be a particularly suitable indication for the deployment of digital pills.

Third, efficacy has been shown for some digital asthma pills (cf. Sub-section 2.3.1.3), and their widespread adoption also seems possible: patients are overwhelmingly open to the concept of digital asthma pills and are interested in trying them out (cf. Sub-section 4.3.2.2). However, openness towards digital pills is contingent upon expected benefits (cf. Sub-section 5.4.1). Therefore, to facilitate adoption of digital pills, they have to be developed according to patients' needs (and not only based on technological opportunities or clinical necessity).

Fourth, patients have distinct unmet needs (cf. Sub-section 4.3.1.2) along the clinical pathway. Three opportunities were identified for digital asthma pills to create patient value:

- Before diagnosis, case finding interventions (Schatz, 2018) would be beneficial. Through digital triage services, for example, tentative diagnoses could be proposed, and patients could be referred more efficiently to specialists. This would facilitate timely diagnoses. One example of such an intervention, which is currently being tested by the National Health System in parts of the United Kingdom, is the aforementioned triage chatbot developed by Babylon Health (Mahase, 2019).
- Around the time of diagnosis, an intervention introducing patients to their disease would create value by distributing credible information to patients and by explaining the disease and treatment options. In Switzerland, such a digital pill is currently being evaluated: Max, a digital coach, provides fundamental asthma knowledge prepared by clinical experts to children (Kowatsch et al., 2019).
- After diagnosis, risk stratification interventions (Schatz, 2018) seem promising. Patients are afraid of asthma attacks and unpredictable symptom fluctuations constitute a daily hassle. A monitoring intervention, which allows patients to understand their symptom fluctuations better, indicates their risk for adverse events, and warns them in case of deteriorations, would meet currently unmet patient needs. Furthermore, research in this dissertation found support for the notion that patients' perceived clinical needs are not necessarily aligned with their actual clinical needs (cf. Sub-section 4.3.2.2) – suggesting that a correction loop enabled by a digital monitoring pill might be useful to help patients refine their risk perceptions. The remainder of this section will present design recommendations for digital pills enabling risk stratification.

Fifth, to enable daily and long-term use of digital asthma pills for risk stratification, they need to create as little additional effort for patients as possible (cf. Sub-section 4.3.1.2). Passive nocturnal symptom monitoring based on nocturnal cough and sleep quality was found to be a promising option for within-patient risk stratification and was also endorsed by patients (cf. Section 5.3).

Sixth, a digital asthma pill for risk stratification should contain the following core functionalities: an early deterioration warning system, an overview of the current symptoms, and a longitudinal visualization of symptoms (cf. Sub-section 4.3.2.2).

Seventh, patients' attitudes towards digital pills and their functions are mostly independent of patients' actual clinical needs. Therefore, an all-purpose approach towards the development, sale, and marketing of digital pills could be suitable (cf. Sub-section 4.3.2.2).

Eighth, without further research that refines the biomarker performance of nocturnal cough and sleep quality, a digital pill based on these digital biomarkers needs to account for the low specificity of the classification and prediction models (cf. Sub-section 5.4.3).

Finally, a potential digital pill can be envisioned despite the discussed limitations of CDBs monitoring and prognostic performances: instead of using the models' classifications and predictions as direct cues for pharmaceutical interventions or physician referrals, the digital pill could use the model predictions as cues for monitoring through less convenient, but more specific methods (e.g., peak flow action points; Honkoop et al., 2013). Therefore, a digital pill based on passive monitoring of nocturnal cough and sleep quality may be designed as a triage intervention for asthma monitoring. Its objective would be to promote the use of monitoring methods that are clinically recognized, but only in times of actual necessity (i.e., in states of vulnerability and opportunity; Nahum-Shani et al., 2015). From a behavioral science perspective, it can be argued that such a digital pill would be highly effective in changing patients' behavior: the likelihood of performing a desired target behavior (i.e., monitoring of asthma with less convenient methods) can be conceptualized as the product of a person's motivation, ability, and a prompt to do so (e.g., a notification on the patient's smartphone; Fogg, 2009). All of the intervention requirements are already in place today and can be easily implemented by patients, which suggests a high ability of patients to perform the target behavior (e.g., ownership of a peak-flow device constitutes the standard of care in asthma; alternatively, validated questionnaires are available as clinical markers (cf. Sub-section 2.2.2.1), which could even be directly distributed on the smartphone). Furthermore, the already extensively discussed fear of patients to suffer from a potentially fatal asthma attack (cf. Sub-section 4.3.1.2) seems like a very potent motivating factor, so that a high motivation of patients can be assumed. In cases of high ability and high motivation, so-called *signal interventions* (i.e., reminders, that are neither designed to motivate patients nor to facilitate the target behavior) are

considered to be the most effective prompts – more elaborate interventions would be perceived by patients as "annoying or condescending" (Fogg, 2009, p. 6).

6.4 Contributions and Future Research

In addition to the contributions presented in the discussion sections of the empirical chapters, this dissertation also makes a contribution as a complete oeuvre. After examining this overall contribution, avenues for future research will be explored.

6.4.1 Overall Contribution

In this dissertation, a promising foundation for future digital asthma pills has been developed. The foundation was proposed by detecting unmet clinical needs in literature and was refined and evaluated through the versatile employment of methods from multiple fields of research (e.g., systematic review techniques, qualitative methods, descriptive analysis, time-series methods, explanatory modelling, and predictive modelling). Evidence from multiple sources suggests that the proposed digital pill foundation is highly innovative and has the potential to create patient value and medical value. Although many of the analyses performed were exploratory in nature and the study designs and sample sizes do not justify claims of broad generalizability, a successful proof of concept for passive nocturnal asthma monitoring based on nocturnal cough and sleep quality has been delivered in this dissertation.

The potential of novel measurements in the scientific enterprise cannot be underestimated. In an interview with *The Economist*, Sinan Aral, professor of management at the Massachusetts Institute of Technology, put it eloquently: "revolutions in science have often been preceded by revolutions in measurement" (Kitchin, 2014, p. 1). To some extent, this notion is observable in the domain of digital pills for the promotion of physical activity: the widespread adoption of technology that enables automatic physical activity tracking (i.e., pedometers integrated into a smartphone or wearable) has led to a renaissance in physical activity research (Vandelanotte et al., 2016). It can be argued that one by-product is the emergence of methodological research frameworks, like just-in-time adaptive interventions (Nahum-Shani et al., 2015), which capture the epistemological value created by close-mashed measurements. This dissertation may serve as an initial spark for the development of a "pedometer for asthma". However, instead of inferring physical activity from steps,

asthma control and asthma attack risk would be assessed through the passive measurement of nocturnal cough and sleep quality. These two CDBs could become proximal outcomes or surrogate endpoints for asthma in the future, thereby stimulating future research.

