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# Asthma and Sleep Disturbances

*Associations to Comorbidities and Asthma Control*

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ACTA  
UNIVERSITATIS  
UPSALIENSIS  
UPPSALA  
2019

ISSN 1651-6206  
ISBN 978-91-513-0596-7  
urn:nbn:se:uu:diva-377945

Dissertation presented at Uppsala University to be publicly examined in Enghoffsalen, Akademiska sjukhuset, ingång 50 by, Uppsala, Friday, 3 May 2019 at 09:00 for the degree of Doctor of Philosophy (Faculty of Medicine). The examination will be conducted in Swedish. Faculty examiner: Jon Konradsen (Karolinska Institutet).

### **Abstract**

Sundbom, F. 2019. Asthma and Sleep Disturbances. Associations to Comorbidities and Asthma Control. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine 1552*. 78 pp. Uppsala: Acta Universitatis Upsaliensis. ISBN 978-91-513-0596-7.

This thesis aimed to investigate the associations between asthma control, asthma-related comorbidity, and sleep. Insomnia symptoms with asthma are common, and have commonly been explained by poor asthma control and asthma symptoms during the night, which affect most asthmatics to some degree. The impact of asthma-related comorbidity, however, is not fully known. Further aims were to analyze the effects of asthma control and comorbidities on asthma-related quality of life, and to analyze the effects of co-existing asthma and obstructive sleep apnea on objective sleep quality.

Four different populations were investigated: the two large community-based cohorts GA2LEN (n=25,610) and LifeGene (n=23,875), a cohort of 369 young asthma patients (MIDAS), and a polysomnography study of 384 women (SHE).

The GA2LEN study confirmed that insomnia symptoms remain a common problem among asthmatics. Poor asthma control and nasal congestion were important risk factors for insomnia symptoms. Smoking and obesity were other risk factors for insomnia symptoms among asthmatics.

Asthma control, as assessed using the Asthma Control Test (ACT), was identified as the most important predictor of asthma-related quality of life in the MIDAS study. Combining the ACT score with data on insomnia, anxiety, and depression showed considerable additive effects of the conditions.

In the SHE study, co-existing asthma and OSA were associated with worse objective sleep quality and more profound nocturnal hypoxemia than either of the conditions alone. The group with both asthma and OSA had the highest levels of the markers of systemic inflammation CRP and IL-6.

Uncontrolled asthma was a risk factor for all insomnia symptoms in the LifeGene study. Asthma-related comorbidity had a great impact on sleep quality; in particular, the combination of uncontrolled asthma and any comorbidity was unfavorable. Chronic rhinosinusitis was a risk factor for both insomnia symptoms and uncontrolled asthma.

These findings have a high clinical relevance and underline the importance of structured evaluation of asthma control and attention to comorbidity in asthma care, as insomnia symptoms are common and affect quality of life. Optimizing asthma control is crucial for sleep quality, but treating asthma-related comorbidity must not be overlooked.

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ISSN 1651-6206

ISBN 978-91-513-0596-7

urn:nbn:se:uu:diva-377945 (<http://urn.kb.se/resolve?urn=urn:nbn:se:uu:diva-377945>)

*I would like to understand things better, but  
I don't want to understand them perfectly.*

Douglas R. Hofstadter



# List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

- I Sundbom, F., Lindberg E., Bjerg A., Forsberg, B., Franklin K., Gunnbjörnsdóttir M., Middelveld R., Torén, K. & Janson C. Asthma symptoms and nasal congestion as independent risk factors for insomnia in a general population: Results from the GA(2)LEN survey. *Allergy* **68**, (2013).
- II Sundbom, F., Malinowski, A., Lindberg, E., Alving, K. & Janson, C. Effects of poor asthma control, insomnia, anxiety and depression on quality of life in young asthmatics. *The Journal of asthma : official journal of the Association for the Care of Asthma* **53**, 398-403, (2016).
- III Sundbom, F., Janson, C., Malinowski, A. & Lindberg, E. Effects of Coexisting Asthma and Obstructive Sleep Apnea on Sleep Architecture, Oxygen Saturation, and Systemic Inflammation in Women. *Journal of Clinical Sleep Medicine* **14**, 253-259, (2018).
- IV Sundbom, F., Malinowski, A., Lindberg, E., Almqvist C. & Janson, C. Insomnia symptoms and asthma control – Interrelations and importance of comorbidities (submitted)

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# Abbreviations

ACO	Asthma-COPD overlap
ACQ	Asthma Control Questionnaire
ACT	Asthma Control Test
AHI	Apnea-hypopnea index
AQLQ	Asthma Quality of Life Questionnaire
AR	Allergic rhinitis
ATS	American Thoracic Society
BHR	Bronchial hyper-responsiveness
BMI	Body mass index
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CRP	C-reactive protein
CRS	Chronic rhinosinusitis
DAG	Direct acyclic graph
DIS	Difficulty initiating sleep
DMS	Difficulty maintaining sleep
EDS	Excessive daytime sleepiness
EMA	Early morning awakenings
ERS	European Respiratory Society
ESS	Epworth Sleepiness Scale
FeNO	Fractional exhaled nitric oxide
FEV <sub>1</sub>	Forced expiratory volume in one second
FVC	Forced vital capacity
GERD	Gastro-esophageal reflux disease
GINA	The Global Initiative for Asthma
HADS	Hospital Anxiety and Depression Scale
HRQoL	Health-related quality of life
ICS	Inhaled corticosteroids
Ig	Immunoglobulin
IL	Interleukin
ILC2	Type-2 innate lymphoid cells
LABA	Long-acting beta agonist
LTRA	Leukotriene receptor antagonist
mAQLQ	Mini asthma quality of life questionnaire
NO	Nitric oxide
NSAID	Nonsteroidal anti-inflammatory drug

OCS	Oral corticosteroids
ODI	Oxygen desaturation index
OR	Odds ratio
OSA	Obstructive sleep apnea
PEF	Peak expiratory flow
REM	Rapid eye movement
SABA	Short-acting beta agonist
Th	T helper cell
TNF	Tumor necrosis factor
TST90	Total sleep time spent with oxyhemoglobin saturation <90%

# Introduction

“...An attack of asthma of unbelievable violence and tenacity – such is the depressing balance sheet of my night, which obliged me to stand on my feet in spite of the early hours at which I got up yesterday...”

## Sleep and insomnia

The quote above is from the French writer Marcel Proust, found in a letter to his mother from 1900.<sup>1</sup> Proust suffered continuously from poor health. He had difficult asthma since childhood and developed severe insomnia, depression, and anxiety. He spent his last years in isolation and died of pneumonia at an age of 51.

Sleep is a basic human need, and we spend almost one-third of our lives sleeping. Sleep was considered as a passive state between wakefulness and death into modern ages, and until the later half of the 20<sup>th</sup> century most scientific focus was on dreams and dream interpretation. Today, sleep is recognized as a dynamic process, which involves complex neural systems and is vital to maintain cognitive, endocrine, and immune functions. The objective, physiological, changes that occur in the body during sleep can be recorded with polysomnography, including changes in the brain activity, eye movements, muscle activity, respiratory airflow, respiratory effort, heart rate, and peripheral pulse oximetry.<sup>2</sup> Sleep consists of both rapid eye movement (REM) sleep and non-REM sleep. Non-REM sleep is further divided into light stage N1 and N2 sleep as well as deep stage N3 sleep. Sleep during a polysomnography recording can be illustrated as a hypnogram, where sleep cycles consisting of all sleep stages repeat approximately every 90 minutes.<sup>2</sup> Since arousals and breathing can also be recorded by polysomnography, it is considered the gold standard for diagnosing obstructive sleep apnea (OSA).

About 10% of the population suffer from insomnia.<sup>3</sup> Insomnia is defined as the presence of subjective sleep disturbances (difficulty initiating sleep (DIS), difficulty maintaining sleep (DMS), or early morning awakenings (EMA)) in combination with daytime consequences for at least three times a week, despite adequate opportunity for sleep.<sup>4</sup> Insomnia has several adverse daytime effects, also after adjusting for comorbidity and social factors. Individuals with insomnia have impairments with regard to concentration,

memory, and attention; use more healthcare resources; have elevated work absenteeism; and are more often involved in accidents.<sup>5</sup> Persistent insomnia is also a risk factor for depression.<sup>6</sup>

Risk factors for insomnia include lifestyle factors such as being overweight, being physically inactive, and alcohol dependence.<sup>7</sup> Insomnia is also more common in the presence of a chronic medical condition, and the prevalence is higher with multi-morbidity.<sup>8</sup>

Asthma is one of the most common medical conditions with an association to insomnia. Investigating the associations between asthma and sleep is the rationale for this thesis.

# Background

## The history of asthma

The first written record of the word “asthma” is found in Homer’s *Iliad*, written about 2,700 years ago, and refers to a short-drawn breath with open mouth. A soldier could be wounded in battle and die with “asthma and perspiration.”<sup>9</sup> Hippocrates (460-360 BC) also used the term asthma, but it is likely that he considered asthma as a symptom rather than as a separate clinical entity. Five hundred years later, Aretaeus the Cappadocian described asthma as a chronic disease resulting in periodic dyspnea; he was also the first to describe asthma attacks.<sup>10</sup> However, the struggle of defining and labeling asthma seems to be as old as the history of medicine itself: after Aretaeus, followed the more famous Galen (129-199 AD), who often shared Hippocrates opinions, and asthma was again considered as a type of dyspnea.<sup>9</sup>

The description of asthma remained vague until the second half of the 19<sup>th</sup> century. The first modern definition of asthma is attributed to the British physician Henry Hyde Salter, who stated in his major work *On asthma: Its pathology and Treatment* from 1860: “Paroxysmal dyspnea of a peculiar character, generally periodic with intervals of healthy respiration between the attacks.”<sup>11</sup> Salter had further noticed worsening of asthma during sleep and recommended strong coffee and avoidance of opiates. The cause of asthma was still unknown and usually described as “a perverted nervous action.” The Canadian physician Sir William Osler, famous for connecting clinical observations to pathology and physiological mechanisms, refined the definition and added to the knowledge about the pathophysiology of asthma.<sup>12</sup> His famous textbook *Principles and Practice of Medicine* from 1892 describes asthma as the result of bronchospasm, swelling of the bronchial membrane, and inflammation in the bronchioles. Thus, the view of asthma as a distinct, single disease with a specific cause and clinical expression was established in the late 19<sup>th</sup> century.<sup>12</sup>

The American physician Francis M. Rackemann published a famous paper on asthma in 1918.<sup>13</sup> He had examined 150 patients with asthma and defined them as either having “extrinsic” or “intrinsic” asthma, based on the clinical expressions. The group with extrinsic asthma was defined by the presence of any allergy. The group with intrinsic asthma was far more heterogeneous, and it is easy for a modern reader to suspect that some of the

patients that Rackemann describes probably suffered from heart failure, COPD, or obesity hypoventilation syndrome rather than what we today would define as non-allergic asthma. Rackemann's division into these two main groups of asthma was clinically useful and became established, but he also emphasized the importance of comorbidity. His patients suffered from rhinitis, sinonasal infections, gastro-esophageal reflux, gastric ulcers, obesity, and nervous symptoms, and as the treatment options for asthma were very limited, Rackemann suggested that treating the comorbidities was a way to improve the asthma symptoms.

## Asthma today

In 2006, *The Lancet* published an editorial with the somewhat sensational heading "A plea to abandon asthma as a disease concept."<sup>14</sup> The authors stated that the term "asthma," just like in ancient Greece, was too vague and imprecisely defined to be meaningful. Maybe asthma should no longer be considered as a disease, but rather as a symptom of something else?

Although inhaled corticosteroids had revolutionized asthma treatment and asthma mortality, and hospitalization rates had decreased dramatically during the later part of the 20<sup>th</sup> century, many patients still reported poor asthma control and frequent exacerbations.<sup>15</sup> Most patients with allergic asthma showed the expected eosinophil-dominated inflammatory pattern, but there was growing evidence that a refined classification of asthma was needed. For example, an alternative classification of asthmatics into four inflammatory phenotypes could be made based on the proportions of eosinophils and neutrophils in sputum.<sup>16,17</sup> Cluster analysis could identify further groups of asthmatics, based on combinations of clinical findings and inflammatory biomarkers.<sup>18,19</sup> A two-dimensional division of asthmatics into clinical phenotypes, based on both clinical characteristics and inflammatory markers, was proposed in 2012.<sup>20</sup>

A "label-free" approach for airway diseases has emerged during recent years.<sup>21-23</sup> It has been argued that the "Oslerian diagnostic labels asthma and COPD" have low clinical relevance today and instead, a concept of "treatable traits" in airway diseases has been proposed.<sup>22</sup> Treatable traits may be either pulmonary (e.g., airflow limitation, eosinophilic inflammation, or bronchiectasis) or extra-pulmonary (e.g., obesity, chronic rhinosinusitis, or gastro-esophageal reflux). Approaching each treatable trait directly, instead of using the umbrella terms asthma and COPD, would lead to an individualized precision medicine strategy in chronic airway diseases.<sup>21,22</sup>

At the same time, the guidelines from the Global Initiative for Asthma (GINA) have become more and more detailed, giving the practicing physician good and evidence-based support in treatment decisions. GINAs standardized stepwise approach for adjusting asthma treatment is well-

established and works well for the majority of asthma patients,<sup>24,25</sup> although sometimes criticized for not taking the underlying phenotypes into account.<sup>21</sup>

Asthma is evidently not only a heterogeneous disease. Even the opinion on what asthma is, when underlying molecular and cellular mechanisms should be evaluated, and even if the term itself is relevant is apparently heterogeneous.

Considering the increasing knowledge about the heterogeneity of asthma and the impact of comorbidity, it is a challenge to conduct epidemiological research in the field. It is of great importance to use standardized measures and definitions, and to make structured studies. The key terms and measures of exposure and outcome in this thesis will be presented and discussed in the following section.

## Defining asthma

The Global Initiative for Asthma (GINA) revised the definition of asthma in 2015: “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 over time and in intensity, together with airflow limitation.”<sup>26</sup> Hence, asthma is a clinical diagnosis without definitive diagnostic criteria.

Guidelines emphasize the confirmation of variable airway obstruction, but significant reversibility is not obligatory for an asthma diagnosis if the patient reports typical symptoms.<sup>25</sup> Even among patients managed for severe asthma in a specialist setting, only 54% had an objectively confirmed asthma diagnosis in a Danish, retrospective cohort study.<sup>27</sup> Still, asthma is defined by bronchial hyper-responsiveness (BHR) in many studies, and it has been discussed how asthma should be defined in epidemiology. There is currently no consensus or standardized definition.<sup>28</sup>

Pekkanen reviewed the validity of symptom questionnaires and bronchial hyper-responsiveness testing in 1999, and found that BHR testing had too low sensitivity for diagnosing asthma in population-based studies.<sup>29</sup> Combining BHR with symptom questionnaires increased specificity, but the sensitivity was still lower than with symptom questionnaires only. A 2014 review of the 100 most-cited cross-sectional studies on asthma prevalence found no less than 29 different ways to define “current asthma,” of which most relied on self-reported questionnaire data.<sup>28</sup> The main multinational studies on asthma prevalence in adults, The European Community Respiratory Health Survey (ECRHS) and The Global Allergy and Asthma European Network (GA<sup>2</sup>LEN), used similar questionnaires for assessing asthma prevalence, defining asthma as self-reported asthma attacks in the last 12 months and/or current use of asthma medication.<sup>30,31</sup> De Marco et al. examined 811 ECRHS participants further to investigate the relationship between clinical and epidemiological diagnosis of asthma.<sup>32</sup> The asthma

prevalence was underestimated by questions on self-reported current asthma and overestimated by questions on wheezing, in relation to clinical judgment. However, the ECRHS questionnaire was considered valid, and it is widely used today.<sup>30</sup>

Population-based register data can also be used for epidemiological asthma research in some countries. A Danish study compared the asthma prevalence using three different methods in the same cohort of children: self-reports from parents, prescription data, and hospitalization data.<sup>33</sup> The asthma prevalence was highest using prescription data and lowest in the hospitalization registry. A British study compared general practitioner-recorded asthma in children with self-reports from parents, and found that the question “Has a doctor ever diagnosed your child with asthma?” had a high sensitivity and a high specificity.<sup>34</sup>

