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EXPLORING THE PREVALENCE AND INFLUENCE OF RISK FACTORS AND COMORBIDITIES ON CLINICAL OUTCOMES IN THE ASTHMA PATIENT POPULATION

PhD thesis

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List of Abbreviation

ACQ: Asthma Control Questionnaire
AMI: Acute Myocardial Infarction
AERD: Aspirin Exacerbated Respiratory Disease
AF: Atrial fibrillation
ACT: Asthma Control Test
BMI: Body Mass Index
CeVD: Cerebrovascular Diseases;
CI: Confidence Intervals
COPD: Chronic Obstructive Pulmonary Disease
COVID19: Coronavirus Disease 2019
CV: Cardiovascular
CVD: Cardiovascular Diseases
CYP3A4: Cytochrome P450 3A4 enzyme
DM: Diabetes Mellitus
eCRF: electronic Case Report Form
EIA: Exercise-induced Asthma
EPR-3: Expert Panel Report 3
FVC: Forced Vital Capacity
FEV1: Forced Expiratory Volume in 1 s
GERD: Gastroesophageal Reflux Disease
GCP: Good Clinical Practice
GINA: Global Initiative for Asthma
GP: General Practitioner
HR-QoL: Health-related Quality of Life
HF: Heart Failure
HT: Hypertension
ICS: Inhaled Corticosteroid
ICS/FOR: Inhaled Corticosteroid/Formoterol fixed combination
IGT: Impaired Glucose Tolerance
IFG: Impaired Fasting Glucose
IHD: Ischemic Heart Disease
LABA: Long-acting Beta Agonist
LAMA: Long-acting Muscarinic Antagonist
LD: Liver Disease
MART: Maintenance and Reliever Therapy
OCS: Oral Corticosteroid
PFT: Pulmonary Function Test
RA: Rheumatoid Arthritis
SABA: Short-acting Beta Agonist
SAE: Severe Acute Exacerbation
SAMA: Short-acting Muscarinic Antagonist
SMART: Single/Symbicort Maintenance and Reliever Therapy
SYGMA: SYmbicort Given as needed in Mild Asthma

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1. Introduction

1.1. The challenge in achieving asthma control

1.1.1. Definition and description of asthma

Asthma is a complex, chronic and heterogeneous respiratory disease caused primarily by inflammatory processes, as well as constriction of the smooth muscles and remodelling of the airways, resulting in reversible airflow obstruction and increased responsiveness of the airways to various stimuli (1,2).

The severity and appearance of symptoms, which include wheezing, shortness of breath, chest tightness and coughing vary over time and in intensity. Basically, asthma is characterized by reversible airflow obstruction but it could later become irreversible in some cases. Asthma is usually associated with airway hyperresponsiveness and airway inflammation, but these are not essential or sufficient to make the diagnosis. Asthma affects people of all ages but often starts in childhood.

Recognizable clusters of demographics, clinical and/or pathophysiological characteristics are often called asthma phenotypes; however, these do not correlate strongly with specific pathological processes or treatment responses (1).

Asthma Phenotypes refer to the classification of asthma based on clinical features, such as age of onset, presence of allergies, and response to treatment (3–5). Figure 1. show the clinically observed characteristics used to describe asthma phenotypes (6).

Asthma Endotypes refer to the underlying inflammatory pathways, which may change over time with environmental interactions. Originally, we distinguished type 2 inflammation and non-type 2 inflammation. However, there are more specific subtype of a condition defined by distinct pathophysiological mechanism (3,4,7). Figure 2. illustrates theoretical grouping of emerging asthma phenotypes based on the distinction between TH2-high asthma and non-TH2 asthma (7).