6.4.2 Future Research

Based on the findings presented in this dissertation, four directions for future research will be proposed in the following.

First, in line with the biomarker developed pipeline outlined in Sub-section 2.3.3.5, the biomarker performance figures from this study need to be externally validated. By testing both biomarkers in novel samples, prediction models can be properly evaluated and, if necessary, recalibrated. To this end, it would be recommended to increase sample size and to collect more data per patient in the validation studies so that prediction models can be personalized (cf. discussions in Sub-sections 5.4.2 and 5.4.3). This is particularly important due to the limited number of asthma attacks and weeks with clinically meaningful changes in asthma control discussed in Sub-section 5.4.2. Additionally, considering the generalizability concerns outlined therein, stratified sampling could be employed. For example, by defining the strata based on asthma control and smoking habits, more representative biomarker performance figures could be estimated. Furthermore, asthma has a higher prevalence in children than in adults (cf. Sub-section 2.1.2.1), so future studies could investigate the applicability of both CDBs in children and adolescents.

Second, instead of focusing on biomarker performance, future research could also strive to better understand both biomarkers separately and in conjunction:

- For nocturnal cough, the association with lung functions is contrary to findings of prior research and could thus be examined. Moreover, the analyses presented in Chapter 5 were based on c/n or aggregations thereof. However, within-night parameters may provide additional insights (e.g., the proportion of coughs that occurred in isolation vs. part of a cough episode). It may also be the case that coughs from specific times of the night (e.g., beginning of the night) or after specific events (e.g. a change in sleeping position) may be more meaningful and thus enhance classification and prediction performance.

- For sleep quality, different operationalizations could be explored with regard to their relationship with asthma control. While the PSQI is particularly useful for screening purposes (Mollayeva et al., 2016), it produces different estimates for sleep quality than objective measures, such as actigraphy or polysomnography (Buysse et al., 2008; Matthews et al., 2018). Furthermore, the PSQI is an aggregated measure and thus suffers from a low temporal resolution. For example, no insights with regard to sleep stages within one night can be obtained.
- Except for the statistical analyses in which the interaction effect of nocturnal cough and sleep quality was considered, the relationships between both biomarkers were not further examined and are subject to future research. For example, if sleep quality is measured with a higher temporal resolution, the relationship between both CDBs can be studied on a within-night level (e.g., association of nocturnal cough and sleep stages).

Third, future research could focus on building more performant prediction models. This dissertation investigated the clinical utility of nocturnal cough and sleep quality as digital biomarkers for asthma. Future research could use both CDBs and additional predictors to build the best overall classifier for asthma control or prediction model for asthma attacks. For example, pollen counts obtained through matching the smartphone's GPS data with meteorological data bases could be integrated into these models, which might be particularly relevant for patients with allergic asthma.

Fourth, this dissertation suggests that a digital pill based on both CDBs could create medical value (and patient value). However, it is unclear whether both biomarkers provide *additional* medical value for assessing asthma control and predicting asthma attacks. Even though patients' ad-hoc assessments are known to be of limited validity (cf. Sub-section 2.3.2.3), they could theoretically provide similar or even better results. In this case, the predictions and assessments based on both biomarkers would be redundant, so that little *additional* medical value would be created. Therefore, future research could investigate whether nocturnal monitoring based on nocturnal cough and sleep quality would provide additional value. This could be done, for example, in a randomized controlled trial with two arms: while the control group would receive the standard of care, the experimental group would additionally receive a digital pill as proposed in Section 6.3. Higher levels of asthma control and fewer asthma attacks in the experimental group would suggest that additional medical value can be created through the proposed digital pill.

6.5 Concluding Remark

As stated in the introduction, progress in improving asthma outcomes has been "slow and inacceptable" (Kleinert & Horton, 2018, p. 1). Epidemiological data clearly indicates a stagnation in asthma mortality in the recent decade (cf. Sub-section 2.1.3.2). This worrying era of stagnation, observable in less critical outcomes as well, was commented on in a recent *Lancet* commission as follows:

> *"We believe that the most important cause of this stagnation is a continued reliance on outdated and unhelpful disease labels, treatment and research frameworks, and monitoring strategies, which have reached the stage of unchallenged veneration and have subsequently stifled new thinking." (Pavord et al., 2018, p. 4)*

By leveraging the potential of digital medicine, this dissertation strives to contribute to a new thinking about asthma, in particular with regard to monitoring strategies.

Chapter 7

Appendices

7.1 Appendix 1: Methodological Aspects (Chapter 5)

7.1.1 Description of Nocturnal Sensor Recordings

Nocturnal smartphone sensor data were recorded by default from 23:00 onwards for a recording length of 9 hours and 40 min to account for the sleeping patterns of the general Swiss population (i.e., inferring from a citizen science study (Walch, Cochran, & Forger, 2016), 95% of nocturnal sleep sessions are shorter than this default recording length). Furthermore, participants could manually start (after 21:00) and stop (after 04:00) the sensor data recording, thereby overwriting the default recording settings. If a participant started the recording manually after the recording had already been started automatically (i.e., after 23:00), the default recording length was extended so that it encompasses 9 hours and 40 min from the moment of manual initiation. Reasons for missed sensor recordings can be technology-related (e.g., app crash) or patient-related (e.g., turned off smartphone at night).

7.1.2 Variable Centering

To clarify the notion of centering variables as described by Enders (2013), formulas (9) and (10) provide exemplary regression models with ACT as the outcome and c/n as the predictor.

$$ACT_{ij} = \beta_0 + \beta_1\left(c/n_{ij} - \overline{c/n}\right) + u_{0j} + \varepsilon_{ij} \qquad (9)$$

Formula (9) depicts grand mean centering in a multi-level regression model. The ACT score for patient *j* on day *i* is modelled through the sum of an intercept (β_0), which varies

by person (u_{0j})[36], c/n centered around the grand mean centered (i.e., c/n for patient *j* in night *i* (c/n_{ij}) minus the mean of c/n of the entire sample ($\overline{c/n}$)) and an individual error term (ε_{ij}). In this model, β_1 quantifies only the between-patient association of c/n on ACT.