## Inflammation and phenotypes

Asthma is usually an inflammatory disease. Allergic asthma is characterized by type-2 inflammation, where CD4+ T-cells develop into T-helper type 2 (Th2) cells. Th2-cells produce pro-inflammatory cytokines including IL-13 and IL-4, which stimulate B-cells to produce allergen-specific IgE antibodies, as well as IL-5, which activate eosinophils.<sup>35</sup> IL-13 induces airway hyper-responsiveness, and both IL-4 and IL-13 increase epithelial nitric oxide (NO). Type 2-inflammation in asthma has been much in focus during recent years, since monoclonal antibody treatment targeting IgE, IL-5, IL-4, and IL-13 has been developed,<sup>36-38</sup> and the role of the recently described type-2 innate lymphoid cells (ILC2) as an alternative source of Th2 cytokines in non-atopic type-2 asthma has also been investigated.<sup>39</sup> Type 2-inflammation in asthma is not only restricted to the airways, and elevated peripheral blood eosinophils can be used as a biomarker with correlation to asthma control, IL-5 mediated inflammation, and exacerbation risk.<sup>40</sup> The other main biomarker of inflammation in type-2 asthma is fractional exhaled nitric oxide (FeNO), which correlates to IL-4/13 driven inflammation and asthma control.<sup>41,42</sup> These biomarkers are of limited use for diagnosing asthma, but they can be useful in phenotyping and monitoring asthma control.<sup>24</sup> IgE sensitization may also be used as a marker for allergic asthma.<sup>43</sup>

Non-type-2 inflammatory asthma is common in adults, but it has been much less investigated. Non-type-2 phenotypes are more common in smokers, obese, and elderly patients, of which some have overlapping features of asthma and COPD.<sup>44</sup> IL-8-induced neutrophilic airway inflammation and systemic inflammation with elevated pro-inflammatory cytokines such as tumor necrosis factor  $\alpha$  (TNF $\alpha$ ) and IL-6 have been demonstrated, but there are no established biomarkers of non-type-2 asthma to date.<sup>45</sup> However, several markers of systemic inflammation have been

linked to asthma. IL-6 stimulates hepatic production of acute phase proteins such as C-reactive protein (CRP), which is elevated in non-allergic asthma but not in allergic asthma.<sup>46</sup> Until recently, IL-6 was considered as an unspecific marker of systemic inflammation, but circulating IL-6 has been demonstrated to be involved in airway inflammation by modulation of the Th1 and Th2 balance.<sup>47</sup> IL-6 is currently most often used as a biomarker of systemic inflammation and metabolic dysfunction, but it is elevated in asthma and correlates to worse asthma severity and lower FEV<sub>1</sub>.<sup>48</sup> Late-onset asthma patients with elevated levels of IL-6 had more comorbidity, lower lung function, and higher need of ICS in a Finnish study.<sup>49</sup> TNF $\alpha$  has regulating effects on immune cells and is also involved in IL-6 regulation. Elevated TNF $\alpha$  in severe asthma has been demonstrated, but asthma treatment with TNF $\alpha$  antagonists has a modest effect.<sup>50</sup> Furthermore, inflammation in obesity-associated non-type-2 asthma may be mediated by adipokines. Adipokines are cytokines produced by the adipose tissue and its resident macrophages, which have effects on several systems, including glucose metabolism, lipid metabolism, blood pressure regulation, and systemic inflammation.<sup>35</sup> Leptin and adiponectin are probably the most important adipokines in airway diseases, but adipocytes can also produce IL-6 directly. Leptin has been pointed out as a mediator of non type-2-mediated inflammation, while adiponectin seems to have anti-inflammatory effects on both B-cells and T-cell response in airway diseases.<sup>35,47,51</sup> Together, these mechanisms add links between obesity, systemic inflammation, and non-type-2 inflammatory asthma.

## Asthma control

Asthma control refers to the degree to which asthma symptoms are minimized by current treatment, and is the basis for asthma management and treatment decisions.<sup>24,25</sup> As asthma, by definition, has several components (symptoms, airway obstruction, and typically inflammation), more than one endpoint is needed for the assessment of asthma control.<sup>26</sup> For example, treatment with a beta agonist may have positive effects on lung function and asthma symptoms, but does not reduce airway inflammation or bronchial hyper-responsiveness and thereby does not improve all aspects of asthma control.<sup>52</sup> The different domains of asthma correlate poorly to each other. Thus, symptoms, lung function, and exacerbation history should be considered as independent measures.<sup>53,54</sup>

The common definition of asthma control was developed by an American Thoracic Society and European Respiratory Society (ATS/ERS) task force in 2009 and consists of two main domains: the level of clinical asthma control and the risk of future adverse events including exacerbations and loss of lung function.<sup>53</sup> Accordingly, GINA guidelines assess symptoms and risk factors separately.<sup>24</sup> The GINA asthma control evaluation consists of four items:

daytime symptoms, nocturnal waking, frequency of short-acting beta agonist (SABA) use, and activity limitation. A revised definition of uncontrolled asthma from the ATS/ERS guidelines on severe asthma from 2014<sup>54</sup> is also commonly used today, defining uncontrolled asthma as at least one of the following:

1. Poor symptom control (ACT<20, ACQ>1.5 or not well controlled, according to GINA guidelines)
2. Frequent severe exacerbations: two or more bursts of OCS in the previous year
3. Serious exacerbations: at least one hospitalization in the previous year
4. Airflow limitation: FEV<sub>1</sub> <80% predicted after bronchodilator

Asthma control varies over time. Therefore, measures of asthma control should relate to a certain time period. Asthma control is by consensus usually measured over periods of 1 to 4 weeks.<sup>53</sup>

There are several composite measures in which asthma control is expressed as numeric variables. These measures are easy to use and record and are suitable for both clinical use and for research. The most common measure of asthma control in clinical practice in Sweden is the Asthma Control Test (ACT). The test consists of five questions on different symptoms: shortness of breath, nocturnal waking, activity limitation, frequency of SABA use, and self-rated asthma control. The maximum 25 points indicate good asthma control, while a score of less than 20 corresponds to uncontrolled asthma.<sup>55</sup> Another common instrument is the Asthma Control Questionnaire (ACQ), consisting of questions on shortness of breath, nocturnal waking, symptoms on waking, activity limitation, wheeze, and frequency of SABA use in combination with a FEV<sub>1</sub> measurement.<sup>56</sup> A mean score of less than or equal to 0.75 represents well-controlled asthma, and a value greater than 1.50 represents not well-controlled asthma.<sup>57</sup> ACT and ACQ have similar sensitivity and specificity for detecting uncontrolled asthma.<sup>58</sup> Both ACQ and ACT should routinely be combined with evaluation of exacerbation history, and ACT also with a lung function test, to assess both domains of asthma control in accordance with the GINA guidelines.<sup>24</sup> Additional measures of asthma control include biomarkers such as blood eosinophils<sup>40</sup> and FeNO.<sup>41,42</sup>

## Asthma-related quality of life

Health-related quality of life (HRQoL) is a broad measure of physical, mental, and emotional well-being, as perceived by a patient or study

participant. Quality of life is usually measured using validated questionnaires, which can be either generic or disease-specific. Measuring quality of life in asthma adds information on the problems that are most important to the majority of patients,<sup>59</sup> whereas the outcomes of asthma control typically focus on the areas of most importance to the clinician.<sup>53</sup> A standardized questionnaire can be an advantage over an informal interview, and quality of life measures can also be used as primary endpoints in clinical trials.<sup>36</sup>

Common questionnaires for assessing asthma-related quality of life are the Asthma Quality of Life Questionnaire (AQLQ)<sup>60</sup> and its shorter version, the mini Asthma Quality of Life Questionnaire (mAQLQ).<sup>59</sup> The mAQLQ consists of 15 questions covering four domains: asthma symptoms, activity limitation, emotional function, and environmental stimuli. Patients score their experiences on a 7-point scale, where 1 stands for severe impairment and 7 stands for no impairment at all. St. George's Respiratory Questionnaire (SGRQ) was developed for assessment of quality of life in COPD, but it is also validated for asthma.<sup>61</sup> SF-36 is the most common generic quality of life questionnaire and is also used for asthma.<sup>62</sup> All quality of life questionnaires provide important complementary information on a patient's or study participant's health status in asthma and are significantly associated with asthma control, but the correlation to specific measures of asthma control (e.g., symptoms or airflow limitation) is generally low.<sup>53</sup>

Asthma-related quality of life was surveyed in two cross-sectional analyses within the Swedish PRAXIS study, showing a generally good asthma-related quality of life, but no improvement between 2005 and 2015.<sup>63</sup> Asthma control is considered as the most important predictor of asthma-related quality of life.<sup>64</sup> Other risk factors for worse asthma-related quality of life include female sex,<sup>65</sup> smoking,<sup>65</sup> exacerbations,<sup>63</sup> and comorbidities such as rhinitis,<sup>63,66</sup> chronic rhinosinusitis,<sup>67</sup> gastro-esophageal reflux (GERD),<sup>68</sup> obesity,<sup>63,69</sup> obstructive sleep apnea,<sup>70</sup> and depression.<sup>63,65</sup> High level of education and self-reported knowledge on self-management is associated with better asthma-related quality of life.<sup>63</sup>

Since the concept of asthma-related quality of life deals with many aspects of asthma, from symptoms to psychological stress and avoiding going outside, it represents a wider picture of the disease than the strictly symptom-oriented measures of asthma control. Hence, aspects of asthma that result in impaired asthma-related quality of life are of great importance to the patient, even though they may be considered to be in the periphery of the asthma syndrome.

## Asthma control and sleep

Both asthma and insomnia affect quality of life, and insomnia symptoms are very common with asthma.<sup>71</sup> This association is seen both in adolescents and adults, and insomnia symptoms are more common in women than in men.<sup>72</sup>

Insomnia symptoms in asthma have commonly been explained by poor asthma control and asthma symptoms during the night, since nocturnal asthma symptoms to some degree affect most asthmatics.<sup>71,73</sup> The asthma patient is vulnerable at night due to several mechanisms. Decreased ventilation and lung volumes, increased lower airway resistance, increased airway inflammation, and altered hormonal signaling occurs during sleep.<sup>73</sup> There are circadian variations of the chronic inflammation, airway hyper-responsiveness, and reversible airway obstruction in asthma, with worsening at 4 a.m. compared to 4 p.m.<sup>74</sup> Alveolar eosinophils and macrophages increase at night in nocturnal asthma.<sup>75</sup> IL-5 producing CD4+ T cells increase in the airways during the night, and the inflammatory biomarker serum periostin is the highest in the morning.<sup>76,77</sup>

The association between asthma control and insomnia symptoms has been verified in a number of studies. Janson et al. demonstrated that asthma was a major risk factor of DIS, EMA, and daytime sleepiness already in 1996.<sup>71</sup> Many studies on sleep disturbances in the general asthma population were published during the 1990s, while more recent studies mainly focus on severe asthma: Luyster et al. investigated sleep in the Severe Asthma Research Program (SARP) in 2012 and found a high prevalence of insomnia symptoms with asthma, an association between sleep quality and asthma control, and that sleep quality was worse with severe asthma.<sup>78</sup> Another study from the same group showed an insomnia prevalence of 37% among asthmatics, and concluded that asthmatics with insomnia had significantly worse asthma control, lower lung function, more exacerbations, higher need for oral corticosteroids, and worse asthma-related quality of life.<sup>79</sup> Interestingly, 25% of the asthmatics in this study reported insomnia without any asthma symptoms during the night, suggesting that poor asthma control cannot fully explain the prevalence of insomnia with asthma.

Short sleep duration is associated with several adverse health effects including increased mortality. Furthermore, short sleep duration was associated with respiratory symptoms such as wheezing, waking up with chest tightness, shortness of breath, and coughing in the large longitudinal population-based European Community Respiratory Health Survey (ECRHS), independently of asthma-related comorbidity.<sup>80</sup>

Although most studies on asthma and sleep are cross-sectional, one randomized control trial showed that sleep quality improved with better asthma control during six months, in mild to moderate asthma patients.<sup>81</sup> Conversely, subjects with insomnia symptoms at baseline in the Norwegian

HUNT-study had a higher risk of developing asthma during an 11-year follow-up period than subjects without insomnia.<sup>82</sup>

In summary, many studies have underlined asthma control as an important factor for subjective sleep quality. However, most of them identify at least one association between sleep quality and any asthma-related comorbidity, such as allergic rhinitis,<sup>71</sup> GERD,<sup>78</sup> obesity,<sup>80</sup> depression, or anxiety.<sup>72,78</sup> The few studies on asthma and sleep that do not specify any associations between comorbidities and sleep disturbance have generally not focused on comorbidity at all.<sup>83</sup>

## Asthma-related comorbidity and sleep

Comorbidity is commonly defined in relation to a specific index condition, whereas multi-morbidity refers to co-occurrence of two or more medical conditions within one person, without any reference to an index condition. However, these terms are not uniformly defined and are often used interchangeably.<sup>84</sup> In evaluation of asthma, the term comorbidity commonly refers to a number of medical conditions with close relation to or etiological association with asthma.<sup>85,86</sup> Conditions such as hypertension, diabetes, and ischemic heart disease are often, but not always, considered as multimorbidity.<sup>87</sup> Comorbidities with relevance for airway symptoms are considered as “extra-pulmonary treatable traits” and integrated in the precision medicine concept of airway diseases.<sup>22</sup>

Comorbidity is very common in asthma, but the exact prevalence varies depending on the definitions. The Swedish register study PACEHR showed that most asthma patients in primary care had at least one other medical condition, most commonly rhinitis or respiratory tract infections, and that the prevalence of multi-morbidity increased with higher age.<sup>87</sup> The prevalence is higher in difficult asthma, with a median of 3 extra-pulmonary asthma-related comorbidities among patients undergoing systematic assessment at a specialist center in Australia.<sup>88</sup> Tay et al. evaluated 93 patients with difficult asthma and found that 74.4% had any comorbidity, and that comorbidities had greater impact on asthma control and asthma-related quality of life than conventional asthma parameters such as FEV<sub>1</sub> or blood eosinophil count.<sup>69</sup> It is likely that these effects are partly intermediated by poor sleep, since most asthma-related comorbidities are independently associated with sleep quality. Common asthma-related comorbidities, with effects on both asthma control and sleep quality, will be presented in the following section.

## Rhinitis and chronic rhinosinusitis

Rhinitis is very common, with a prevalence of more than 30% in the general population.<sup>30</sup> Like asthma, rhinitis is considered as a syndrome with a

number of clinical phenotypes: allergic rhinitis and several phenotypes of non-allergic rhinitis.<sup>89</sup> Allergic rhinitis is characterized by IgE-mediated, type-2 inflammatory response, and exhibits inflammation in the upper airway corresponding to the lower airway inflammation seen with allergic asthma.<sup>90</sup> More than 80% of patients with allergic asthma also have allergic rhinitis.<sup>91</sup> Since the 1990s, the two conditions are often referred to as two aspects of the same disease, “united airway disease.”<sup>92</sup> Hence, allergic rhinitis and allergic asthma are sometimes considered as parts of a spectrum rather than two comorbid diseases: a treatable trait within the allergic asthma phenotype.<sup>21</sup>

Both allergic and non-allergic rhinitis may result in more severe nasal syndromes such as chronic rhinosinusitis (CRS). CRS is sometimes considered as a rhinitis phenotype, but it can also be divided into different endotypes depending on the underlying pathophysiological background. CRS is a common symptom of nasal polyps, which is overrepresented with asthma and more prevalent with more severe asthma.<sup>93</sup> Nasal polyposis may occur with or without atopy and is associated with NSAID-sensitive asthma. CRS without allergic rhinitis is overrepresented with late-onset asthma.<sup>94</sup> A large Swedish cross-sectional study found that the prevalence of CRS in asthma was 8% and that the prevalence of asthma in CRS was 24%.<sup>95</sup> In addition, the prevalence of asthma increased with the number of nasal symptoms, and the prevalence of nasal symptoms increased with the number of asthma symptoms.

Allergic rhinitis is commonly defined as any patient-reported nasal allergy including hay fever. CRS is defined as having at least two of the following symptoms: nasal blockage/congestion, nasal discharge, facial pain/pressure, or reduction of smell, with at least one symptom being nasal blockage or nasal discharge and a minimum symptom duration of 4 weeks.<sup>96</sup> Nasal polyposis is usually a clinical diagnosis.