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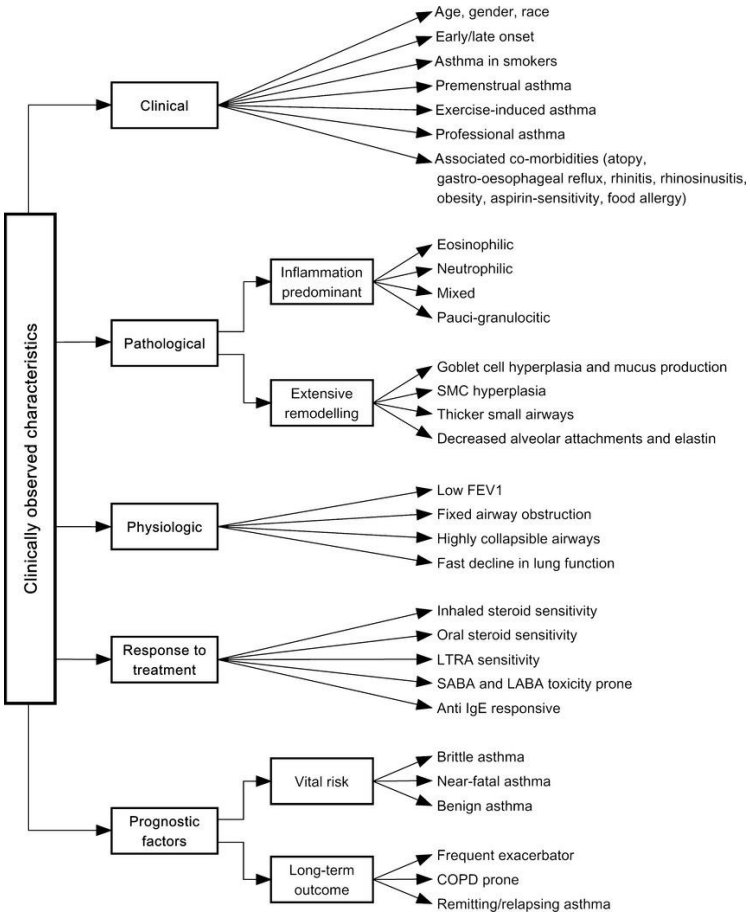

Figure 1. Clinically observed characteristics used to describe asthma phenotypes (6)

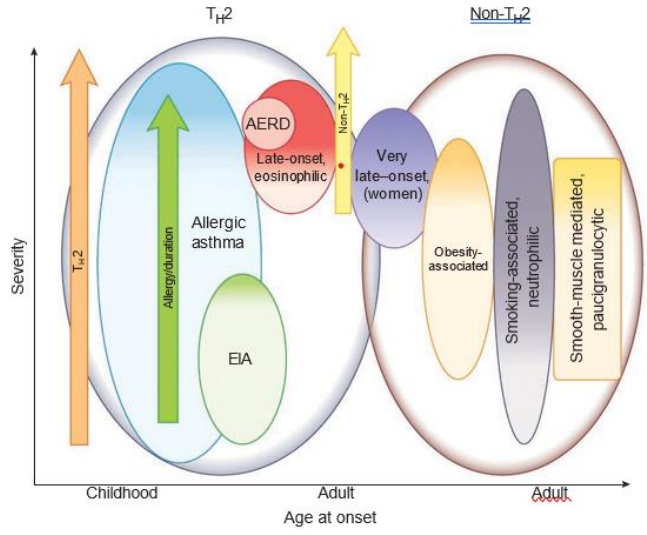

Figure 2. Theoretical grouping of emerging asthma phenotypes based on the distinction between TH2-high asthma and non-TH2 asthma. TH2 asthma consists of both early- and later-onset disease over a range of severities. It is likely that the majority of early-onset allergic asthma is mild but that an increasing complexity of immune processes leads to

greater severity. Later-onset eosinophilic asthma without traditional allergic elements is more likely to be severe, whereas EIA is a milder form of TH2 asthma. Non-TH2 asthma includes very late–onset, obesity-associated asthma as well as smoking-related and neutrophilic asthma, and asthma in which affected individuals show little inflammation (7).

The distinction between asthma phenotypes and endotypes is crucial for understanding the heterogeneity of asthma. In the past 30 years, we have reached the point where asthma is no longer considered a single disease, but rather a complex condition comprising multiple subtypes, leading to the need for more personalized approaches to diagnosis and management.

1.1.2. Epidemiology of asthma

In 2017, the incidence of asthma was 43.12 million new cases per year (0.56% of the global population). In the same year, the global prevalence of asthma was 272.68 million cases (3.57% of the global population) (8). Asthma was the second leading cause of death among chronic respiratory diseases, with 457 0000 deaths due to asthma in 2017 (9).

The prevalence of diagnosed and registered asthmatics in Europe ranges between 5-7%, although significant differences exist among certain countries (10). When comparing the prevalence between countries, we have to take into consideration the terminological inaccuracies and differences in the interpretation of asthma diagnosis. Furthermore, variations in healthcare systems also contribute to differences because in some countries besides pulmonologist general practitioners and internists are also authorized to diagnose asthma, resulting in a higher proportion of registered asthma patients. However, in countries where exclusively pulmonologists and allergologists are responsible for diagnosing asthma, the population may be underdiagnosed, but more reliable data is generated and registered.