In contrast, β_1 in formula (10) quantifies the within-patient effect of c/n. The regression model is similar to formula (9), with the exception that instead of centering c/n of night *i* in patient *j* around the mean of the complete sample ($\overline{c/n}$), it is centered around each patient's own mean ($\overline{c/n_j}$). In this way, only changes of c/n within a patient (i.e., changes over time) are considered when modeling the ACT score of this patient.

$$ACT_{ij} = \beta_0 + \beta_1\left(c/n_{ij} - \overline{c/n_j}\right) + u_{0j} + \varepsilon_{ij} \qquad (10)$$

7.1.3 Validation of the Weekly Adaptation of the Asthma Control Test

Correlational analyses demonstrate the validity of the weekly adaption of the ACT: The mean of the four weekly ACT measurements is highly correlated with the monthly ACT score ($r = .80$, $p \leq 0.001$). Moreover, the weekly (smartphone-based) ACT has outperformed the monthly ACT in terms of observed internal consistency (Cronbach's $\alpha = .73$ vs. $\alpha = .60$). These results indicate that adapting the ACT from its originally monthly frame of reference (Nathan et al., 2004) to a weekly measure has seemingly not decreased the reliability of the questionnaire.

7.1.4 Classification of Asthma Control based on the Asthma Control Test

ACT scores can also be used to classify patients' level of asthma control. In line with the meta-analysis by Jia et al. (2013), the cut-points of ≤ 15 points for uncontrolled asthma, ≥ 20 points for controlled asthma, and between 16 and 19 points for partially controlled asthma were selected to categorize the monthly ACT score. Furthermore, a binary classification of the ACT can be performed based on the cut-point of 19 points (i.e., > 19 points corresponds to controlled asthma, ≤ 19 points to uncontrolled asthma). The binary classification is recommend by the ACT user's guide (Kosinski, Bayliss, Turner-Bowker, & Fortin, 2003) and by Schatz et al. (2006).

[36] An intercept that varies by patient (or group) is commonly referred to as a random intercept (Enders, 2013).

7.2 Appendix 2: Additional Data Description (Chapter 5)

7.2.1 Evaluation of the Digital Study Coach "Clara"

Study participants' attitudes towards "Clara", the digital study nurse, were assessed on six dimensions using the following questions: "How satisfied were you with Clara?" (satisfaction), "How easy was talking to Clara?" (usability), "How much would you like to continue working with Clara?" (continued use), "How would you characterize your relationship with Clara?" (relationship), "Would you rather have talked to your doctor or nurse than Clara?" (preference), "How likely is that you will follow Clara's advice? (adherence). The questions were taken from Bickmore et al. (2010a). Participants' responses are summarized descriptively in Figure 7.1. Furthermore, Table 7.1 provides Pearson correlations between the different evaluation dimensions including the "Bond" subscale of the Working Alliance Inventory (Hatcher & Gillaspy, 2006).

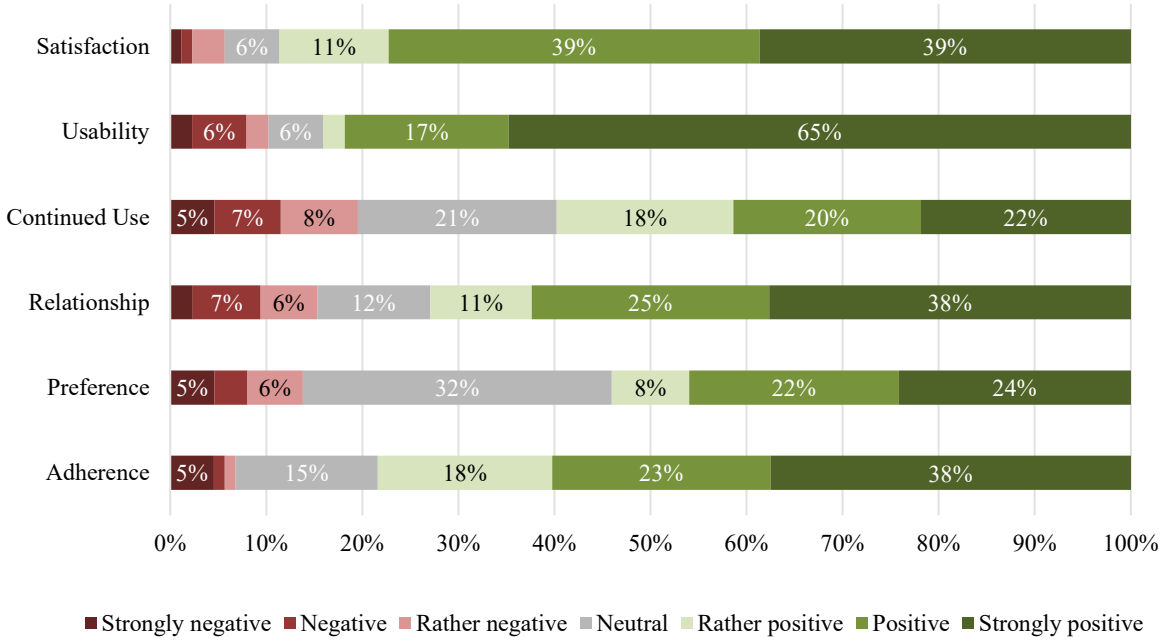


Figure 7.1. Evaluation of the digital study coach "Clara". Satisfaction, Usability, and Adherence: n = 88; Preference and Continued Use: n = 87; Relationship: n = 85. Data labels for frequencies below 5% were suppressed.

Table 7.1. Pearson correlations of digital coach evaluation measures.

	Satisfaction	Usability	Continued use	Relationship	Preference	Adherence
Satisfaction [a]	1					
Usability [a]	.36**	1				
Continued use [a]	.67***	.48***	1			
Relationship [a]	.61***	.44***	.65***	1		
Preference [a]	.33**	.20	.37**	.37**	1	
Adherence [a]	.54***	.33**	.55***	.71***	.38**	1
WAI: Bond scale	.50***	.20	.46***	.59***	.24*	.51***

Note: [a] Single item measures. n = 72; * p < .05; ** p < .01; *** p < .001; WAI: Working Alliance Inventory.

7.2.2 Baseline Characteristics

Table 7.2. Comprehensive table of baseline characteristics (continued on next page).