Apart from being associated with asthma prevalence, rhinitis and nasal symptoms are associated with worse asthma control<sup>66,97</sup> and worse asthma-related quality of life.<sup>66</sup> Data from the ECRHS study demonstrated that both allergic and non-allergic rhinitis are risk factors for developing asthma in adults.<sup>98</sup> The risk was higher with allergic rhinitis, especially in the presence of asymptomatic bronchial hyper-responsiveness at baseline. More severe AR is associated with worse asthma control, and non-use of nasal corticosteroids is a risk factor for worse asthma control among asthma patients with rhinitis.<sup>99</sup>

Insomnia symptoms with rhinitis may be caused directly by nasal congestion, with an additive adverse effect of inflammatory cytokines with a direct negative effect on sleep.<sup>100</sup> However, it may also be mediated by the high prevalence of asthma and worse asthma control with untreated allergic rhinitis. A meta-analysis of sleep impairment in allergic rhinitis found that intranasal corticosteroids could reduce nasal congestion and improve sleep

impairment and quality of life.<sup>100</sup> Nasal obstruction at night has been pointed out as the most important type of rhinitis for subjective sleep impairment, but findings on the impact of nasal obstruction on objective sleep quality are inconsistent.<sup>100-102</sup> However, allergic rhinitis affects subjective sleep quality, daytime sleepiness, and school and work productivity.<sup>103,104</sup> The total cost of allergic rhinitis is very high and is explained by absenteeism and reduced working capacity at work, where daytime sleepiness is an important factor.<sup>105</sup>

## Gastro-esophageal reflux

The association between gastro-esophageal reflux disease (GERD) and respiratory symptoms has been known for many years. GERD is common in chronic cough, but symptomatic gastro-esophageal reflux is also overrepresented with difficult-to-treat asthma.<sup>106</sup> There are two main mechanisms linking asthma to acid reflux: First, the reflux theory, explaining respiratory symptoms as a direct effect of micro-aspirations of acid refluxate and second, the reflex theory, explaining bronchial constriction as a result of stimulation of vagal nerve endings in the esophagus. Cough and increased respiratory effort in asthma may further increase the pressure gradient across the lower esophageal sphincter, and thereby worsen the reflux.<sup>106,107</sup> A systematic review of 28 prevalence studies confirmed that asthma is more common with GERD, and that GERD is more common with asthma.<sup>107</sup> Several definitions of GERD are used, but most studies use patient-reported symptoms of heartburn and/or acid regurgitation, and only a few studies have monitored esophageal pH.<sup>107</sup>

Gastro-esophageal reflux is associated with worse asthma control and worse quality of life.<sup>68</sup> Longitudinal studies have demonstrated higher incidence of asthma and sleep apnea symptoms with persistent GERD,<sup>108</sup> and that GERD and obesity are independently associated with higher incidence of asthma and increased nocturnal respiratory symptoms.<sup>109</sup> There are however contradictory findings, where obstructive sleep apnea but not gastro-esophageal reflux is associated with poor asthma control in obese patients.<sup>110</sup> Several studies have investigated the effects of proton pump inhibitors (PPIs) on asthma, and treatment may have effects on morning PEF.<sup>111</sup> A meta-analysis of 11 trials did not identify any significant effect on other asthma outcomes,<sup>112</sup> and investigation of occult GERD in uncontrolled asthma is not supported.<sup>106</sup>

Gastro-esophageal reflux is associated with subjective insomnia symptoms and objective sleep fragmentation due to arousals and awakenings.<sup>113</sup> GERD and sleep apnea syndrome share many risk factors, including obesity, and the relationship may be bidirectional. However, GERD has direct effects on sleep and is often considered as an independent risk factor for sleep disturbance.<sup>113</sup>

## Obesity

Asthma is over-represented with obesity and obesity is over-represented with asthma, and obese asthmatics report more severe asthma than non-obese asthmatics.<sup>114,115</sup> Participants in the American TENOR II study, focusing on severe asthma, had a mean BMI of 30.6.<sup>116</sup> Obese asthmatics require higher doses of inhaled corticosteroids, use more short-acting beta-agonists, and have a more frequent need for steroid bursts.<sup>117</sup> A post hoc analysis of 3,073 participants with asthma in a randomized control study demonstrated decreasing response to inhaled corticosteroids with higher BMI.<sup>118</sup> Serum IgE levels, sputum eosinophils, and levels of exhaled NO are often low with obesity, while gastro-esophageal reflux is over-represented.<sup>117,119</sup> Hence, asthma in obesity is typically non-allergic and non-type-2-mediated.

Obesity has direct physiological effects on ventilation. Excess abdominal and thoracic fat increases the intra-abdominal pressure and reduces the mobility of the chest. This results in reduced lung volumes, with a mildly restrictive lung function pattern. Secondary to the smaller lung volumes, there can be a mild reduction in FEV<sub>1</sub>, but the FEV<sub>1</sub>/FVC ratio is usually normal.<sup>120</sup> Hence, obesity does not result in any direct obstructive effects as measured with spirometry. Studies on bronchial hyper-responsiveness in obesity are contradictory, with no clear evidence on the causation between obesity and bronchial hyper-responsiveness.<sup>120,121</sup>

Obesity is often associated with other comorbidities, of which obstructive sleep apnea, gastro-esophageal reflux, and depression are related to worse asthma control. Obesity seems to have effects on asthma independent of comorbidity, as the associations between obesity and worse asthma outcomes remain after adjusting for these factors.<sup>122,123</sup> Longitudinal studies show that being overweight or obese is a risk factor for developing asthma, with or without allergy.<sup>115,124,125</sup> One Mendelian randomization study has demonstrated a causal relation between higher BMI and higher asthma prevalence and lower lung function, but not with any markers of allergy.<sup>126</sup> Another study showed that high BMI was a risk factor for wheezing without asthma, but not for asthma without wheezing.<sup>127</sup> The relative risk of developing asthma increases with the severity of obesity, and this association has been demonstrated for both general obesity (BMI) and central obesity (waist circumference).<sup>124</sup>

It is well known that the risk of developing obesity is higher with short sleep duration, and both obesity and weight gain have been associated with poor sleep quality.<sup>128-130</sup> Although strongly associated with sleep apnea, obesity had only a weak association with insomnia symptoms in a recent meta-analysis of 67 studies, and there was no association between obesity and having an insomnia diagnosis.<sup>131</sup> Obstructive sleep apnea may thereby be considered as a partial mediator between obesity and sleep disturbance, and as a confounding factor in obesity and asthma.

## Obstructive sleep apnea

Obstructive sleep apnea (OSA) is the most common sleep-related breathing disorder. OSA is characterized by recurrent episodes of complete or partial airway obstructions during sleep, resulting in apneas and hypopneas, despite continued respiratory effort. OSA is currently defined as the occurrence of 15 or more such respiratory events per hour of sleep, in the absence of sleep-related symptoms.<sup>4</sup> In the presence of excessive daytime sleepiness or certain medical conditions, an apnea-hypopnea-index (AHI) of 5 or more is sufficient for an OSA diagnosis. OSA is very common in the general population, with 49.7% of men and 23.4% of women fulfilling the diagnostic criteria in a Swiss population-based study.<sup>132</sup> A corresponding prevalence of 19.6% was found in an Icelandic study, but the correlation between AHI and symptoms of poor sleep was weak and most subjects with previously undiagnosed OSA did not suffer from daytime sleepiness or any sleep-related symptoms.<sup>133</sup> It has further been demonstrated that daytime sleepiness is associated with snoring, but not to AHI.<sup>134</sup> Hence, the current classification of OSA severity based on AHI has been questioned.<sup>133</sup>

Asthma is more prevalent with OSA and vice versa. Asthma severity, female sex, and GERD are positive moderators of the OSA risk in asthma, besides obesity.<sup>135</sup> The prevalence of OSA in asthma patients is highly variable between different studies. A meta-analysis of OSA prevalence in asthma using pooled estimates demonstrated that the OR of having OSA was 2.64 (1.76-3.52) with asthma, in comparison to participants without asthma.<sup>136</sup> The overall prevalence of OSA with asthma was 49.5%, but varied considerably between studies. OSA risk is another measure, which sometimes is used in epidemiology. OSA risk is assessed by validated screening questionnaires such as the Berlin Questionnaire and STOP-BANG<sup>70</sup> and is also consequently higher with asthma than without asthma.<sup>136</sup> High OSA risk also correlates with worse asthma control.<sup>137</sup>

Julien et al. performed polysomnography studies in asthma patients and identified a higher prevalence of OSA, higher AHI, and lower mean oxygen saturation in subjects with severe asthma as compared to those with moderate asthma.<sup>138</sup> Results from the Wisconsin Sleep Cohort point out asthma as an important risk factor for developing OSA, as identified with repeated polysomnography studies at 4-year intervals.<sup>139</sup>

It has been proposed that the development of OSA in asthmatic patients affects asthma control, which in turn worsens OSA in a self-reinforcing cycle.<sup>139</sup> Patients with co-existing asthma and OSA have a predominantly neutrophilic airway inflammation, which supports the hypothesis that OSA is associated with obesity-related, non-type-2 inflammatory asthma phenotypes.<sup>140</sup> Systemic inflammation is also present in OSA, with higher serum levels of IL-6, CRP, and TNF $\alpha$ . However, the extent to which this

depends on AHI, hypoxemia, or BMI is not fully known, as studies are inconsistent.<sup>141,142</sup>

CPAP treatment of OSA may have beneficial effects on asthma outcomes, but there is a lack of controlled studies. A Spanish study followed 99 patients with asthma and OSA (respiratory disturbance index >20) during 6 months of CPAP treatment and found significant improvements in asthma-related quality of life, asthma control, FeNO, and BHR.<sup>143</sup> The first randomized control study on CPAP treatment in asthma was published in 2018. This study demonstrated improved asthma control during CPAP treatment, but the untreated control group also improved and no significant difference was seen between the groups.<sup>144</sup> A systematic review of the twelve first studies on asthma outcomes during CPAP treatment for OSA was published in 2018. Meta-analysis indicated that asthma-related quality of life improved during the CPAP treatment, but no evidence of significant improvement of asthma control or lung function was found.<sup>145</sup>

## Anxiety and depression

There is a long-known association between depression and asthma, where depression has adverse effects on patient-reported asthma outcomes. The prevalence of depression in asthma varies in a wide range from 1-45% between studies, as different definitions of both conditions have been used.<sup>146</sup> Hence, it is still unclear whether persons with asthma are at a higher risk for depression. Some specific asthma symptoms, such as nocturnal awakenings and morning symptoms, are commonly associated with depression.<sup>147</sup> One important explanation for the worse asthma control with depression is worse adherence to asthma treatment. Misinterpretation of the symptoms of both depression and anxiety as asthma symptoms (and vice versa) is also described.<sup>146</sup> Although most studies are cross-sectional, there are some longitudinal data. Symptoms of both anxiety and depression improved with better asthma control during standardized asthma treatment in a recent Spanish study.<sup>148</sup> A longitudinal study followed 3,614 participants for 25 years and analyzed the incidence of asthma and depression bidirectionally. Depression was identified as a risk factor for incident asthma, while asthma was not a risk factor for incident depression.<sup>149</sup>

There is an even more complex inter-dependence between asthma and anxiety.<sup>150</sup> Prominent, specific anxiety is an expected reaction during a severe asthma attack, since it is a potentially lethal situation. However, some patients develop fear of asthma attacks, and anxiety is not only over-represented among asthmatics but also associated with more asthma symptoms, more frequent medical service trips, and inadequate symptom perception.<sup>151</sup> As adequate symptom perception is important for correct use of as-needed medication, this may lead to over-treatment and worse

subjective asthma control. Conversely, asthma symptoms may be interpreted as anxiety symptoms, leading to under-treatment of asthma.<sup>150</sup>

Screening for symptoms of anxiety and depression can be performed with validated questionnaires. One of the most well known screening questionnaires is the Hospital Anxiety and Depression Scale (HADS), which consists of two subscales (HAD-A for anxiety and HAD-D for depression).<sup>152</sup> Self-reported diagnoses of depression or anxiety disorders are also used in epidemiology.

All insomnia symptoms (DIS, DMS, and EMA) are very common with both anxiety and depression. Insomnia often precedes a depression diagnosis, while insomnia usually onsets at the same time as an anxiety disorder.<sup>6,153</sup>

## Trigger factors, treatment, and asthma severity

Apart from asthma control and asthma-related comorbidity, there are further components in asthma that may have relevance for sleep.

### **Trigger factors and environmental factors**

Both asthma and sleep may be affected by external factors, or exposures. Smoking is such a risk factor for poor asthma control, which also is independently related to worse sleep quality.<sup>154</sup> Passive smoking is also associated with higher prevalence of asthma and respiratory symptoms, including nocturnal symptoms.<sup>155</sup> Physical activity, on the other hand, is associated with less insomnia symptoms and mainly positive asthma outcomes.<sup>156</sup> Allergen exposure is of great importance in allergic asthma, where seasonal allergens result in worsening of asthma control during the pollen season. An independent increase of sleep disturbances and excessive daytime sleepiness, related to rhinitis and allergic inflammation, can be seen simultaneously.<sup>103</sup> Further, the indoor environment is associated with nocturnal worsening of asthma and the prevalence of sleep disturbances.<sup>157</sup> Low educational level or low socioeconomic status are other factors independently associated with worse asthma control and higher insomnia prevalence.<sup>78,79</sup>

### **Treatment and adherence**

The adherence to asthma treatment is low, and incorrect inhaler technique is common. A systematic review found that the mean level of adherence to ICS treatment was 22-63%.<sup>158</sup> Poor adherence was more common among young patients, among patients with short education and with mild asthma. Poor adherence is a risk factor for worse asthma control, including nighttime symptoms.

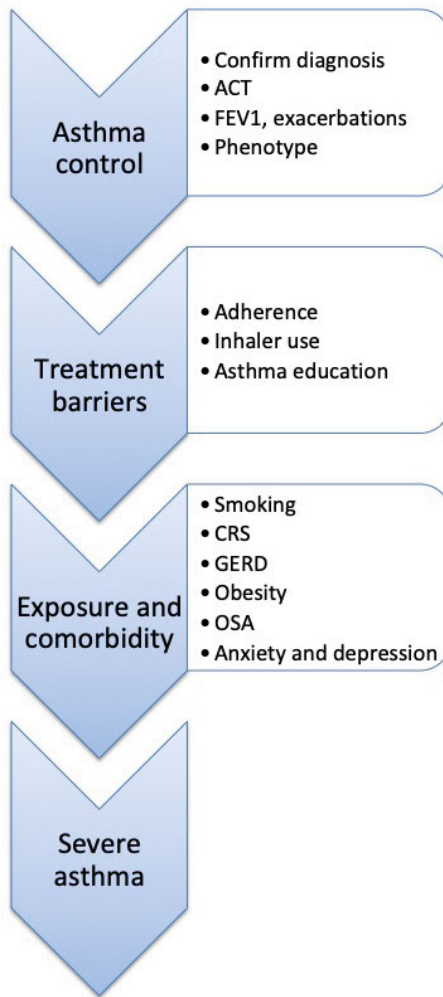
On the other hand, the systemic side effects of corticosteroids include sleep disturbances. Although inhaled corticosteroids in therapeutic doses have limited systemic effects, oral corticosteroids (OCS) are still used in severe asthma. It has been reported that side effects such as cataracts, hypertension, and increased bruising affect up to 30% of participants in severe asthma cohorts.<sup>116</sup> At least one study has indicated that high-dose treatment with inhaled corticosteroid also affects the upper airway collapsibility, suggesting a new potential link between intensive asthma treatment and development of OSA.<sup>159</sup>

### **Asthma severity and structured asthma assessment**

The term asthma severity refers to the intrinsic intensity of the disease, and several studies have found associations between insomnia and asthma severity.<sup>78,140</sup> However, the uniform definition of asthma severity has only been available since 2014. This must be taken into consideration while interpreting older studies, where the terms severe asthma, difficult asthma, uncontrolled asthma, and refractory asthma sometimes have been used interchangeably.

Severe asthma, according to the ATS/ERS guidelines, is defined as asthma requiring high-intensity treatment to maintain asthma control, or asthma being uncontrolled despite high intensity treatment, even after all comorbidities and exposures are considered and treated.<sup>54</sup> In practice, this means that before a diagnosis of severe asthma can be made, a systematic asthma assessment is required. Hence, relatively few studies on asthma and sleep actually evaluate severe asthma by its current definition. An algorithm for systematic asthma assessment, considering the most common comorbidities, is presented in Figure 1.

A diagnosis of severe asthma requires information on adherence to pharmacological treatment and optimization of non-pharmacological care, since the treatment response is a part of the evaluation. Thereby, the concept of asthma severity is complicated to evaluate in population-based studies. Much of the recent research on asthma and sleep is conducted in selected, severe-asthma populations attending specialist care.<sup>78,140</sup> The proportion of asthmatics with severe disease was 4.2% in a recent Swedish study and 8.1% in a Danish study.<sup>160,161</sup>



*Figure 1.* Systematic assessment of asthma, including common asthma-related comorbidities. Adapted from the Nordic consensus statement on systematic assessment and management of possible severe asthma in adults from 2018.<sup>86</sup>

# Aims

## General aim of the thesis

The rationale for this thesis was to investigate the associations between asthma control, asthma-related comorbidity, and sleep. This was investigated with patient-reported outcomes and epidemiological methods (Papers I and IV) as well as with polysomnography studies (Paper III). The associations between insomnia, asthma control, and asthma-related comorbidity in relation to quality of life were specifically investigated in Paper II.