According to Eurostat (Figure 3.), almost 6% of the EU population was affected by asthma in 2019. Researchers detected a small increase compared to 2014 (+0.3 percentage points). Among EU countries, Finland had the highest prevalence (9%), followed by Germany and France (8%). Hungarian prevalence was a bit under the European average. In contrast, only 2% of people reported having asthma in Romania and Bulgaria (10).

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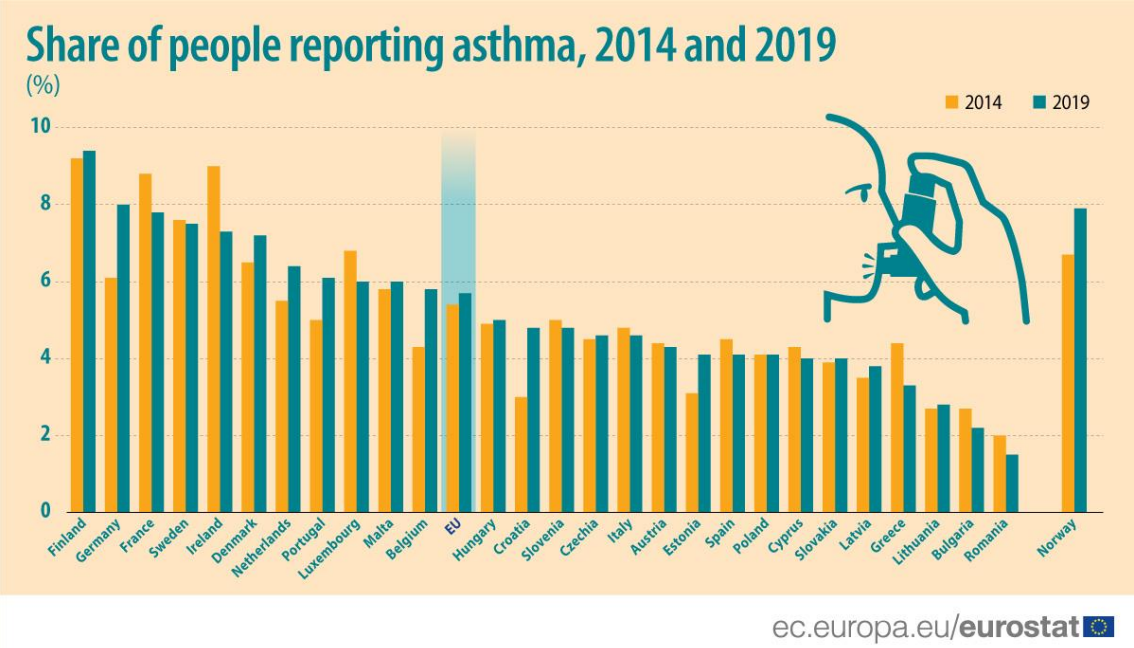

Figure 3. Share of people reporting asthma in EU (10)

In Hungary, based on the national registry called Korányi Bulletin there were 324 954 adult asthmatic patients nationwide (not counting the paediatric population) in 2022, which indicates 3.3% prevalence (11). However, significant asthma cases are diagnosed during childhood and approximately half of all children diagnosed with asthma have a decrease or disappearance of symptoms by early adulthood (12). Based on these pieces of evidence the Hungarian real prevalence could be between 4-6%, which is in line with the Eurostat data. The number of patients registered with new diagnosis of asthma between 2000 and 2019 ranged between 13 420 and 19 298, falling below 10 thousand in 2020 and 2021 (9 181, 9 233 respectively). The temporary fall was evidently due to the special circumstances caused by the COVID19 pandemic. In 2022, the numbers of new diagnosis were again similar to previous years (11). Asthma is predominantly found in boys in childhood, with a male to female ratio of 2:1 until puberty, when the ratio starts to reverse. The current national adult female rate is 62% (11).

1.1.3. Importance of targeting asthma control

The main goal of asthma management is to achieve a significant reduction or eliminate asthma symptoms, improve pulmonary function, enable patients to lead a normal or near-normal life and prevent exacerbation. Asthma is considered under control when these

clinical outcomes are achieved. Asthma control level is a paramount driver of therapy intensity and indicates when treatment needs to be adjusted (1).