Category, measurement, and unit	**Median (Q_1 – Q_3) or count (%)[a]**
Demographics	
Age, years	45 (30-59)
Male; count (%)	41 (44%)
Female; count (%)	53 (56%)
Height, cm	170 (163-176)
Weight, kg	71 (63-83)
Body mass index, kg/m^2	25 (22-28)
Smoking status; count (%)	
Current	3 (3%)
Former	27 (29%)
Never	64 (68%)
For current or former smokers	
Years smoked	15 (9-20)
Cigarettes per day	14 (10-20)
Pack years	10 (4-15)
Lung functions	
FEV_1, liters	2.9 (2.3-3.4)
FEV_1, % predicted	88 (77-101)
FeNO, ppb	20 (12-34)
GINA-stage; count (%)	
1	15 (16%)
2	20 (21%)
3	44 (47%)
4	13 (14%)
5	2 (2%)
Asthma severity; count (%)	
Intermittent	13 (14%)
Mild	42 (45%)
Moderate	35 (37%)
Severe	4 (4%)

Category, measurement, and unit	Median (Q_1 – Q_3) or count (%)[a]	
Asthma control test at baseline, points	21 (19-23)	
Asthma control at baseline; count (%)		
Controlled	66 (70%)	
Partially controlled	18 (19%)	
Uncontrolled	9 (10%)	
Incomplete measurements	1 (1%)	
Type of asthma (multiple choices possible); count (%)		
Intrinsic	64 (68%)	
Allergic	61 (65%)	
Late onset	1 (1%)	
Fixed airflow limitation	4 (4%)	
Obesity	6 (6%)	
Exercise induced	44 (47%)	
Cough variant	6 (6%)	
Occupational	1 (1%)	
Nighttime	5 (5%)	
Asthma medication; count (%)	*prescribed*	*used*
SAMA	5 (5%)	3 (3%)
SABA	52 (55%)	41 (44%)
ICS	86 (91%)	77 (82%)
LABA	78 (83%)	71 (76%)
LAMA	9 (10%)	8 (9%)
Theophylline	0 (0%)	0 (0%)
Systemic corticosteroids	1 (1%)	0 (0%)
LTRA	10 (11%)	10 (11%)
Anti-IgE	0 (0%)	0 (0%)
Anti-IL5	2 (2%)	2 (2%)
Exacerbation in the last 12 months; count (%)		
No	34 (36%)	
Yes	60 (64%)	
If yes, number	2 (1-2)	
Hospitalizations due to asthma (last 12 months)	4 (4%)	
ED visits due to asthma (last 12 months)	11 (13%)	
Comorbidities; count (%)[b]		
Allergic rhinitis	18 (19%)	
Chronic rhinitis	39 (41%)	
Arterial hypertension	14 (15%)	
Other	23 (25%)	
Non-asthma medication; count (%)[b]		
Aspirin	5 (5%)	
Statins	5 (5%)	
ACE-inhibitors	10 (11%)	
Other	32 (34%)	

Note: [a] Median (Q_1-Q_3) by default, count (%) only if explicitly stated. [b] Answer options with frequencies below 5% suppressed. Q_1: First quartile (25th percentile); Q_3: Third quartile (75th percentile); FEV_1: Forced expiratory volume in 1 second; FeNO: Fractionated exhaled nitric oxide; ppb: Parts per billion; GINA: Global Initiative for Asthma; SAMA: Short-acting muscarinic antagonist; SABA: Short-acting beta-agonist; ICS: Inhaled corticosteroid; LABA: Long-acting beta-agonist; LAMA: Long-acting muscarinic antagonist; LTRA: Leukotriene-receptor-antagonist; IgE: Immunoglobulin E; IL5: Interleukin-5; ED: Emergency department; ACE: Angiotensin-converting enzyme.

7.2.3 Distribution of Sleep Quality, Nocturnal Cough, and Weekly Asthma Control Test Score

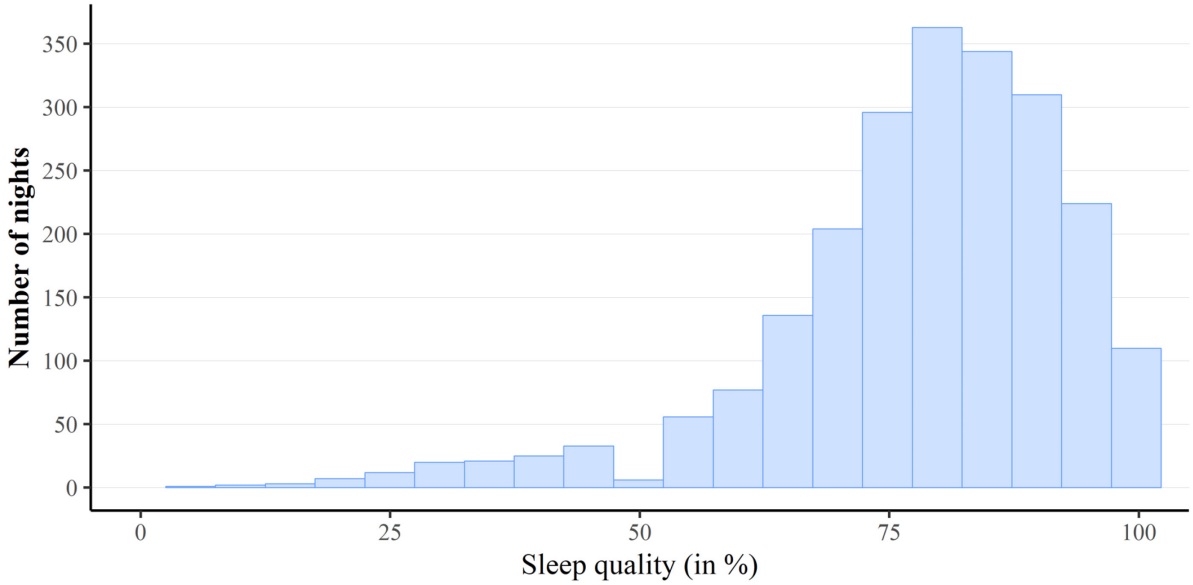


Figure 7.2. Histogram of sleep quality. Data from 2,250 nights (n = 79 patients).