The general aims of the thesis were to; identify risk factors for insomnia symptoms in asthma; to assess the impact of asthma on objectively measured sleep; and to evaluate the effects of asthma, insomnia, and comorbidities on asthma-related quality of life.

## Specific aims

- I To analyze the association between asthma, nasal symptoms, and insomnia symptoms and to identify risk factors for insomnia symptoms among patients with asthma, using a large population-based set of material.
- II To investigate the determinants of asthma-related quality of life in a population of young subjects with asthma.
- III To analyze the effects of asthma, OSA, and the combination of asthma and OSA on objectively measured sleep and systemic inflammation.
- IV To analyze the associations between insomnia symptoms, asthma control, asthma severity, and asthma-related comorbidity.

# Methods

## Study populations

### **GA<sup>2</sup>LEN (Paper I)**

The Global Allergy and Asthma European Network (GA<sup>2</sup>LEN) is a network for research on asthma and allergic diseases, with participating centers in 22 European countries. The Swedish GA<sup>2</sup>LEN survey was sent to 45,000 randomly selected subjects aged 16-75 years in Uppsala, Stockholm, Gothenburg, and Umeå in 2008, and 25,610 subjects participated.<sup>94</sup>

### **MIDAS (Paper II)**

The Minimally Invasive Diagnostics for Asthma and Allergic Diseases Study (MIDAS) is an industry-academic collaboration project in the field of allergology and respiratory medicine in Uppsala.<sup>162</sup> The study cohort consists of 529 children and young adults (10-35 years), of which 411 have asthma. Participants were recruited from both primary care and specialist care facilities. Only asthmatic subjects over 12 years of age (n=369) were included in the present study. Asthma was physician-diagnosed in medical records, and all participants were treated daily with inhaled corticosteroids or oral anti-leukotriene antagonists for at least three months in the year before inclusion.

### **SHE (Paper III)**

Sleep and Health in women (SHE) is an ongoing, population based study in Uppsala, in which 7,051 randomly selected women aged >20 years were included in 2000. From 2001 to 2004, 400 women aged 20-70 years (with oversampling of snorers) were selected from the study cohort to perform a full-night polysomnography recording.<sup>163</sup> Complete data were available from 384 participants.

### **LifeGene (Paper IV)**

LifeGene is an ongoing prospective cohort study in Sweden.<sup>164</sup> Data from 23,875 participants aged 18-45 years were available. Index persons between 18 and 45 years of age were randomly selected from the government person address register (Statens Personadressregister, SPAR). The invitations were

sent by mail, and the index persons were encouraged to invite family members to the study. There was also a possibility for anyone to register for participation at the LifeGene web site.

## Definitions and questionnaires

Asthma was defined from questionnaire data in Papers I, III, and IV. Asthma control was assessed by the number of self-reported asthma symptoms in Paper I, and in accordance with the GINA guidelines in Paper II and Paper IV. Insomnia symptoms were evaluated in all of the studies. The definitions of asthma diagnosis, asthma control, and insomnia symptoms in each paper are presented in Table 1.

Table 1. *Definitions of asthma, asthma control, and insomnia symptoms*

	<b>Paper I GA<sup>2</sup>LEN</b>	<b>Paper II MIDAS</b>	<b>Paper III SHE</b>	<b>Paper IV LifeGene</b>
Asthma definition	Current medication or asthma attack <12 months	Current medication and asthma diagnosis in medical records	Current medication or asthma attack <12 months	Current medication and self-reported physician's diagnosis
Asthma control	Number of symptoms	ACT/GINA	-	GINA
Insomnia symptoms	DIS, DMS, or EMA $\geq 3$ nights/week	DIS, DMS, or EMA $\geq 3$ nights/week and daytime sleepiness	DIS, DMS, and EMA analyzed separately	DIS, DMS, or EMA $\geq 4$ nights/week

The GA<sup>2</sup>LEN questionnaire used in Paper I included further questions on asthma, rhinitis, insomnia, chronic bronchitis, eczema, cardiovascular disease, physical activity, and workplace and environmental exposure. Nasal congestion was defined as having a blocked nose for at least 12 weeks during the last 12 months. The following asthma-related symptoms, reported at any time in the last 12 months, were chosen as the markers of asthma control:

1. Wheezing or whistling in the chest
2. Waking up with chest tightness
3. Being awakened by shortness of breath

ACT was used as a marker of the impairment dimension of asthma control in Paper II, while the risk dimension was assessed from exacerbation history and FEV<sub>1</sub> in accordance with the GINA guidelines. The MIDAS questionnaires also included the mini Asthma Quality of Life Questionnaire

(mAQLQ) and the Hospital Anxiety and Depression Scale (HADS). HADS was used for screening for comorbidity in depression and/or anxiety, and having 8 points or more on either subscale (HADS-A or HADS-D) was considered as significant.<sup>152</sup> Insomnia symptoms in combination with daytime sleepiness at least 3 days/week were defined as insomnia.

The SHE questionnaire included questions on sleep disturbances and snoring, airway diseases, allergies, co-morbidity, and current medication. DIS, DMS, and EMA were evaluated with a five-point scale, where 4 (severe problem) and 5 (very severe problem) were considered positive.<sup>101</sup> Daytime sleepiness was assessed with Epworth Sleepiness Scale (ESS), and a score of  $\geq 10$  was considered significant.<sup>165</sup>

The LifeGene questionnaire included questions on asthma control, exacerbation history, and asthma treatment, and could thereby provide information on asthma severity. Comorbidity was assessed in all study populations, but some definitions were inconsistent, as presented in Table 2.

Table 2. *Definitions of asthma-related comorbidity*

	<b>Paper I</b>	<b>Paper II</b>	<b>Paper III</b>	<b>Paper IV</b>
Rhinitis	Self-reported hay fever	Self-reported hay fever	Self-reported hay fever	Self-reported hay fever
CRS	Nasal congestion $\geq 12$ weeks	EPOS criteria <sup>96</sup>	-	EPOS criteria <sup>96</sup>
GERD	-	Any nocturnal heartburn	-	Self-reported symptoms
Obesity	BMI $\geq 30$	BMI, continuous	BMI, continuous	BMI $\geq 30$
OSA	-	-	AHI $\geq 15$	-
Anxiety	-	HADS-A $\geq 8$	-	Self-reported diagnosis
Depression	-	HADS-D $\geq 8$	-	Self-reported diagnosis

## Blood samples

Blood samples were available from the MIDAS and SHE populations. Blood eosinophil count, total IgE and IgE against a mix of aeroallergens (Phadiatop) were analyzed in the MIDAS study.<sup>162</sup> Plasma c-reactive protein (CRP), interleukin 6 (IL-6), and tumor necrosis factor alpha (TNF $\alpha$ ) were measured in the SHE study.<sup>142</sup>

## Lung function tests and FeNO

Participants in the MIDAS study performed spirometry, in accordance with the ATS/ERS guidelines,<sup>166</sup> and the highest values for forced expiratory volume in one second (FEV<sub>1</sub>) and forced vital capacity (FVC) were recorded. A bronchial provocation test was performed using a single concentration of methacholine and stepwise increasing doses and repeated measures of FEV<sub>1</sub> for calculation of PD<sub>20</sub> FEV<sub>1</sub>.<sup>162</sup> Fractional exhaled nitric oxide (FeNO) measurement was also performed in the MIDAS study.<sup>162,167</sup>

## Polysomnography

Polysomnography (PSG) recording was performed in the homes of the SHE participants using a portable sleep recorder. Sleep staging, respiratory, and arousal analysis were performed and checked by a licensed sleep technician. An obstructive apnea was defined as the cessation of airflow in both nasal pressure and oronasal thermistor for at least 10 seconds, despite continuing abdominal and thoracic movements. An obstructive hypopnea was defined as a 50% reduction from baseline in both oronasal thermistor and nasal pressure for at least 10 seconds, accompanied by abdominal and thoracic movements in combination with an arousal or an oxygen desaturation >3%. The obstructive apnea/hypopnea index (AHI) was defined as the mean number of obstructive apneas and hypopneas per hour of sleep.<sup>163</sup> Sleep apnea was considered significant with an apnea-hypopnea index of  $\geq 15$ , regardless of symptoms or multi-morbidity.<sup>142</sup>

## Study designs

The primary outcomes and main exposures in each study are presented in Table 3. In Paper II, several potential explanatory variables were initially tested against mAQLQ, after which the most important variables were used to divide the population into subgroups. In Paper III, the population was first divided into four groups, depending on the presence of asthma and/or OSA. Several polysomnography variables and inflammatory markers were compared between the groups.

Table 3. *Main exposures and primary outcomes*

	<b>Paper I</b>	<b>Paper II</b>	<b>Paper III</b>	<b>Paper IV</b>
Main exposures	Asthma control and nasal congestion	Asthma control, insomnia and anxiety/depression	Asthma and OSA	Asthma control
Primary outcome	Insomnia symptoms	HRQoL	PSG variables Inflammatory markers	Insomnia symptoms

Direct acyclic graphs (DAG) were used for identifying the confounding factors in Paper III and Paper IV. DAGs were created using the browser-based environment DAGitty ([www.dagitty.net](http://www.dagitty.net)).<sup>168</sup> The smallest set of covariates necessary to control for bias was calculated and extracted from DAGitty. In Figure 2, the DAG used for choosing variables for the multiple logistic regression analyses in Paper IV is presented.

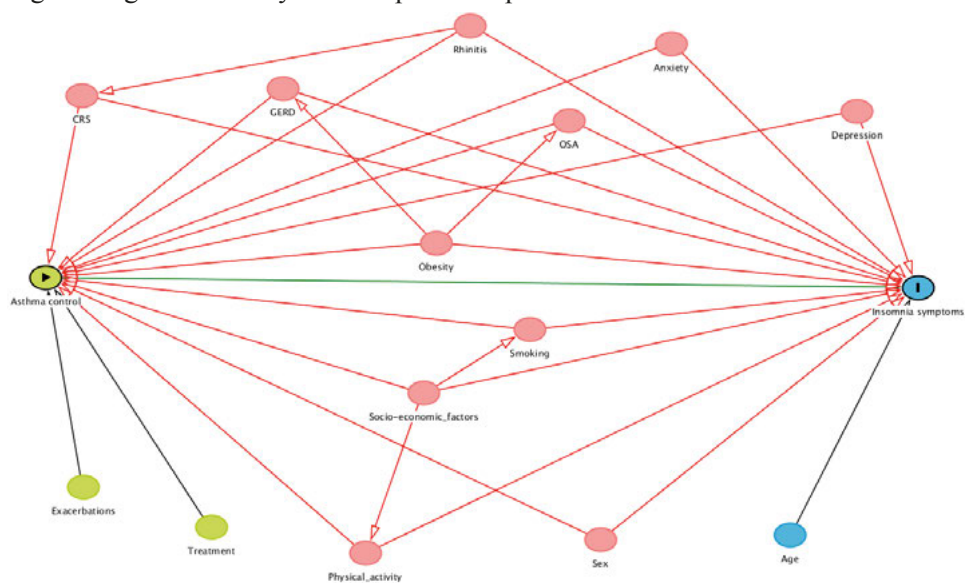


Figure 2. Causal diagram between asthma control and insomnia symptoms. Asthma control is set as the exposure and insomnia symptoms as the outcome in this model. Green arrows indicate causal paths, while the red arrows indicate biasing paths. Green circles indicate ancestors of exposure while the blue circles indicate ancestors of outcome. Red circles indicate ancestors of both exposure and outcome (confounders), which must be considered in statistical analyses. (Figure imported from dagitty.net)

## Statistical methods

All statistical analyses were conducted using STATA 11 (Paper I) and STATA 12 (Papers II-IV) (STATA Corp., Texas, U.S.A.).

Continuous data were presented as mean  $\pm$  standard deviation, or mean with 95% confidence interval (95% CI). Arithmetic mean values were used for normally distributed variables, and geometric mean values (95% CI) were used for variables with skewed to the right distribution.

For continuous variables, differences between two groups were compared with the unpaired t-test. Differences between more than two groups were calculated with one-way analysis of variance (ANOVA) with Bonferroni correction.

For categorical variables, differences between groups were compared with the  $\chi^2$ -test.

Linear regression analysis was used to examine the associations between continuous dependent variables and explanatory variables (Papers II and III). Both single explanatory variables (simple linear regression) and combinations of explanatory variables (multiple linear regression) were tested. Results were presented as regression coefficient, corresponding 95% confidence interval (95% CI), and explanatory value (adjusted  $r^2$ ). Non-normally distributed variables in Paper III were log-transformed using the base-10 log for regression analyses.

Multiple logistic regression analysis was used to examine the associations between dichotomous dependent variables and explanatory variables (Papers I and IV). Results were presented as odds ratios (OR) with corresponding 95% CI.

P-values of  $<0.05$  were considered significant.

## Ethics

Informed consent was obtained from all study participants. All papers in the thesis were approved by the Ethics Committee at the Medical Faculty at Uppsala University.

# Results

## Paper I

In the GA<sup>2</sup>LEN study 1,830 subjects (7.15%) had asthma. Subjects with asthma had a higher prevalence of rhinitis (68.4% vs. 23.7%,  $p < 0.001$ ) and nasal congestion (30.8% vs. 11.9%,  $p < 0.001$ ) than subjects without asthma. Asthmatics were younger, more often female, and had higher BMI.

Insomnia symptoms were reported by 47.3% of the asthmatics and 37.2% of the non-asthmatics, and the prevalence of each insomnia symptom was significantly higher in the group with asthma than in the group without asthma. DMS was the most widespread symptom in both groups (34.3% vs. 27.5%,  $p < 0.001$ ), while the difference was largest for DIS (22.1 vs. 13.1%,  $p < 0.01$ ).

The prevalence of insomnia symptoms was correlated to the number of reported asthma symptoms (Figure 3). In total, 211 out of 317 (66.6%) participants with asthma and three symptoms reported insomnia symptoms, while asthmatics without symptoms reported marginally more insomnia symptoms than non-asthmatics.

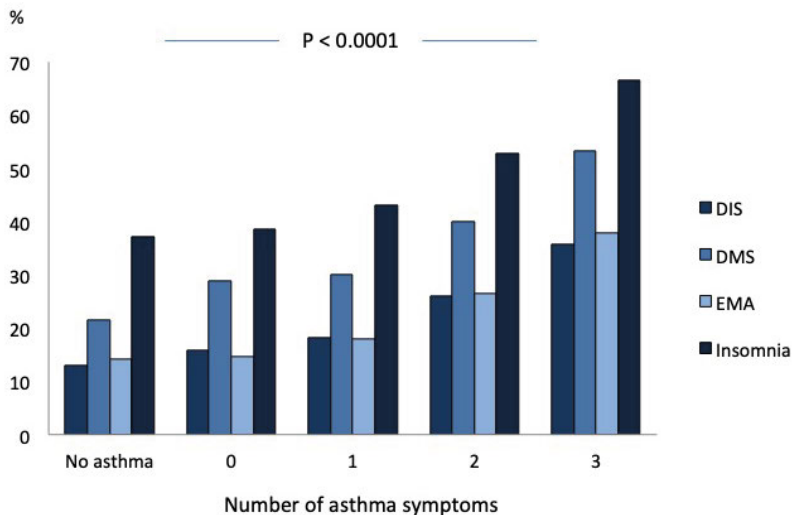


Figure 3. Prevalence of insomnia symptoms, in relation to the number of asthma symptoms

The prevalence of insomnia symptoms was very high in the sub-group with both asthma and nasal congestion: 55.8%, compared to 35.3% in the group without both asthma and nasal congestion ( $p < 0.001$ ). The group with nasal congestion only had a higher prevalence of insomnia symptoms than the group with asthma only (Figure 4).

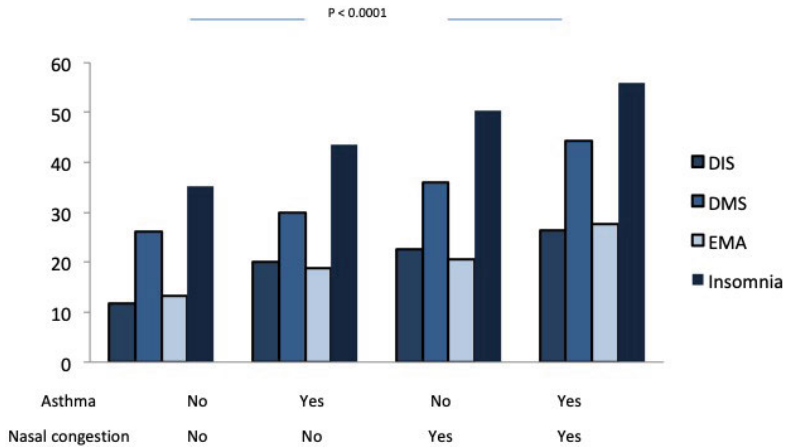


Figure 4. Prevalence (%) of insomnia symptoms, in relation to nasal congestion and asthma

The OR for insomnia was 2.65 (1.83-3.83) with 3 asthma symptoms, in comparison to asthmatics without symptoms. Odds ratios were significantly higher for each insomnia symptom: DIS 2.47 (1.60-3.83), DMS 2.34 (1.59-3.45), and EMA 3.28 (2.07-5.22) with 3 asthma symptoms. There were also independent associations between insomnia and nasal congestion, current smoking, and obesity (Table 4).

Table 4. *Adjusted odds ratio (95%CI)\* for the association between airway symptoms, gender, age, tobacco use and BMI and insomnia symptoms among asthmatics*

	<b>DIS</b>	<b>DMS</b>	<b>EMA</b>	<b>Any insomnia symptom</b>
Asthma symptoms				
0	1.00	1.00	1.00	1.00
1	1.04 (0.70-1.54)	1.07 (0.77-1.50)	1.41 (0.92-2.17)	1.16 (0.86-1.56)
2	1.59 (1.06-2.40)	1.69 (1.19-2.40)	2.16 (1.39-3.35)	1.80 (1.31-2.48)
3	2.47 (1.60-3.83)	2.34 (1.59-3.45)	3.28 (2.07-5.22)	2.65 (1.83-3.83)
Nasal congestion	1.22 (0.93-1.60)	1.75 (1.38-2.22)	1.54 (1.17-2.02)	1.50 (1.19-1.88)
Female	1.51 (1.14-2.01)	1.37 (1.08-1.74)	1.30 (0.98-1.73)	1.42 (1.13-1.77)
Age				
<25	1.00	1.00	1.00	1.00
25-35	0.48 (0.32-0.73)	1.29 (0.86-1.92)	0.86 (0.53-1.39)	0.78 (0.55-1.10)
35-45	0.44 (0.28-0.67)	1.71 (1.14-2.57)	1.22 (0.76-1.98)	0.79 (0.55-1.12)
45-55	0.47 (0.29-0.75)	2.78 (1.80-4.28)	2.24 (1.37-3.66)	1.30 (0.88-1.91)
55-65	0.37 (0.22-0.63)	2.83 (1.77-4.52)	2.22 (1.30-3.77)	1.24 (0.81-1.91)
65-75	0.43 (0.24-0.78)	2.49 (1.49-4.17)	1.88 (1.04-3.42)	1.20 (0.75-1.94)
Smoking history				
Never	1.00	1.00	1.00	1.00
Ex	1.32 (0.95-1.83)	1.27 (0.97-1.66)	1.10 (0.80-1.51)	1.22 (0.95-1.58)
Current	2.84 (1.98-4.06)	1.48 (1.05-2.10)	1.70 (1.16-2.48)	1.71 (1.23-2.39)
Oral tobacco	1.57 (1.09-2.26)	0.80 (0.57-1.13)	0.82 (0.54-1.24)	1.24 (0.91-1.69)
BMI				
<20	1.18 (0.74-1.90)	0.71 (0.44-1.15)	1.13 (0.67-1.92)	0.83 (0.55-1.25)
20-25	1.00	1.00	1.00	1.00
25-30	1.41 (1.03-1.93)	1.34 (1.03-1.75)	1.19 (0.87-1.63)	1.28 (1.00-1.65)
>30	1.91 (1.31-2.79)	1.69 (1.22-2.36)	1.51 (1.04-2.20)	1.54 (1.12-2.13)

*\*The odds ratios are adjusted for all the variables in the table and center, educational level, diabetes, hypertension, and physical activity*

## Paper II

The mean ACT score was  $20.5 \pm 3.3$ , and the mean mAQLQ score was  $5.8 \pm 1.0$ . Simple linear regression with mAQLQ as the dependent variable was analyzed for a large number of potential explanatory variables. Significant associations were identified between mAQLQ and the variables presented in Table 5, while no significant associations between mAQLQ and physical activity, rhinitis, blood eosinophil count, total IgE, FeNO, bronchial hyper-responsiveness, or FEV1/VC were found.

Table 5. *Simple linear regression with mAQLQ as the dependent variable*

	Coefficient	Std error	<i>p</i>	Adj <i>r</i> <sup>2</sup>
Female	-0.301	0.102	<0.01	2.1%
Age, by 10 years	-0.204	0.077	<0.01	1.7%
BMI, by 5	-0.182	0.060	<0.01	2.2%
IgE sensitization	0.337	0.123	<0.01	1.8%
FEV1, by 10%	0.084	0.036	0.02	1.3%
ACT	0.212	0.011	<0.01	51.5%
HAD group				17.0%
Anxiety only	-0.557	0.109	<0.01	
Depression only	-0.541	0.285	0.06	
Anxiety+depression	-1.456	0.189	<0.01	
Insomnia	-0.958	0.125	<0.01	13.8%
CRS	-0.451	0.138	<0.01	2.7%
Snoring	-0.401	0.144	<0.01	1.9%
GERD	-0.851	0.137	<0.01	9.6%
Ex-smoker	-0.570	0.245	0.02	2.4%
Current smoker	-0.617	0.238	0.01	2.4%
Exacerbations	-0.473	0.118	<0.01	4.0%
Treatment group				2.2%
ICS/LTRA	-0.058	0.177	0.74	
ICS+LABA/LTRA	0.072	0.168	0.67	
ICS+LABA+LTRA	-0.481	0.216	0.03	

All variables in Table 5 were further tested as predictors of mAQLQ in a multiple linear regression analysis. ACT, GERD, insomnia, and co-existing depression and anxiety were the only variables with independent associations to mAQLQ in this model (Table 6).

Table 6. *Multiple linear regression with mAQLQ as dependent variable (Adj  $r^2=59.2\%$ )\**

	<b>Coefficient</b>	<b>95% CI</b>	<b>p</b>
Female	-0.077	-0.225, 0.070	0.30
Age, by 10 years	-0.050	-0.171, 0.069	0.41
BMI, by 5	-0.066	-0.153, 0.022	0.14
IgE sensitization	0.128	-0.036, 0.292	0.13
FEV1, by 10%	0.022	-0.025, 0.070	0.36
ACT	0.167	0.144, 0.191	<0.01
Anxiety	-0.164	-0.332, 0.004	0.06
Depression	-0.004	-0.466, 0.473	0.99
Anxiety+depression	-0.554	-0.849, -0.258	<0.01
Insomnia	-0.431	-0.620, -0.241	<0.01
CRS	-0.001	-0.188, 0.186	0.99
Snoring	-0.131	-0.335, 0.073	0.21
GERD	-0.232	-0.434, -0.029	0.03
Ex-smoker	0.050	-0.298, 0.398	0.78
Current smoker	-0.022	-0.534, 0.094	0.17
Exacerbations	-0.145	-0.309, 0.018	0.08

*\*Results are adjusted for all the variables in the table and the level of treatment*

The study population was divided into groups, depending on the presence of uncontrolled asthma (ACT<20), anxiety and depression, and insomnia. The group reporting none of these conditions had the highest mAQLQ score (6.3 units), and belonging to any other group was significantly associated with a lower mAQLQ score (Figure 5). The group reporting uncontrolled asthma, anxiety and depression, and insomnia had the lowest mAQLQ score (3.8 units). The significance remained after adjusting for all the variables in Table 6.

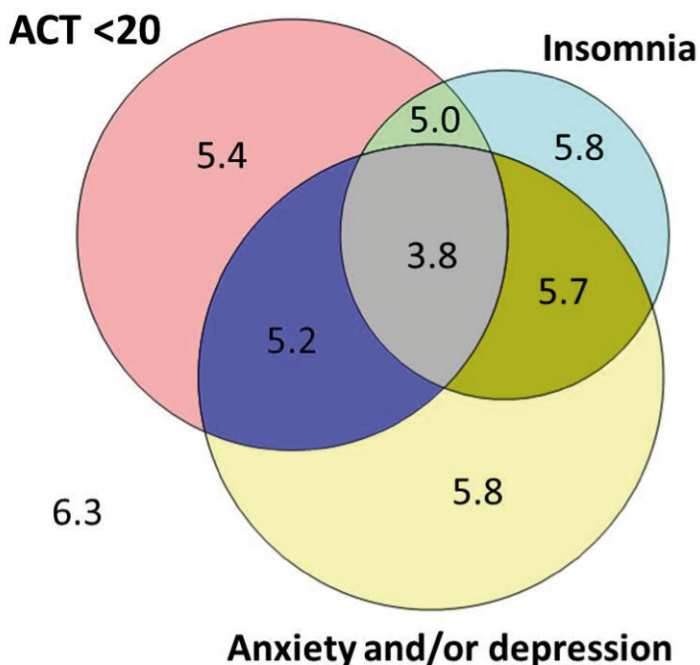


Figure 5: Mean mAQLQ score, depending on ACT, insomnia, and HADS

Sub-group	n	mAQLQ score
ACT $\geq 20$ , no insomnia, HAD-A < 8 and HAD-D < 8	160	6.3 (6.2-6.4)
ACT $\geq 20$ , insomnia, HAD-A < 8 and HAD-D < 8	15	5.8 (5.4-6.2)
ACT $\geq 20$ , no insomnia, HAD-A $\geq 8$ or HAD-D $\geq 8$	52	5.8 (5.6-6.0)
ACT < 20, no insomnia, HAD-A < 8 and HAD-D < 8	51	5.4 (5.2-5.7)
ACT $\geq 20$ , insomnia, HAD-A $\geq 8$ or HAD-D $\geq 8$	21	5.7 (5.3-6.1)
ACT < 20, no insomnia, HAD-A $\geq 8$ or HAD-D $\geq 8$	30	5.2 (5.0-5.5)
ACT < 20, insomnia, HAD-A < 8 and HAD-D < 8	4	5.0 (3.8-6.2)
ACT < 20, insomnia, HAD-A $\geq 8$ or HAD-D $\geq 8$	23	3.8 (3.3-4.2)

## Paper III

The population was divided into four subgroups, depending on the presence of asthma, OSA, or both (Figure 6, Table 7).

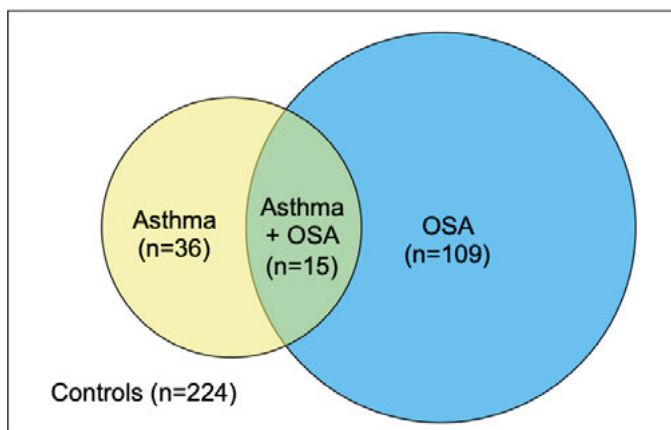


Figure 6: Subgroups of the study population (n=384)

Table 7. Characteristics and self-reported sleep complaints of the subgroups

	Controls	Asthma	<i>p</i> *	OSA	<i>p</i> *	Asthma + OSA	<i>p</i> *
Age, years	47.7±11.3	46.1±11.6	>0.99	55.6±8.8	<0.01	55.5±9.8	0.04
BMI	25.4±4.1	27.0±5.7	0.33	28.2±4.8	<0.01	33.3±8.7	<0.01
Ex-smoker (%)	32.4	30.6	0.85	34.9	0.62	26.7	0.66
Smoker (%)	19.6	22.2	0.72	22.0	0.61	33.3	0.20
>10 pack-years (%)	27.2	30.6	0.68	37.6	0.05	46.7	0.11
Rhinitis (%)	18.0	57.1	<0.01	19.2	0.80	40.0	0.04
Chronic bronchitis (%)	6.3	27.8	<0.01	6.4	0.95	40.0	<0.01
Hypertension (%)	12.1	14.7	0.67	21.3	0.03	26.7	0.11
DIS (%)	10.3	13.9	0.52	12.8	0.48	0.0	0.19
DMS (%)	19.6	33.3	0.06	26.6	0.15	20.0	0.97
EMA (%)	17.4	30.6	0.06	19.3	0.68	13.3	0.69
ESS>10 (%)	36.6	38.9	0.79	44.4	0.14	53.3	0.20

\*=versus control group

The group with both asthma and OSA had higher BMI than the group with only OSA ( $p<0.01$ ) or asthma ( $p<0.01$ ). Rhinitis was more common with asthma and most common with asthma without OSA, but the difference between the two asthmatic groups did not reach statistical significance ( $p=0.26$ ). Fifty-six percent of the asthmatics without OSA had ongoing treatment with ICS and 33% used LABA regularly. Among asthmatics with OSA, 73% had regular ICS treatment and 53% used LABA.

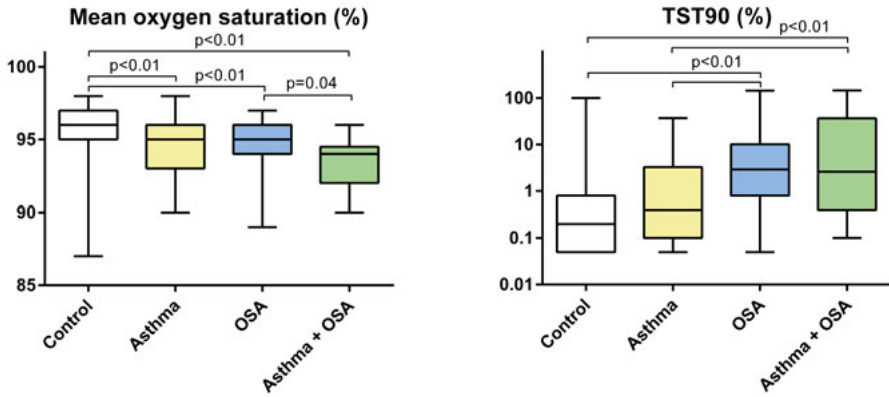


Figure 7. Mean oxygen saturation and TST90\*

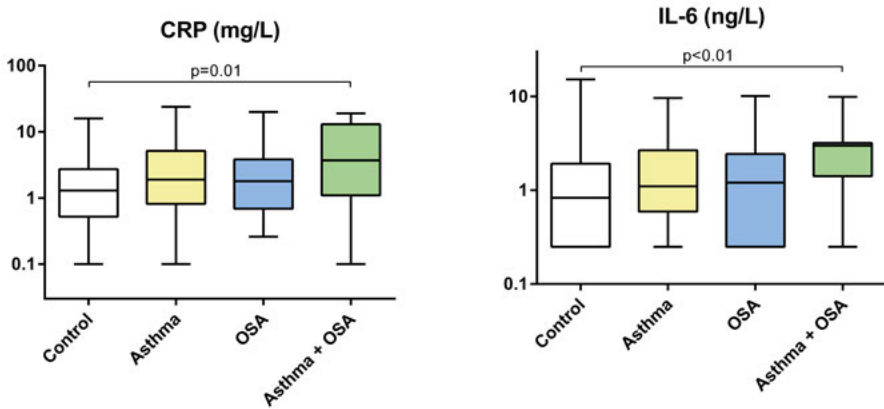


Figure 8. Inflammation markers\*

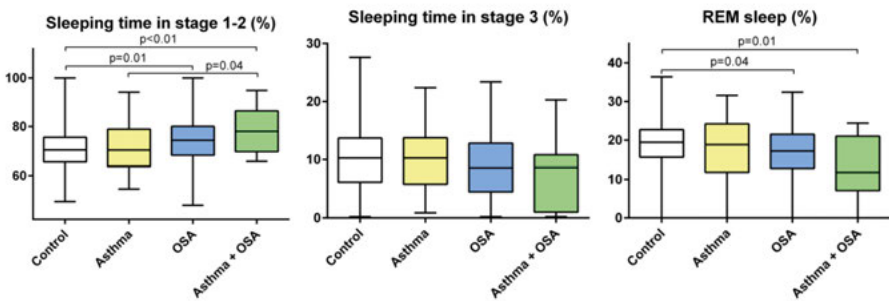


Figure 9. Sleep architecture\*

\*Analysis of variance with Bonferroni correction was calculated for the p values between the groups. All significant p values are presented in the figures.