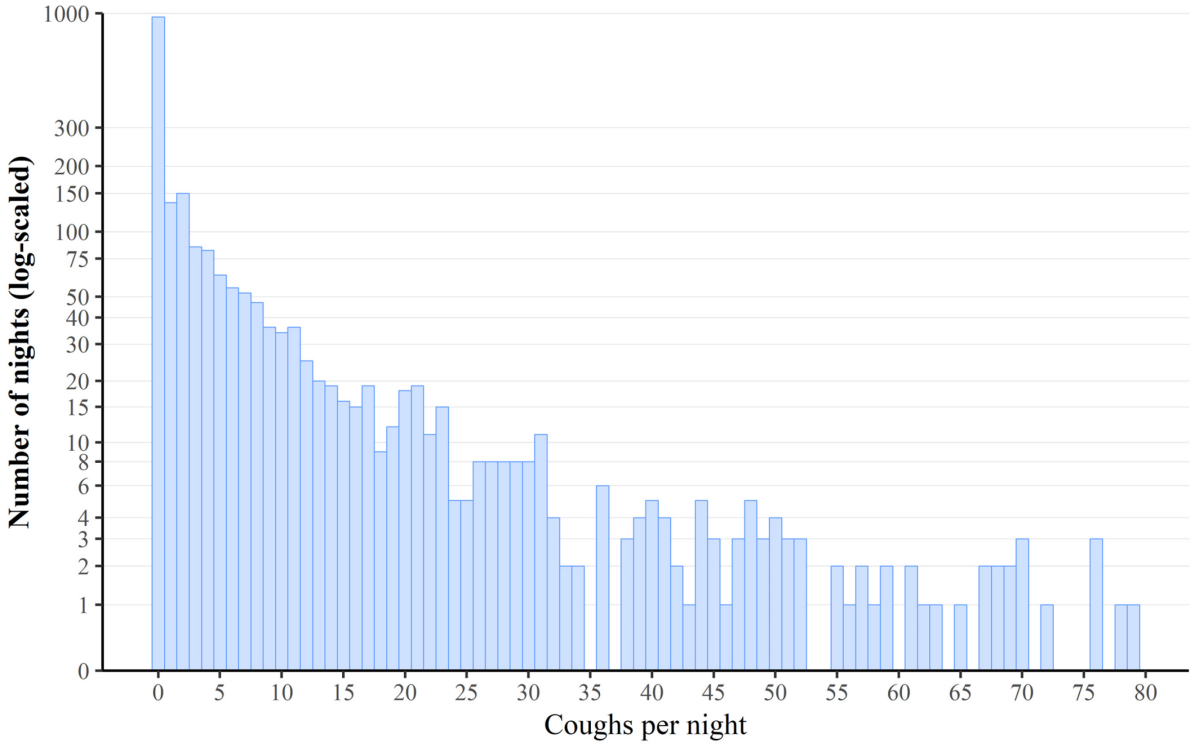


Figure 7.3. Histogram of nocturnal cough. Data from 2,090 nights (n = 79). For scaling purposes, 55 nights with more than 80 coughs were excluded.

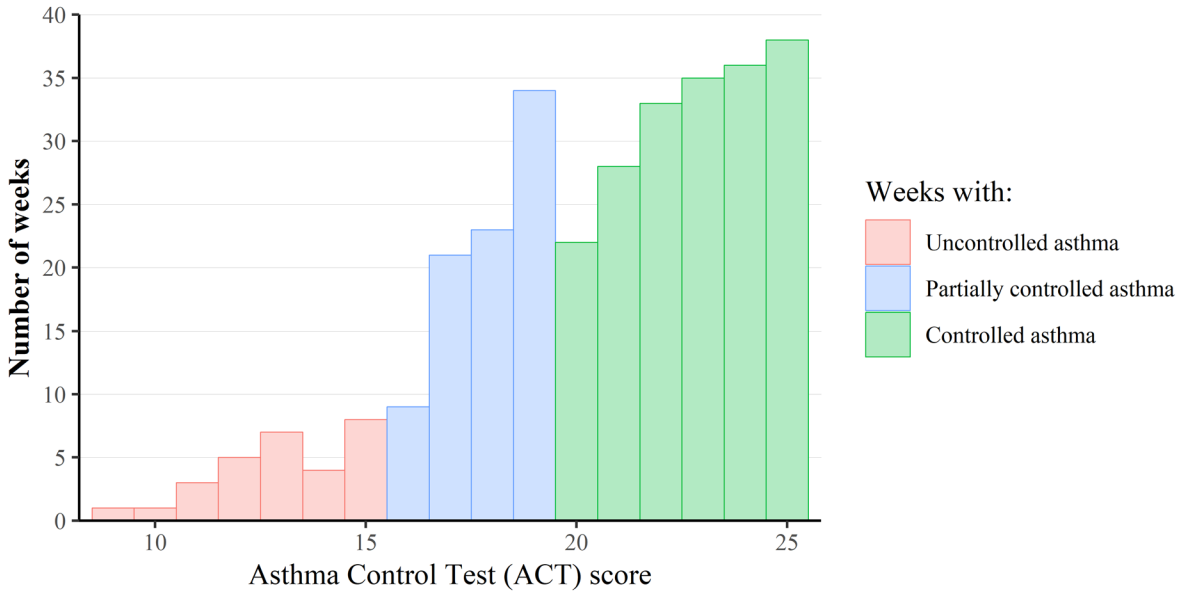


Figure 7.4. Distribution of weekly Asthma Control Test scores (n = 316 weeks of 79 patients).