The mean oxygen saturation was lower with the combination of asthma and OSA than with OSA alone (93.4% vs. 94.7%,  $p=0.04$ ) (Figure 7), but there was no difference in AHI or ODI. The group with both asthma and OSA had higher CRP and IL-6 (Figure 8) and longer sleeping time in stages N1 and N2 sleep, less REM sleep (Figure 9), and more awakenings than the control group.

Isolated asthma, but not isolated OSA, was independently associated with lower oxygen saturation during sleep, also after adjusting for age, BMI, and smoking status (Table 8). In the adjusted model, co-existing asthma and OSA were further associated with longer time spent with oxygen saturation <90%, longer sleeping time in stages 1-2, and higher IL-6.

Table 8. *Associations between polysomnography data, inflammation markers, and the different asthma and OSA groups. Beta regression coefficients (95% CI) from separate multiple linear regression, adjusted for age, BMI, and smoking status.*

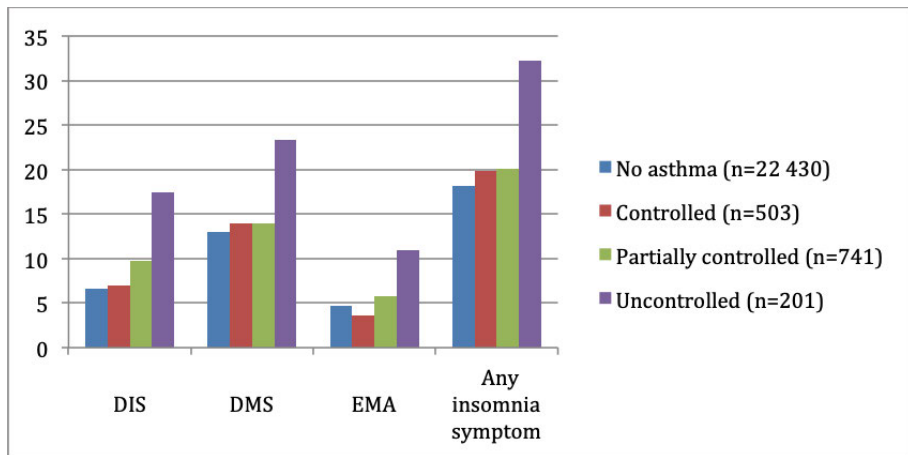
	Asthma		OSA		Asthma + OSA	
	Beta	95% CI	Beta	95% CI	Beta	95% CI
AHI*	-0.02	-0.16, 0.11	<b>0.70</b>	<b>0.60, 0.79</b>	<b>0.76</b>	<b>0.55, 0.98</b>
ODI*	0.07	-0.06, 0.20	<b>0.75</b>	<b>0.66, 0.84</b>	<b>0.74</b>	<b>0.54, 0.94</b>
Mean saturation (%)	<b>-0.91</b>	<b>-1.42, -0.40</b>	-0.30	-0.65, 0.05	<b>-0.97</b>	<b>-1.80, -1.47</b>
TST90*	0.27	-0.01, 0.54	<b>0.62</b>	<b>0.43, 0.82</b>	<b>0.60</b>	<b>0.16, 1.02</b>
Awakenings	-0.71	-2.37, 0.94	<b>1.44</b>	<b>0.28, 2.61</b>	<b>4.06</b>	<b>1.46, 6.66</b>
Stage N1/N2 sleep (%)	0.64	-2.41, 3.69	1.35	-0.79, 3.50	<b>5.68</b>	<b>0.89, 10.5</b>
Stage N3 sleep (%)	-0.02	-2.05, 2.02	-0.66	-2.09, 0.78	-2.31	-5.51, 0.89
REM sleep (%)	-0.59	-2.75, 1.57	-0.72	-2.24, 0.80	-3.37	-6.76, 0.03
CRP*	0.13	-0.03, 0.29	0.02	-0.09, 0.14	0.17	-0.08, 0.42
IL-6*	0.12	-0.05, 0.29	0.02	-0.10, 0.14	<b>0.30</b>	<b>0.04, 0.57</b>
TNF $\alpha$ *	0.01	-0.10, 0.12	-0.01	-0.09, 0.07	-0.06	-0.23, 0.12

*\*Non-normally distributed variables are log-transformed, and regression coefficients are presented for log-transformed variables.*

## Paper IV

The asthma prevalence in the LifeGene population was 5.3% (n=1,272). The prevalence of difficulties inducing sleep, difficulties maintaining sleep, and all comorbidities was higher among participants with asthma than in those without asthma.

Insomnia symptoms were more common in those with uncontrolled asthma than in those without asthma, whereas the prevalence of insomnia symptoms in the groups with controlled or partially controlled asthma was on the same level as in the non-asthmatic participants (Figure 10).



*Figure 10.* Prevalence of insomnia symptoms depending on asthma control. The higher prevalence of DIS, DMS, and EMA with uncontrolled asthma was significant compared to all other groups (p-values  $\leq 0.01$ ). None of the insomnia symptoms were more common with controlled asthma than without asthma.

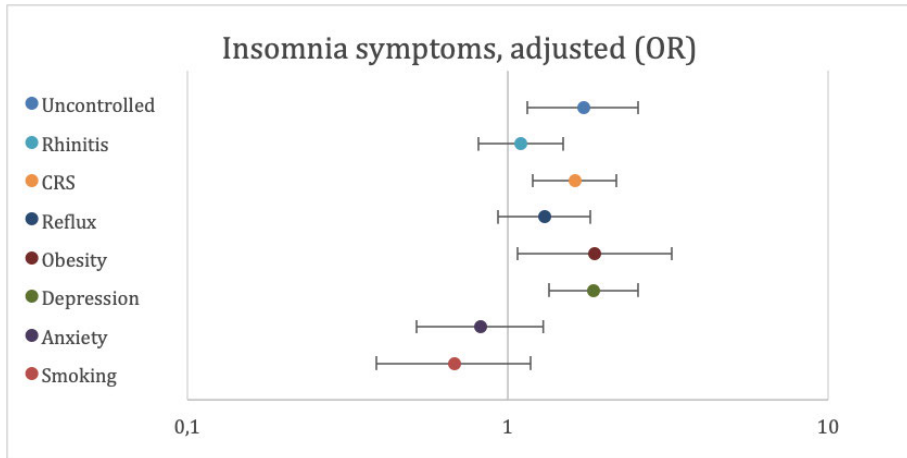
In subjects with asthma, insomnia symptoms were more common with poor asthma control, while no significant association was found between the level of asthma treatment and insomnia symptoms (Table 9). The prevalence of insomnia symptoms was higher among asthmatics reporting any comorbidity. Subjects that had both uncontrolled asthma and comorbidities had a very high prevalence of all insomnia symptoms (Table 9).

Table 9. Prevalence of insomnia symptoms in asthma, depending on asthma control and asthma-related comorbidity

	Any insomnia symptom				DIS			DMS			EMA		
	n	n	%	p	n	%	p	n	%	p	n	%	p
Shortness of breath	260	73	<b>28.1</b>	<b>0.01</b>	38	<b>14.6</b>	<b>0.01</b>	56	<b>21.5</b>	<b>&lt;0.01</b>	24	<b>9.2</b>	<b>&lt;0.01</b>
Waking up due to asthma symptoms	333	97	<b>29.1</b>	<b>&lt;0.01</b>	50	<b>15.0</b>	<b>&lt;0.01</b>	69	<b>20.7</b>	<b>&lt;0.01</b>	30	<b>9.0</b>	<b>&lt;0.01</b>
SABA use >2/w	509	125	24.6	0.13	66	<b>13.0</b>	<b>&lt;0.01</b>	89	17.5	0.16	36	<b>7.1</b>	<b>0.05</b>
Limitation of activity	307	86	<b>28.0</b>	<b>0.01</b>	46	<b>15.0</b>	<b>&lt;0.01</b>	63	<b>20.5</b>	<b>&lt;0.01</b>	31	<b>10.1</b>	<b>&lt;0.01</b>
Uncontrolled asthma	201	65	<b>32.3</b>	<b>&lt;0.01</b>	35	<b>17.4</b>	<b>&lt;0.01</b>	47	<b>23.4</b>	<b>&lt;0.01</b>	22	<b>11.0</b>	<b>&lt;0.01</b>
Exacerbations	81	26	<b>32.1</b>	<b>0.03</b>	14	<b>17.3</b>	<b>0.03</b>	20	<b>24.7</b>	<b>0.02</b>	8	9.9	0.07
Treatment steps 4 or 5	126	32	25.4	0.39	15	11.9	0.48	27	21.4	0.06	11	8.7	0.09
Current smoking	98	24	24.5	0.61	19	<b>19.4</b>	<b>&lt;0.01</b>	19	19.4	0.30	7	7.1	0.46
Rhinitis	842	198	23.5	0.18	94	11.2	0.09	139	16.5	0.28	45	5.3	0.73
CRS	150	55	<b>36.7</b>	<b>&lt;0.01</b>	33	<b>22.0</b>	<b>&lt;0.01</b>	37	<b>24.7</b>	<b>&lt;0.01</b>	17	<b>11.3</b>	<b>&lt;0.01</b>
GERD	248	74	<b>29.8</b>	<b>&lt;0.01</b>	37	<b>14.9</b>	<b>&lt;0.01</b>	60	<b>24.2</b>	<b>&lt;0.01</b>	21	<b>8.5</b>	<b>0.02</b>
Obesity	79	27	<b>34.2</b>	<b>0.01</b>	10	12.7	0.44	21	<b>26.6</b>	<b>&lt;0.01</b>	8	10.1	0.06
Depression	330	108	<b>32.7</b>	<b>&lt;0.01</b>	60	<b>18.2</b>	<b>&lt;0.01</b>	80	<b>24.2</b>	<b>&lt;0.01</b>	33	<b>10.0</b>	<b>&lt;0.01</b>
Anxiety	145	41	28.3	0.07	24	<b>16.6</b>	<b>&lt;0.01</b>	28	14.0	0.21	13	9.0	0.05
Any comorbidity	624	181	<b>29.0</b>	<b>&lt;0.01</b>	91	<b>14.6</b>	<b>&lt;0.01</b>	133	<b>21.3</b>	<b>&lt;0.01</b>	47	<b>7.5</b>	<b>&lt;0.01</b>
Uncontrolled asthma and any comorbidity	111	50	<b>45.1</b>	<b>&lt;0.01</b>	32	<b>28.8</b>	<b>&lt;0.01</b>	38	<b>34.2</b>	<b>&lt;0.01</b>	15	<b>13.5</b>	<b>&lt;0.01</b>

In the entire population, uncontrolled asthma was a significant risk factor for difficulties initiating sleep (OR 1.73 (1.15-2.60)), difficulties maintaining sleep (OR 1.55 (1.09-2.21)), and early morning awakenings (OR 1.77 (1.12-2.82)) after adjusting for age, sex, comorbidity, smoking, educational level and physical activity. Other risk factors for insomnia symptoms were female sex (OR 1.47 (1.36-1.58)), BMI 25-30 kg/m<sup>2</sup> (OR 1.11 (1.00-1.22)), chronic rhinosinusitis (OR 1.40 (1.27-1.53)), gastro-esophageal reflux (OR 1.33 (1.21-1.45)), depression (OR 1.73 (1.58-1.89)), and anxiety (OR 1.45 (1.29-1.62)).

When only analyzing the group with asthma, we found that uncontrolled asthma was a significant risk factor for any insomnia symptom (OR 1.72 (1.15-2.56)), difficulties initiating sleep (OR 2.16 (1.25-3.74)), difficulties maintaining sleep (OR 1.68 (1.07-2.64)), and early morning awakenings (OR 3.05 (1.53-6.10)) also after adjusting for comorbidity and potential confounders. Asthma control, chronic rhinosinusitis, obesity, and depression were the most important risk factors for insomnia symptoms among subjects with asthma (Figure 11).



*Figure 11.* Risk factors for insomnia symptoms among participants with asthma. Adjusted for age, sex, educational level, physical activity, and all variables in the figure.

Among the risk factors for insomnia symptoms, chronic rhinosinusitis was significantly associated with uncontrolled asthma (OR 1.62 (1.15-2.28)) also after adjusting for sex, age, smoking history, educational level, and other comorbidities. Current smoking (OR 1.90 (1.13-3.21)), gastro-esophageal reflux (OR 1.46 (1.00-2.13)), and anxiety (OR 1.76 (1.08-2.86)) were associated with uncontrolled asthma, but not with insomnia symptoms.

# Discussion

## Patient-reported outcomes in relation to asthma and sleep

The number of asthma symptoms was the most important risk factor for insomnia symptoms in Paper I. Uncontrolled asthma, according to the GINA guidelines, was a risk factor for all insomnia symptoms in Paper IV. These associations also remained significant after adjusting for comorbidities. The findings correlate to other studies, demonstrating correlations between insomnia and worse asthma control.<sup>79</sup>

Difficulty maintaining sleep was the most widespread insomnia symptom, both with and without asthma, while the biggest difference between asthmatics and non-asthmatics was seen for early morning awakenings. This aligns with earlier findings, pointing out early morning awakenings as a common problem in asthma.<sup>71</sup> One potential explanation could be the circadian variation of airway hyper-responsiveness and airway inflammation in asthma, which result in a physiological increase of asthma symptoms during the late night and early morning. Late-phase response to inhaled outdoor allergens and exposure to allergens in the bedroom may further contribute. Asthma treatment is typically administered in the morning and in the evening, but non-adherence is common. It is likely that poor asthma control becomes more evident at night among patients with undertreated asthma and high use of short-acting beta-agonists during daytime. Another explanation for the higher prevalence of early morning awakenings with uncontrolled asthma is the similarities in the questionnaires; specifically, early morning awakenings were defined as waking up too early and not being able to get to sleep again, while waking up with chest tightness or being awakened by shortness of breath were included in the asthma symptom variable in both Paper I and Paper IV. Hence, early morning awakenings may be considered as an indirect marker of asthma control.

Difficulty maintaining sleep is a more common symptom in the general population and was less asthma-specific than early morning awakenings. Difficulty maintaining sleep is also more likely to be dependent on comorbidities such as OSA and GERD, which may confound the results of Paper I and to some extent Paper IV.

Excessive daytime sleepiness, which, in combination with the presence of subjective sleep disturbances, constitutes the criteria for an insomnia

diagnosis, was not specifically assessed in Paper I or Paper IV. Instead, daytime sleepiness in asthma was analyzed in detail in another GA<sup>2</sup>LEN publication in 2018.<sup>169</sup> The main risk factors for daytime sleepiness with asthma were self-reported insomnia symptoms, CRS, current smoking, and obesity, and the prevalence of daytime sleepiness increased with a higher number of asthma symptoms.

Asthma control, as assessed with ACT, was the single most important predictor for asthma-related quality of life in Paper II. The ACT score, which represents only the impairment domain of asthma control, had a much stronger correlation to mAQLQ than the measures of the risk domain, FEV<sub>1</sub> and exacerbation history. The association between asthma control and asthma-related quality of life is consistent with previous findings.<sup>64,78,79</sup> Asthma-related quality of life was associated with insomnia, after adjusting for all other variables. This is also consistent with previous findings, indicating that insomnia is associated with a generally impaired quality of life and worse asthma control.<sup>78,79</sup> However, the co-variation between insomnia and mAQLQ may in part be in-built in the mAQLQ questionnaire, as one question in the symptom domain addresses nighttime symptoms directly: “How much of the time during the last two weeks did you have difficulty having a good night’s sleep as a result of your asthma?”<sup>59</sup> Similar overlaps exist, to a limited extent, also between ACT and mAQLQ.

## Correlation between subjective and objective measures

The markers of allergic inflammation, airflow limitation, and bronchial hyper-responsiveness were of minimal importance for asthma-related quality of life in Paper II. There were no significant differences in mAQLQ between allergic and non-allergic asthmatics, as classified by IgE sensitization, after adjusting for symptoms and treatment. These findings are consistent with previous studies.<sup>170</sup> The level of bronchial hyper-responsiveness, blood eosinophils, total IgE, or exhaled NO levels were not correlated with either the mAQLQ or the ACT scores. As the population consisted of both never-smokers and smokers, with either allergic or non-allergic asthma, further sub-group analyses would be required to understand the role of FeNO and eosinophils.<sup>171</sup> FEV<sub>1</sub> was correlated to mAQLQ as a single variable, but did not reach significance in multiple linear regression analysis. FEV<sub>1</sub> was also associated with ACT (regression coefficient 0.26 (95% CI 0.03-0.49, p=0.029) but did not reach significance in the adjusted models.

Asthma was associated with lower mean oxygen saturation in Paper III. Asthma and OSA had synergistic effects on objective sleep quality, and the combination of asthma and OSA was associated with further nocturnal hypoxemia. However, there was no correspondence between self-reported sleep complaints and objectively measured sleep variables, including level of

hypoxemia. This is in accordance with previous polysomnography studies on asthma and COPD.<sup>8,172</sup> Although insomnia has severe health effects, only a limited number of studies have actually analyzed the correlation between subjective complaints of poor sleep and objective sleep quality, and the correlation between subjective sleep and polysomnography findings is weak in most studies.<sup>173</sup> A meta-analysis of 23 polysomnography studies of, in total, 582 subjects with insomnia and 485 good sleeper controls was conducted in 2013, and found diminished sleep efficiency, increased sleep onset latency, increased number of awakenings, reduced sleeping time in stage N3 sleep, and reduced REM sleep in insomnia.<sup>3</sup>

OSA and insomnia have previously been considered as dissimilar, orthogonal conditions where insomnia is characterized by an elevated level of alertness at night, whereas OSA often leads to both daytime and bedtime sleepiness.<sup>174</sup> However, the conditions may co-exist, and OSA with insomnia is potentially more harmful than OSA only.<sup>174,175</sup> The prevalence of insomnia with OSA is not higher than without OSA, and insomnia complaints are not correlated to OSA severity.<sup>175</sup> In a study from the European Sleep Apnea Database (ESADA) including 6,555 participants with AHI>5, 29.8% reported insomnia symptoms and another 23.7% had insomnia symptoms in combination with excessive daytime sleepiness.<sup>176</sup> Moreover, OSA with insomnia is more frequently associated with hypertension and cardiovascular disease than OSA without insomnia.<sup>176,177</sup> Insomnia symptoms, especially difficulties maintaining sleep, generally improve with CPAP treatment although some OSA patients with difficulties initiating sleep may not tolerate CPAP treatment.<sup>178</sup> The number of participants with asthma, insomnia, and OSA was very low in the SHE study (n=4), and insomnia was not more prevalent with OSA.

## Impact of comorbidity and exposures

Nasal congestion and obesity were identified as risk factors for insomnia symptoms in Paper I. Additive effects of asthma-related comorbidity on quality of life was demonstrated in Paper II, where insomnia and depression and/or anxiety were the most important predictors besides asthma control. The synergistic effects of asthma and OSA were highlighted in Paper III, and Paper IV identified the burden of comorbidity as a risk factor of insomnia.

Different asthma phenotypes correlate to different comorbidities, as presented in Table 10.

Table 10. *Relative prevalence of asthma-related comorbidities in different phenotypes of severe asthma. Adapted from Porsbjerg and Menzies-Gow<sup>85</sup>*

	<b>Type 2 inflammation</b>		<b>Non-type 2 inflammation</b>
	Early-onset allergic asthma	Late-onset eosinophilic asthma	Late-onset non-eosinophilic asthma
Allergic rhinitis	+++	+	+
CRS	+	+++	+++
Nasal polyps	+	+++	+
GERD	+	+++	+++
Obesity	+	++	+++
OSA	+	+	++
Anxiety	+	+	+++
Depression	+++	+	+

In the following section, the impact of comorbidities with the closest association to type-2 inflammatory phenotypes (rhinitis and CRS) and non-type-2 inflammatory phenotypes (obesity, OSA, and gastroesophageal reflux) will be discussed separately, in relation to the underlying pathophysiological mechanisms and impact on sleep.

### Rhinitis, nasal congestion, and chronic rhinosinusitis

The combination of nasal congestion and asthma was associated with a very high prevalence of insomnia symptoms in Paper I, and CRS was an independent risk factor for both insomnia symptoms and uncontrolled asthma in Paper IV. Allergic rhinitis, which may be considered as a marker of allergic asthma, was not associated with any insomnia symptoms.

The GA<sup>2</sup>LEN population was further analyzed regarding chronic rhinosinusitis and persistent allergic rhinitis in 2017.<sup>179</sup> The prevalence of CRS by the EPOS definition was 8.4%, and CRS was associated with difficulties initiating sleep, difficulties maintaining sleep, and early morning awakenings, also after adjusting for asthma. A higher number of CRS symptoms were demonstrated to be a more important risk factor for insomnia symptoms, similar to the effects of asthma symptoms in Paper I. The combination of CRS and persistent allergic rhinitis increased the risk of insomnia symptoms further, suggesting an additive adverse effect of nasal congestion and pro-inflammatory mediators in allergic inflammation.

The finding of CRS as an important risk factor for insomnia was confirmed in Paper IV, where CRS was also associated with worse asthma control. Since both sleep quality and asthma control with rhinitis and CRS may be improved by nasal corticosteroid treatment, these findings underline the importance of attention to nasal symptoms in treatment of asthma.

The association between CRS and asthma-related quality of life in Paper II was not significant after adjusting for ACT and insomnia, and rhinitis had

no impact on mAQLQ. These results indicate that only severe rhinitis affects the asthma-related quality of life, either as part of united airway disease with poorly controlled asthma or by causing insomnia.

## **Obesity, obstructive sleep apnea, and gastro-esophageal reflux**

Obesity was identified as an independent risk factor for insomnia among asthmatics in Paper I. Obesity was also associated with worse asthma-related quality of life in Paper II, but the association did not reach statistical significance after adjusting for asthma control, insomnia, anxiety, and depression. BMI was highest in the group with both asthma and OSA in Paper III, and obesity was independently associated with insomnia symptoms in Paper IV.

As obesity is associated with both worse asthma control and OSA, these results were expected. However, there is a considerable risk of misclassification of asthma in obese patients, as breathlessness is a common symptom of both obesity and asthma. Over-diagnosis of asthma is more prevalent in obese patients than non-obese patients. Two different studies have demonstrated that about one-third of obese asthmatics have no reversible obstruction, bronchial hyper-responsiveness, or other measurable evidence of asthma.<sup>180,181</sup> Misdiagnosis of obese, non-asthmatic, participants could possibly have reduced the statistical power in the present study, but not changed the results.

The intersections between obesity, gastro-esophageal reflux, and OSA are complex, since the conditions covariate and have adverse effects on each other. Adjustments could only be made for obesity in Paper I, whereas obesity and gastro-esophageal reflux were analyzed separately in Paper II and Paper IV. OSA could only be assessed specifically in Paper III.

## **OSA in epidemiology**

Conducting epidemiological research on OSA is not uncomplicated as the condition, by its current definition, is under-diagnosed and often asymptomatic in the general population. Assessing co-existing OSA and asthma is not less problematic. Snoring and daytime sleepiness, the cardinal symptoms of OSA, have lower specificity in asthmatics than in the general population, since both symptoms are over-represented with asthma, independent of comorbidity.<sup>71,169</sup> Further, asthma-related comorbidities such as CRS and gastro-esophageal reflux are independently associated with snoring, and rhinitis and depression are associated with daytime sleepiness. Snoring was associated with respiratory symptoms but not with asthma in ECRHS, after adjusting for obesity and GERD.<sup>109</sup> Accordingly, the results in Paper I and Paper IV remained significant after adjusting for snoring. Presented data were not adjusted for snoring or daytime sleepiness, to avoid over-adjusting for variables with low specificity.

Full polysomnography is considered the gold standard for objective evaluation of sleep, whereas an overnight sleep recording in the patient's home is the most common way to diagnose OSA in Sweden today.<sup>182</sup> While most studies on OSA and asthma rely on questionnaire based OSA risk, there are some other polysomnography studies. Most of these studies focus specifically on smaller, selected populations with severe asthma, but a large number of unselected asthma patients were included in the ESADA cohort. ESADA contains data on a very large number of patients referred for sleep studies, mainly with suspected OSA. Bonsignore et al. published a cross-sectional analysis of 16,236 patients referred for suspected OSA in 2018.<sup>183</sup> The prevalence of asthma was 4.8%, and 48% underwent full PSG. Women with asthma were more often obese, whereas the BMI distribution was similar in asthmatic and non-asthmatic men. Asthma was associated with subjective poor sleep, but the distribution of OSA severity was similar in patients with asthma and patients without asthma. No differences in nocturnal hypoxemia were seen between the groups, and the study did not confirm the PSG findings from Paper III. The ESADA study benefits from the very large population, but it does not take asthma control, asthma severity, or phenotypes into account, and it is limited by referral bias.

### **Inflammation in OSA and obesity**

The higher levels of IL-6 with co-existing asthma and OSA in Paper III, which remained significant after adjusting for BMI and waist circumference, suggest an over-representation of non-allergic, obesity-related, asthma in this group. The visceral adiposal tissue is metabolically different than the peripheral adipose tissue, and abdominal obesity is more strongly correlated to asthma in women than in men,<sup>124</sup> but the effects of OSA on airway inflammation are still unclear. IL-6 and CRP are higher in OSA, but meta-analyses have not clearly identified if BMI or AHI is the key factor in the systemic inflammation and the additive effect of co-existing asthmatic inflammation is not fully known.<sup>141</sup> There are a few studies on highly specified asthma patients with co-existing OSA, which support an association between OSA and non-type-2-asthma. Taillé et al. performed bronchoscopy with transbronchial biopsies, analyzed induced sputum, and performed overnight polygraphy in 55 patients with severe asthma.<sup>184</sup> Participants with AHI>5 had less rhinitis, later asthma onset, higher IL-8, and lower IL-5 in sputum. Higher sputum neutrophils and thinner reticular basement membrane were also seen, suggesting effects of OSA in airway remodeling.

No association between asthma and TNF $\alpha$  was found in Paper III. Asthma severity could not be assessed in the SHE study, and it is possible that the lack of association between asthma and TNF $\alpha$  is explained by the absence of participants with severe asthma.

The findings in Paper III support the hypothesis that certain asthma phenotypes are associated with sleep apnea, but the study size and the limited access to asthma biomarkers did not allow for any further phenotyping. The study populations were larger in Paper I and Paper IV, but no biomarkers were available in these studies. However, the absence of an association between rhinitis and insomnia symptoms and the strong associations between obesity, worse asthma control, and insomnia symptoms are compatible with the hypothesis that non-allergic, obesity-related, asthma is overrepresented in insomnia.

### **The role of reflux**

Reflux symptoms were associated with insomnia symptoms in Paper IV, but the association did not reach significance after adjusting for asthma control. Gastro-esophageal reflux was also associated with worse asthma-related quality of life in Paper II. The association between gastro-esophageal reflux and poor sleep is known, but the considerable overlaps between gastro-esophageal reflux and obesity, OSA, and poor asthma control complicates the analyses. Further, two questions on asthma control and three of the four questions in the symptoms domain of mAQLQ may be associated with both reflux and asthma (cough, chest tightness, disturbed sleep). This may result in misclassification of reflux symptoms as asthma symptoms and vice versa; patients may also have difficulties distinguishing asthma from reflux.<sup>59,185</sup> Nocturnal reflux symptoms can also be a mediating variable with respect to sleep disturbances, as alcohol consumption has negative effects on sleep and causes reflux symptoms.

Gastro-esophageal reflux in OSA improves with CPAP treatment.<sup>186</sup> Accordingly, one study of CPAP treatment of co-existing asthma and OSA demonstrated a significant reduction of reflux symptoms alongside improved asthma control.<sup>143</sup>

As persistent GERD is likely to be of greatest importance for respiratory symptoms, the cross-sectional design is a limitation of the present study.<sup>187</sup>

### **Psychological factors, socioeconomic status, and smoking**

Depression and anxiety have a great impact on the quality of life in general, and this is even more evident in the presence of multi-morbidity in chronic medical conditions.<sup>188</sup> The effects of anxiety and depression in Paper II may be partially explained by this effect, though the mAQLQ questionnaire is designed to be asthma-specific. However, the correlations between asthma, anxiety, and depression are well established and previous studies have shown similar results, with strong associations between anxiety, depression, asthma control, and asthma-related quality of life.<sup>79,189</sup> Depression and anxiety were also analyzed in Paper IV, and the association between depression and insomnia symptoms was significant after adjustments. This

result is also expected, as depressive symptoms have an independent impact on sleep quality and co-varies with asthma control and asthma severity.<sup>79,190</sup>

Smoking was associated with worse sleep quality in Paper I and with worse asthma-related quality of life in Paper II. Although smoking is a well-known risk factor for worse asthma control, the impact of active smoking has been surprisingly low in some previous population-based studies.<sup>191</sup> This has been explained by the “healthy smoker effect,” as study participants with more severe asthma are least likely to smoke. The associations between smoking and insomnia symptoms were significant in Paper I, even though the “healthy smoker effect” may have led to an underestimation of the effects of smoking. Nevertheless, current smoking was identified as an important and independent risk factor for insomnia symptoms in asthma.

The relationship between socioeconomic status, asthma prevalence, and asthma control is not fully understood. Previous studies have identified associations between socioeconomic status, based on measures of occupational class and educational level, and asthma prevalence and respiratory symptoms also after adjusting for smoking, environmental factors, and obesity.<sup>192</sup> Educational level was considered as a potential confounder in Papers I and IV, but socioeconomic factors were not analyzed in detail in this study.

## Asthma severity

Asthma severity could be assessed in Paper IV, since the LifeGene study contained information on asthma control and treatment level. Only a small number of participants had high-intensity asthma treatment, and there was no correlation between level of treatment and insomnia symptoms after adjusting for asthma control and comorbidity. This suggests that the achieved asthma control is more important than the intrinsic asthma intensity for insomnia symptoms. These results correspond well to a Spanish study of 1,098 asthma patients, where asthma control and asthma severity were associated with sleep disturbances as single variables, but only asthma control remained a significant determinant of sleep disturbance in adjusted models.<sup>193</sup> Other studies have conversely demonstrated a high prevalence of insomnia symptoms with severe asthma.<sup>78</sup> One explanation for our findings might be the mainly population-based design of the LifeGene cohort, in which the number of participants with severe asthma despite optimal treatment was likely quite low, whereas poor asthma control and undertreated asthma-related comorbidities were widespread problems. Information on treatment was available also in Paper II, but the level of treatment and the overall good asthma control in the MIDAS cohort suggest that most participants had mild or moderate asthma.<sup>43</sup> It is likely that cohorts consisting of well-defined severe asthma patients undergoing specialist

treatment may provide more valid information regarding asthma severity and insomnia, although many such studies lack control groups. Further studies on asthma severity and insomnia are required.

## Limitations of the study

This thesis benefits from large datasets of information from two large study populations (GA<sup>2</sup>LEN and LifeGene) and two smaller, well-defined study populations (SHE and MIDAS). The studies however are not without limitations. The main limitation is that all four papers are based on cross-sectional data. Hence, it is not possible to determine whether there are any true cause-effect relationships between the examined variables, or to determine the directions of potential cause-effect relationships. Longitudinal follow-up studies are needed for analyzing causality.

### Definitions of asthma and OSA

One important methodological consideration, as previously discussed in detail, is the definition of asthma. Asthma was defined from questionnaires in Papers I, III, and IV, which may be considered as a limitation. The questions used have nevertheless been evaluated in other surroundings, where a high specificity for asthma has been demonstrated.<sup>32</sup> The positive predictive value of symptom questionnaires is not uniform, since the asthma prevalence is different in different populations, but the validation within EHCRS indicates that the questionnaire is valid for the European setting. Definitions including previously “doctors-diagnosed” asthma may lead to over- or underestimation of asthma in some countries and populations, but should be valid for use in Sweden.<sup>28</sup>

The upper age limit was high in the GA<sup>2</sup>LEN and SHE studies, resulting in possible inclusion of COPD patients in Paper I and Paper III. Asthma and COPD may overlap and converge, and the distinction between the conditions may be difficult in clinical practice.<sup>194</sup> This distinction is not less difficult in questionnaire-based studies: Asthma patients with airflow limitation may have been misclassified as having COPD, and patients with COPD may have been classified as having asthma, while some patients may have features of both asthma and COPD.<sup>195</sup> The third umbrella term “asthma COPD overlap” (ACO) is used to describe this patient group.<sup>24</sup> ACO and insomnia symptoms were specifically analyzed in a population consisting of 25,429 participants from the GA<sup>2</sup>LEN and the Respiratory Health in Northern Europe (RHINE) studies in 2018.<sup>196</sup> The prevalence of ACO was 1.0%, and this group reported significantly higher prevalence of all insomnia symptoms and respiratory symptoms than participants with either asthma or COPD, also after adjusting for age, BMI, and smoking status. The associations between insomnia symptoms, asthma symptoms, nasal congestion, and obesity in

Paper I, however, were significant also when only never-smokers were included, as were the results in Paper III after adjusting for smoking history. The MIDAS and LifeGene cohorts consisted of younger participants, where COPD and ACO are unlikely to be found.