7.3 Appendix 3: Additional Analyses (Chapter 5)

7.3.1 Distribution of Spontaneous Attitudes towards the Proposed App Concept

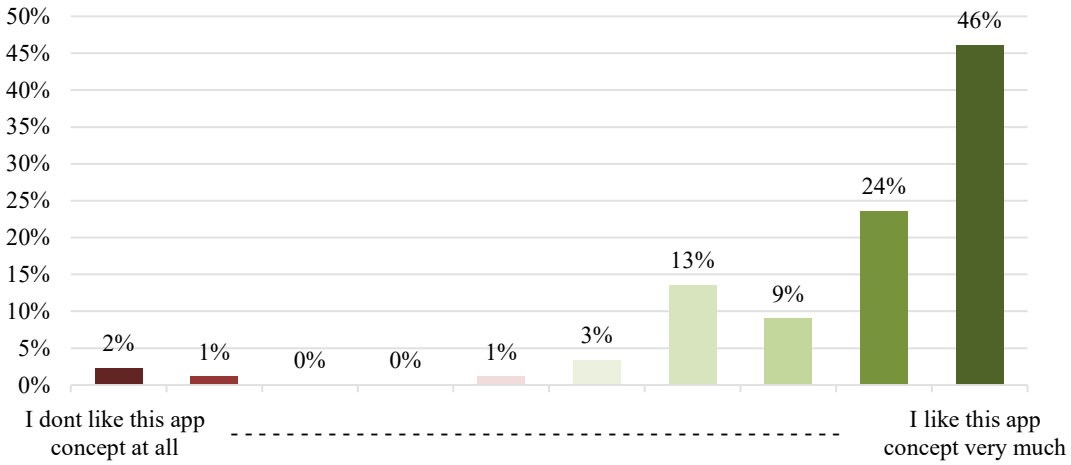


Figure 7.5. Spontaneous attitude towards the proposed app concept based on passive nocturnal symptom monitoring (n = 89) on a scale from 1 to 10 with two anchor points.

7.3.2 Correlations between Measures of Patient Acceptance and Patient Characteristics

Spontaneous attitude towards the app concept, openness to try it out and performance expectancy were highly correlated (r's = .59 - .72, all p's < .001). As shown in Table 7.3, measures of patient acceptance were largely independent of other factors such as asthma control, years lived with the disease, and age. However, the spontaneous attitude towards the app concept worsened with increasing age.

Table 7.3. Pearson correlations between app acceptance and patient factors.

	Asthma Control Test Score	Years lived with the disease	Age
Spontaneous attitude	r = -.10	r = -.07	r = -.30*
Openness to try	r = -.04	r = -.02	r = -.18
Performance expectancy	r = -.06	r = .05	r = -.17

Note: n = 81, * p < .05

7.3.3 Exploratory Subgroup Analysis

To investigate subgroup differences for the association of the two CDBs with asthma control, a patient-specific proxy for the association strength between each parameter and asthma control was estimated. More specifically, two linear regressions were fit for each patient with weekly aggregated values of nocturnal cough and sleep quality as the predictor, respectively, and the ACT score as the outcome. Two dummy-coded variables were derived from the patient-specific slope of each predictor: the first variable describes whether a predictor is associated with asthma control in the expected direction (e.g., whether more cough/lower sleep quality is associated with lower levels of asthma control) and the second variable codes whether this association was statistically significant. Both variable codes were then used as the outcomes in logistic regressions. Patient characteristics were used as predictors in separate regressions.

In total, 42 patient characteristics were considered in the analysis, resulting in 168 fitted logistic regressions. As shown in Table 7.4, the only variable which explained whether nocturnal cough and asthma control are associated with statistical significance in the expected direction is the standard deviation of the repeated measurements of the ACT score. Larger standard deviations in ACT scores increased the likelihood that an increase/decrease in nocturnal cough was statistically associated with worse/better asthma control. The ACT score's standard deviation per person was also relevant for

sleep quality: More fluctuations in asthma control were associated with a higher likelihood of better/worse sleep quality being statistically significantly associated with higher/lower levels of asthma control. Therefore, all regressions were controlled for the effect of this patient characteristic.

Furthermore, when considering whether nocturnal cough is associated with asthma control in the expected direction (but not with statistical significance), one additional patient characteristic was identified: patients, who have reported to usually not cough at night, had a higher chance that more/less nocturnal cough is associated with lower/higher levels of asthma control. In other words, for patients for which nocturnal cough is abnormal, the occurrence of nocturnal cough seems to be clinically more relevant. For sleep quality, no additional patient characteristics were found to explain marker performance.

Table 7.4. Summarized logistic regression results for subgroup identification of marker performance.

Patient characteristic	Estimate	Standard error	*z* [a]	*p*
Outcome (positive class): Direction of the association between nocturnal cough and asthma control is as expected and statistically significant [b,c]				
SD_{ACT} [d]	2.50	.78	3.20	.001
Outcome (positive class): direction of the association between nocturnal cough and asthma control is as expected [b,c]				
Usually coughs at night (1 = yes; reported by 35 patients)	-2.43	1.10	-2.22	.03
Outcome (positive class): Direction of the association between sleep quality and asthma control is as expected and statistically significant [b,e]				
SD_{ACT}	2.99	1.09	2.74	.01
Outcome (positive class): Direction of the association between sleep quality and asthma control is as expected [b,e]				
No statistically significant patient characteristic found				

Note: [a] Test statistic for Wald test. [b] Based on the dummy-coded patient-specific slope of the corresponding between-patient linear regression. [c] n = 74. [d] Standard deviation of the repeated asthma control test (ACT) measurements. [e] n = 75. The following patient characteristics were dummy-coded and considered as predictors: Type of asthma (allergic, intrinsic, late onset, with fixed airflow limitation, obesity, exercise-induced, cough variant, occupational, and night-time), usual time when coughed (morning, midmorning, afternoon, evening, night), medication used during study duration (short-acting muscarinic antagonist, SABA (short-acting β-agonist), ICS (inhaled corticosteroids), long-acting β-agonist, long-acting muscarinic antagonist, Leukotriene receptor antagonists, theophylline, systemic corticosteroids, Anti Immunoglobulin E, Anti Interleukin-5), sex, rhinitis (allergic, chronic, allergic & chronic), smoking status (ex-smoker, never smoked). The following metric predictors were considered: Body mass index, forced expiratory volume in one second (FEV_1; in l and in % of norm values), forced vital capacity (FVC, in l and in % of norm values), FEV_1/FVC, exhaled nitric oxide (in parts per billion), mean and standard deviation of the ACT, percentage of days suffering from a cold. The following ordinal-scaled predictors were considered: Global Initiative for Asthma stage, self-rated relevance of cough symptoms, and asthma severity. All regressions were controlled for the standard deviation of the repeated asthma control test (SD_{ACT}).

7.3.4 Comparison of Variable Distributions between Weeks with and without a Clinically Significant Deterioration in Asthma Control

Figure 7.6 reveals that while there was a substantial overlap between the density distribution of sleep quality in weeks with clinically significant deteriorations and in weeks without deterioration (72%), the overlap for nocturnal cough was considerably smaller (42%). The descriptive statistics listed in Table 7.5 further confirm that patients cough more (and sleep worse) in weeks with deteriorations and that this difference seems to be more prominent in nocturnal cough.

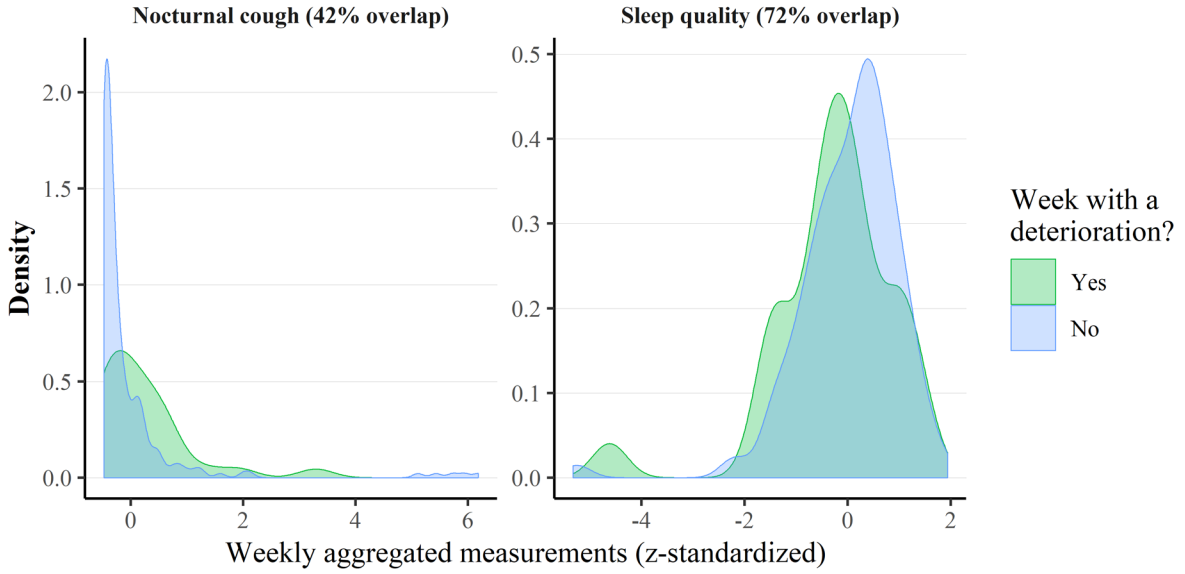


Figure 7.6. Overlap of distributions for nocturnal cough and sleep quality. Based on data from 227 weeks (with 29 clinically meaningful deteriorations; n = 79 patients).

Table 7.5. Descriptive statistics of nocturnal cough and sleep quality in weeks with and without cinically meaningful deteriorations in asthma control.

	Nocturnal cough [a]		**Sleep quality [b]**	
	Weeks without deterioration [c]	**Weeks with deterioration [c]**	**Weeks without deterioration [c]**	**Weeks with deterioration [c]**
Mean (SD)	57.56 (131.43)	91.03 (106.10)	78.47% (10.18%)	75.15% (12.59%)
Median (IQR)	18.00 (51.75)	65.00 (116.00)	80.45% (12.02%)	76.69% (10.53%)

Note: [a] Aggregated count over the whole week. [b] Aggregated score over the whole week, divided by 7 to match daily scale. [c] Defined as a score decrease in the Asthma Control Test score by the minimal clinically important difference in comparison to the preceding week. SD: Standard deviation; IQR: Interquartile range.

7.3.5 Specifications of Machine Learning Models

Table 7.6. Machine learning model specifications.

Algorithm (abbreviation)	Cross-validation [a]	Tuned hyperparameters	Balancing
K-nearest neighbors (knn)	10-fold with 3 repeats	Number of neighbors	Synthetic minority over-sampling technique (Chawla, Bowyer, Hall, & Kegelmeyer, 2002)
Neural net (nnet)		Number of hidden units and weight decay	
Extreme gradient boosting (xgbTree)		Number of boosting iterations, max tree depth, shrinkage, minimum loss reduction, subsample ratio of features, minimum sum of instance weight, subsample percentage	
Support vector machines [b] (svm)		Sigma and cost	
Logistic regression (glm)	Leave-one-out cross-validation	-	Weighted observations [c]
Random forest (ranger)		Number of randomly selected predictors, splitting rule and minimal node size	
Decision tree (rpart)		Complexity parameter	
Gradient boosting machine (gbm)		Number of boosting iterations, maximum tree depth, shrinkage, minimal terminal node size	

Note: Implementation using the caret and model-specific packages (Kuhn, 2015). Outcomes were weeks with clinically meaningful deteriorations in asthma control (two classes: yes/no). [a] For hyperparameter tuning in the train data set. [b] With a radial basis function kernel. [c] Multiple weight combinations were evaluated (up to a triple penalty for false positives or false negatives, respectively) and the model with the best Cohen's kappa was selected.

7.3.6 Model Result Tables

Table 7.7 and Table 7.8 show the detailed monitoring performance (cf. Sub-section 5.3.5) and prognostic performance (cf. Sub-section 5.3.6) model results, respectively.

Table 7.7. Results table of monitoring performance models.