The OSA diagnosis in Paper III is based entirely on AHI, which is in accordance with present guidelines, although AHI as a single measure of OSA severity has been questioned.<sup>133</sup>

### **Study populations**

The response rate in the GA<sup>2</sup>LEN study (54.9-59.1%) was somewhat lower than in previous population-based asthma studies in Sweden.<sup>71</sup> Non-response bias may lead to overestimation of symptom prevalence.<sup>197</sup> The effects of non-response were analyzed in detail in another cross-sectional study assessing respiratory health in western Sweden, with an initial study sample of 30,000. The participation rate was slightly higher than in GA<sup>2</sup>LEN (62%), and the effects of non-response were limited, except from underestimation of smoking.<sup>198</sup>

The LifeGene population is not by definition population-based, as it was possible for anyone to participate in the study. This must be taken into consideration while interpreting prevalence data in LifeGene, although the associations demonstrated in Paper IV should be applicable on the population level. Further, the results from the LifeGene study align well to the earlier GA<sup>2</sup>LEN findings.

Although the MIDAS cohort was partly recruited from both primary and specialist care facilities, the large number of participants with well-controlled asthma suggests that the population is not representative of asthmatics undergoing specialist care.

The SHE study has an all-female study design, and the results of Paper III cannot be directly generalized to apply to men. Nevertheless, the female population, the higher mean age, and the higher BMI in the SHE study make it suitable for studying non-allergic asthma, which was hypothesized to be most important with concomitant OSA. This asthma phenotype is less likely to be found in the young MIDAS population. Analyzing the same biomarkers in the SHE and MIDAS populations, however, would have strengthened the possibilities to analyze phenotypes.

# Conclusions

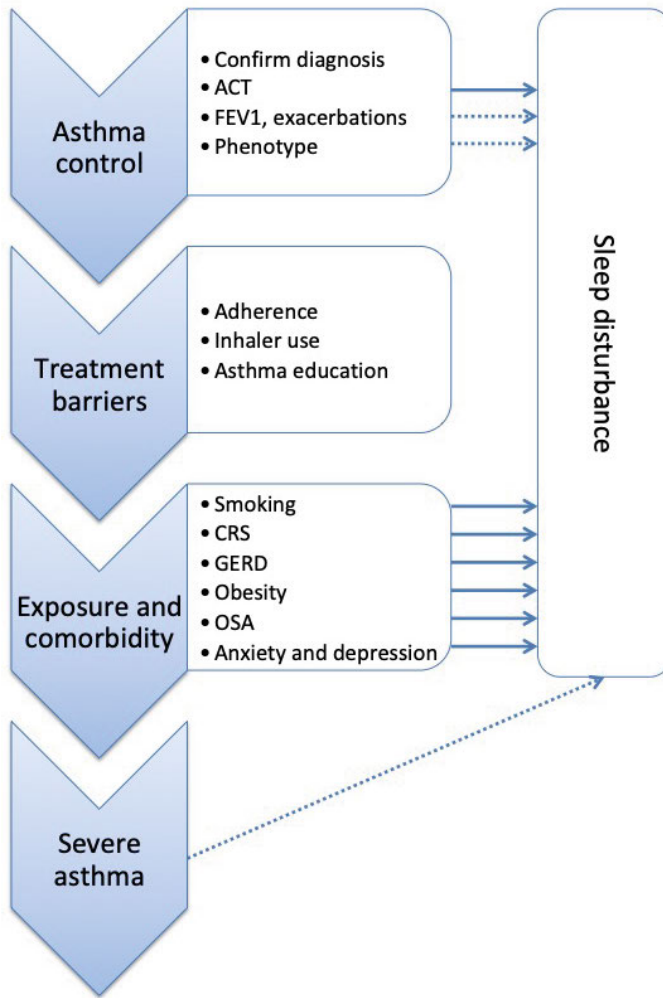
- I Insomnia symptoms remain a common problem among asthmatics. Poor asthma control and nasal congestion were important risk factors for insomnia symptoms. Smoking and obesity were other risk factors for insomnia symptoms among asthmatics.
- II The ACT score was the most important predictor of asthma-related quality of life. Combining the ACT score with data on insomnia, anxiety and depression showed considerable additive effects of the conditions.
- III Co-existing asthma and OSA was associated with worse objective sleep quality and more profound nocturnal hypoxemia than either of the conditions alone. The group with both asthma and OSA had the highest levels of CRP and IL-6.
- IV Uncontrolled asthma was significantly associated with insomnia symptoms, while controlled or partially controlled asthma was not. Asthma-related comorbidity was of great importance and asthma control seems to be more important than asthma severity for sleep quality.

## Clinical implications and future perspectives

Insomnia symptoms are still common in asthma, despite modern treatment. The impact of comorbidity is significant, and insomnia affects asthma-related quality of life. Modern asthma care and structured assessment focus on patient education, adherence to treatment, and optimization of comorbidity, but insomnia symptoms are not routinely addressed. As the components of structured asthma assessment include all the demonstrated main risk factors for sleep disturbances among asthma patients, the algorithm for structured asthma evaluation could easily be expanded to include insomnia symptoms (Figure 12).

Optimizing asthma treatment, treating asthma-related comorbidities, and addressing lifestyle factors are likely the most important ways to improve sleep quality in asthma. As asthma patients with symptomatic OSA might benefit from CPAP treatment, OSA must not be overlooked in the treatment of asthma. Screening for OSA should be done routinely in difficult-to-treat asthma patients with elevated OSA risk. There are even a few experimental studies of CPAP treatment of asthma patients without OSA. The rationale for these trials is the hypothesis that positive airway pressure would cause airway smooth muscle stretch, which has a bronchoprotective effect and possibly reduces BHR.<sup>199</sup> Busk et al. first showed that CPAP treatment of asthma patients without OSA could reduce airway reactivity in a small, uncontrolled study in 2013,<sup>200</sup> but no difference in BHR was seen after 12 weeks of CPAP treatment in a randomized control study of 194 asthma patients with low OSA risk.<sup>201</sup>

The main findings in this thesis have a high clinical relevance and highlight the importance of structured evaluation of asthma control and attention to undertreated comorbidity in asthma care. Optimizing asthma control is crucial for sleep quality, but treating asthma-related comorbidity such as nasal congestion and OSA must not be overlooked.



*Figure 12.* Sleep disturbance in relation to the components of structured asthma assessment. Solid arrows indicate the independent associations demonstrated in this thesis, whereas the dotted arrows indicate associations of likely but yet uncertain significance.

## Is insomnia an asthma-related comorbidity?

In line with the increasing interest in severe asthma and structured asthma assessment, a number of review articles focusing on the importance of comorbidity and multidimensional assessment have been published during recent years.<sup>85,202</sup> Focus has been on the common and treatable comorbidities investigated in this thesis: allergic rhinitis, CRS, GERD, obesity, OSA,

anxiety, and depression, as well as more uncommon comorbidities of importance for severe asthma, such as allergic bronchopulmonary aspergillosis, bronchiectasis and eosinophilic granulomatosis with polyangiitis. With regard to the demonstrated co-variation of asthma and insomnia symptoms, which is not only dependent on asthma control, insomnia may be considered as an asthma-related comorbidity. This alternative view would possibly highlight the importance of insomnia symptoms in asthma, which should be considered by all physicians treating asthma patients.

## Future study questions

It was demonstrated that insomnia symptoms are common in asthma and that insomnia symptoms correlate with worse asthma-related quality of life. Asthma control was identified as a key measure, and co-morbidity was of great importance. However, longitudinal studies are still needed to confirm causality. Follow-up information from the MIDAS cohort has already been obtained. The SHE study is also longitudinal, and will further be merged with a corresponding male population, Men in Uppsala: A Study of sleep, Apnea and Cardiometabolic Health (MUSTACHE).

An ideal study of the impact of asthma on sleep would consider both subjective and objective sleep quality, as well as all aspects of asthma: asthma control, asthma severity, asthma phenotypes, and asthma-related comorbidity. This would require a large, well-defined cohort with additional information on lung function, over-night sleep recordings, and biomarkers including blood eosinophils and FeNO. The recently completed Swedish CARDioPulmonary bioImage Study (SCAPIS) contains this information. An additional study based on the available cross-sectional SCAPIS data would be another interesting continuation of the studies in this thesis.

## Summary in Swedish – populärvetenskaplig sammanfattning på svenska

Astma är en av våra allra vanligaste folksjukdomar. Trots förbättrade behandlingsmöjligheter besväras många astmapatienter fortfarande av ofullständig symtomkontroll. Traditionellt sett har astma delats upp i huvudtyperna allergisk respektive icke-allergisk astma. Mycket tyder dock på att en mer heterogen syn på astma än så är nödvändig, och en rad mer detaljerade fenotyper av astma har beskrivits. Hos vuxna är icke-allergiska fenotyper vanliga, i synnerhet vid sen sjukdomsdebut och samtidig övervikt.

Att personer med astma har mer sömnbesvär än andra har varit känt sedan länge. Detta har vanligen förklarats av bristande astmakontroll och förekomst av nattliga astmasymtom, vilket de flesta astmatiker drabbas av i någon grad. Det finns dock betydligt fler faktorer som spelar in, och som har stor betydelse för sömnkvaliteten vid astma. Det är till exempel vanligt att personer med astma besväras av samsjuklighet (komorbiditet) såsom hösnuva (allergisk rhinit), kronisk bihåleinflammation (CRS), gastroesofageal reflux (GERD), fetma, obstruktiv sömnapné (OSA), ångest och depression. Alla dessa tillstånd samvarierar med astmaförekomst och astmakontroll, och är därtill i sig associerade med ökad förekomst av sömnbesvär. Sambanden mellan astmakontroll, komorbiditet och sömnbesvär är således komplexa och ofullständigt kartlagda, och viss komorbiditet är därtill starkare förknippad med vissa astmafenotyper. Dessutom påverkar astmakontroll, komorbiditet och sömnbesvär livskvaliteten, men det är inte klarlagt vilka parametrar som har störst betydelse för detta utfallsmått.

Sömnbesvär skattas ofta subjektivt, men sömnkvalitet kan även mätas objektivt med polysomnografi. En polysomnografiundersökning ger bland annat information om sömnstadier, syresättning och andningsuppehåll, och är ett sätt att diagnostisera sömnapné. Det har gjorts ett mindre antal polysomnografistudier av patienter med astma, och kunskapen om effekterna av samtidigt förekommande astma och sömnapné är därför begränsad. Vissa inflammationsmarkörer som är förknippade med sömnapné och fetma är dock förhöjda i blodet även vid astma av icke-allergisk fenotyp.

I detta avhandlingsarbete har sambanden mellan astma, sömn och livskvalitet studerats på flera olika sätt i fyra olika populationer. I delarbete I undersöktes sambanden mellan astmasymtom, nästäppa och sömnbesvär i

den stora populationsbaserade studien GA<sup>2</sup>LEN med 25 610 deltagare, varav 1 830 hade astma. Studien kunde bekräfta att förekomsten av sömnbesvär var markant högre bland personer med astma än bland personer utan astma. Antalet astmasymtom och förekomst av nästäppa identifierades som de viktigaste riskfaktorerna för sömnbesvär. Rökning och fetma var också betydande riskfaktorer för sömnbesvär bland personer med astma.

I delarbete II studerades en mindre population, bestående av 369 unga Uppsalabor med astma (MIDAS). Huvudsyftet var att identifiera vilka variabler som påverkar den astma-relaterade livskvaliteten. Astmakontroll (skattad med det i kliniskt bruk vanligt förekommande formuläret ACT) var den enskilt viktigaste variabeln, men även sömnstörningar och komorbiditet, i synnerhet i ångest- och depressionsbesvär, hade stor betydelse för den astma-relaterade livskvaliteten. Personer som samtidigt hade okontrollerad astma, sömnbesvär, ångest- och depressionsbesvär hade allra sämst astma-relaterad livskvalitet.

Det tredje delarbetet utgick från sömnstudien SHE, i vilken 384 kvinnor genomgick polysomnografi och undersöktes med blodprov för systemisk inflammation. Syftet var att undersöka effekterna av samtidigt förekommande astma och sömnapné. 36 personer hade endast astma, 109 endast sömnapné och 15 uppfyllde kriterierna för båda tillstånden. Gruppen med både astma och sömnapné hade lägre syresättning under natten och därtill högst nivåer av inflammationsmarkören IL-6, som även tidigare har kopplats till övervikt, sömnapné och icke-allergisk astma.

I delarbete IV undersöktes den stora populationsbaserade kohorten LifeGene avseende sömnbesvär, astmakontroll, och astma-relaterad komorbiditet. Data fanns tillgängliga från 23 875 personer, varav 1 272 hade astma. 201 hade okontrollerad astma och dessa personer hade signifikant högre förekomst av alla sömnbesvär. I synnerhet var kombinationen av okontrollerad astma och komorbiditet ogynnsam. Okontrollerad astma, kronisk bihåleinflammation, fetma och depression var förknippade med ökad risk för sömnbesvär även i justerade modeller.

Sammanfattningsvis har studierna i detta avhandlingsarbete kunnat bekräfta att sömnbesvär fortfarande är mycket vanliga bland personer med astma, och att bristande astmakontroll och astma-relaterad komorbiditet är viktiga och behandlingsbara riskfaktorer för sömnbesvär. Samma faktorer är dessutom avgörande för graden av astma-relaterad livskvalitet. Astma och sömnapné verkar därtill ha en synergistisk effekt och påverka den objektiva sömnkvaliteten negativt. Fynden har stor klinisk betydelse och understryker vikten av strukturerad utvärdering av astmakontroll och fokus även på komorbiditet vid omhändertagande av astmapatienter. Utöver optimering av astmakontroll bör behandling av komorbiditet som nästäppa och sömnapné inte förbises.

# Acknowledgements

I wish to express my appreciation to everyone who has helped me to complete this thesis. Special thanks to:

**Christer Janson**, Professor, main supervisor and role model, for introducing me to scientific work, encouraging and believing in me, and providing great opportunities for professional development.

**Eva Lindberg**, Professor and co-supervisor, for sharing your deep knowledge and enthusiasm for science and education, and for introducing me to the world of sleep medicine (Figure 13).

**Andrei Malinovski**, Professor and co-supervisor, for your enthusiasm, attention to details, and patience with my endless questions on statistics and methodology.

My co-authors **Catarina Almqvist, Kjell Alving, Anders Bjerg, Bertil Forsberg, Karl Franklin, Maria Gunnbjörnsdottir, Roelinde Middelveld, and Kjell Torén** for cooperation and input.

**Mary Kämpe**, Head of the Department of Respiratory Medicine, clinical supervisor, mentor and role model, for encouragement, professional opportunities, and support.

**Inger Dahlén**, former Head of the Department, who initially recruited me to the field of respiratory medicine (and thereby saved me from a future in cardiology or infectious diseases).

My senior colleagues and mentors **Gustav Broman, Carl Axel Karlsson, and Kristina Lamberg**, for patiently sharing your broad knowledge and great clinical experience during almost a decade of post-graduate training.

My colleagues **Shadi Amid Hägg, Viiu Blöndal, Erika Broström, Jens Ellingsen, Emil Ekblom, Össur Emilsson, Sebastian Gagateg, Mirjam Ljunggren, Stephanie Mindus, Ida Mogensen, and Terezia Pincikova** for good friendship, collaboration and support.

All friends and co-workers at the **Department of Respiratory Medicine** and the **Department of Medical Sciences: Respiratory, Allergy and Sleep Research** for good cooperation and a nice work environment. Special thanks to **Gun-Marie “Gunnis” Bodman Lund** for making everything work.

**Friends and family.** My parents **Mats and Wivianne** for always encouraging me and believing in me, and **Henrik**, my brother and lifelong intellectual sparring partner.

**Renée.** For love, support, understanding, and teamwork.

**Malte, Ester, and Edith.** För allt ni lär mig om nyfikenhet och källkritik, och för att ni ständigt påminner mig om vad som egentligen är viktigt.

This work was supported by grants from The Bror Hjerpstedt Foundation (Bror Hjerpstedts stiftelse), the Uppsala County Association Against Heart and Lung Diseases (Uppsala läns förening mot hjärt- och lungsjukdomar), and the Swedish Heart-Lung Foundation (Hjärt-lungfonden).



*Figure 13.* The author participating in the MUSTACHE study

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