Predictor	Cohen's kappa	Sensitivity	Specificity	PPV	NPV
K-nearest neighbors (knn)					
Nocturnal cough	-.03 (.16)	.18 (.14)	.76 (.08)	.11 (.11)	.86 (.03)
Sleep quality	-.01 (.11)	.30 (.22)	.69 (.10)	.12 (.08)	.87 (.02)
Both combined	.01 (.11)	.39 (.17)	.64 (.07)	.14 (.05)	.87 (.05)
Neural net (nnet)					
Nocturnal cough	-.03 (.18)	.29 (.28)	.66 (.14)	.11 (.10)	.86 (.06)
Sleep quality	.06 (.16)	.46 (.29)	.67 (.08)	.16 (.10)	.90 (.04)
Both combined	-.03 (.09)	.35 (.21)	.62 (.10)	.11 (.06)	.87 (.02)
Extreme gradient boosting (xgbTree)					
Nocturnal cough	.12 (.14)	.59 (.14)	.61 (.18)	.20 (.08)	.90 (.05)
Sleep quality	.02 (.08)	.49 (.25)	.58 (.10)	.14 (.04)	.89 (.05)
Both combined	-.01 (.08)	.39 (.17)	.61 (.08)	.13 (.05)	.87 (.03)
Support vector machines (svm)					
Nocturnal cough	-.04 (.10)	.42 (.39)	.54 (.28)	.10 (.07)	.88 (.08)
Sleep quality	.06 (.10)	.48 (.18)	.62 (.12)	.16 (.07)	.89 (.02)
Both combined	.14 (.15)	.39 (.17)	.78 (.14)	.24 (.13)	.89 (.03)
Logistic regression (glm)					
Nocturnal cough	.06 (.04)	.87 (.14)	.30 (.05)	.16 (.03)	.94 (.05)
Sleep quality	.09 (.07)	.52 (.13)	.64 (.03)	.18 (.04)	.90 (.03)
Both combined	.07 (.14)	.39 (.17)	.70 (.08)	.17 (.09)	.88 (.03)
Random forest (ranger)					
Nocturnal cough	.30 (.22)	.39 (.26)	.91 (.03)	.39 (.16)	.91 (.04)
Sleep quality	.03 (.08)	.07 (.09)	.96 (.04)	nA	.88 (.01)
Both combined	.18 (.18)	.18 (.18)	.97 (.03)	nA	.89 (.02)
Decision tree (rpart)					
Nocturnal cough	.26 (.15)	.49 (.25)	.85 (.03)	.30 (.09)	.92 (.04)
Sleep quality	.05 (.10)	.63 (.13)	.46 (.12)	.15 (.06)	.89 (.04)
Both combined	.23 (.24)	.53 (.21)	.77 (.10)	.28 (.17)	.92 (.04)
Gradient boosting machine (gbm)					
Nocturnal cough	.27 (.14)	.34 (.16)	.91 (.05)	.47 (.31)	.90 (.03)
Sleep quality	.14 (.14)	.56 (.22)	.68 (.11)	.21 (.09)	.91 (.03)
Both combined	.19 (.25)	.29 (.22)	.91 (.06)	.30 (.24)	.90 (.03)
Threshold-based models					
Nocturnal cough	.21 (.12)	.54 (.26)	.76 (.10)	.26 (.09)	.92 (.05)
Sleep quality	-.01 (.04)	.82 (.18)	.15 (.12)	.13 (.03)	.86 (.16)
Both combined	.15 (.20)	.32 (.24)	.86 (.05)	.23 (.16)	.90 (.03)

Note: Standard deviations (across the five folds) in parenthesis. PPV: Positive predictive value; NPV: Negative predictive value; nA: Not available (e.g., division by zero in at least one test-fold). N = 227 weeks (predicted class: 29 weeks with a clinically meaningful deterioration in asthma control).

Table 7.8. Results table of prognostic performance models.

Lag [a]	Length [a]	Threshold [b]	Sensitivity	Specificity	BAC	PPV	NPV
Nocturnal cough							
0	5	.61 (0)	.62 (.52)	.63 (.10)	.63 (.25)	.01 (.01)	>.99 (.01)
1	5	.61 (0)	.75 (.46)	.63 (.10)	.69 (.22)	.01 (.01)	>.99 (<.01)
2	4	.59 (.02)	.62 (.52)	.61 (.09)	.62 (.24)	.01 (.01)	>.99 (.01)
3	2	.55 (.04)	.75 (.46)	.58 (.09)	.67 (.21)	.01 (.01)	>.99 (<.01)
4	2	.66 (.03)	.50 (.53)	.68 (.09)	.59 (.26)	.01 (.02)	>.99 (.01)
5	1	.61 (.04)	.50 (.53)	.66 (.06)	.58 (.27)	.01 (.01)	>.99 (.01)
6	1	.52 (.12)	.50 (.53)	.57 (.06)	.53 (.25)	.01 (.01)	>.99 (.01)
7	1	.77 (.14)	0 (0)	.79 (.16)	.40 (.08)	nA (nA)	.99 (<.01)
Sleep quality							
0	1	.49 (.05)	.75 (.46)	.61 (.07)	.68 (.24)	.01 (.01)	>.99 (<.01)
1	6	.67 (.01)	.62 (.52)	.69 (.13)	.65 (.27)	.02 (.02)	>.99 (.01)
2	5	.69 (.02)	.62 (.52)	.70 (.13)	.66 (.27)	.01 (.02)	>.99 (.01)
3	2	.37 (0)	1 (0)	.38 (.10)	.69 (.05)	.01 (0)	>.99 (<.01)
4	3	.72 (0)	.62 (.52)	.73 (.10)	.68 (.26)	.02 (.02)	>.99 (.01)
5	3	.75 (.02)	.50 (.53)	.76 (.08)	.63 (.28)	.02 (.02)	>.99 (.01)
6	1	.62 (.23)	.50 (.53)	.65 (.26)	.57 (.20)	.01 (.01)	>.99 (.01)
7	1	.78 (.08)	.12 (.35)	.79 (.08)	.46 (.17)	<.01 (.01)	.99 (<.01)
Both combined							
0	1	.56 (.05)	.88 (.35)	.57 (.05)	.72 (.16)	.01 (.01)	>.99 (<.01)
1	6	.65 (.05)	.75 (.46)	.64 (.08)	.70 (.25)	.01 (.01)	>.99 (<.01)
2	5	.66 (.02)	.75 (.46)	.66 (.07)	.71 (.24)	.01 (.01)	>.99 (<.01)
3	4	.71 (.02)	.75 (.46)	.69 (.06)	.72 (.24)	.01 (.01)	>.99 (<.01)
4	3	.72 (.03)	.75 (.46)	.69 (.07)	.72 (.24)	.01 (.01)	>.99 (<.01)
5	2	.81 (.01)	.50 (.53)	.77 (.05)	.64 (.27)	.01 (.01)	>.99 (.01)
6	2	.74 (.02)	.62 (.52)	.71 (.05)	.67 (.26)	.01 (.01)	>.99 (.01)
7	1	.64 (.36)	.25 (.46)	.65 (.32)	.45 (.16)	0 (0)	.99 (.01)

Note: Standard deviations (of the eight folds) in parenthesis. [a] Window lag and window length are statistically significantly associated ($r = -.61$, $p < .01$), indicating that models with lower lags took advantage of their possibility of longer window lengths (lag and length were not allowed to exceed 8 days together). [b] Percentile of the distribution in the complete sample (values that reach or exceed this threshold result in a prediction of an attack). BAC: Balanced accuracy; PPV: Positive predictive value; NPV: Negative predictive value; nA: Not available. N = 2,004 days (predicted class: eight days with asthma attacks).

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