The main implications of uncontrolled asthma:

1. Higher risk of exacerbation (13,14).
2. Impaired quality of life: uncontrolled asthma can significantly impact daily activities, quality of sleep, which lead to a negative impact on overall quality of life (13,14).
3. Higher healthcare utilization: poor asthma control could cause additional emergency visits and hospitalizations, as well as higher healthcare costs (15).
4. Uncontrolled asthma population imposes burden on society through loss of productivity (1).
5. Higher risk of adverse effects because uncontrolled patients more often require systemic corticosteroid therapy (osteoporosis, peptic ulcers, diabetes, cataracts, and fractures etc) (16).
6. Impact on mental health: uncontrolled asthma can worsen psychiatric diseases like depression, anxiety, and stress, which can make difficulties in the management of asthma (13,14).
7. Increased risk of mortality: Uncontrolled status is a significant risk factor for mortality, particularly in severe asthma cases (17).
8. Impact on comorbidities: poor asthma control can trigger complications if patient has co-existing diseases like COPD, heart and/or vascular disease, and mental health disorders etc (18).

As it was detailed above unsatisfactory asthma control has significant implications for the health and well-being of patients therefore one of the most important aims of asthma treatment to reach asthma control (19,20).

1.1.4. Development of GINA guideline regarding required clinical outcome in asthma

The first GINA guideline, published in 1995, aimed to improve asthma management in response to rising asthma prevalence and mortality (21). During that period, the main driver of maintenance therapy was asthma severity before treatment period. The patients

were categorized into intermittent, mild persistent, moderate persistent and severe persistent groups according to severity (21).

Later, the primary goal of asthma management became achieving control, including minimizing symptoms, reducing reliever use, preventing activity limitations, improving lung function, and preventing exacerbations. To assess and achieve these goals, some standardized questionnaires were developed and validated (e.g. Asthma Control Questionnaire, Asthma Control Test) (22,23). Then when these questionnaires were used in clinical trials, results have shown that the overall level of asthma control was often poor (24). In the AIRE study, 46% of patients reported daytime symptoms, and 30% experienced asthma-related sleep disturbances weekly, highlighting challenges in achieving good asthma control in practice. The GOAL study was a real milestone in asthma management (25). The primary objective of the GOAL study was to compare the proportion of individuals who achieved a composite guideline-based definition of total asthma control (25,26). Table 1. summarize these definitions.

Table 1. Definitions of well controlled and totally controlled asthma based on Global Initiative for Asthma aims of treatment (21,26–28)

	Goals of GINA/NIH	Totally Controlled Each Week All of	Well Controlled Each Week 2 or More of
Daytime symptoms	Minimal (ideally no)	None	<2 days with symptom score
Rescue beta2-agonist use	Minimal (ideally no)	None	Use on<2 days and <4 occasions/week
Morning PEF	Near normal	>80% predicted every day	>80% predicted every day
			All of
Night-time awakening	Minimal (ideally no)	None	None
Exacerbations	Minimal (infrequent)	None	None
Emergency visits	No	None	None
Treatment-related adverse events	Minimal	None enforcing change in asthma therapy	None enforcing change in asthma therapy

The study found that while it was possible to achieve total asthma control only a small proportion of patients were able to reach this level of control despite the use of high doses of inhaled corticosteroids (29). The study yielded an unexpected result: similar proportions of patients were able to achieve the same levels of asthma control and quality of life improvements, regardless of the severity of their asthma at baseline (25). All in all, the GOAL study highlighted the challenges in achieving total asthma control, as defined by the complete absence of symptoms. Nevertheless, the results demonstrated significant benefits in terms of improved quality of life when guideline-based asthma management strategies were implemented (25,26,29). The GOAL study proved that achieving total control is a too ambitious goal, and the majority of patients can only achieve partial or uncontrolled status. Afterwards the criteria for defining controlled, partially controlled, or uncontrolled asthma were clearly established in subsequent GINA guidelines.

In the following years, acute asthma exacerbations gained recognition as key indicators and complications of poor asthma control. Frequent exacerbations were linked to a significant decline in FEV1 and a higher risk of mortality compared to patients without exacerbations (30,31). In order to reduce the risk of exacerbations, new treatment concepts were developed, including the single maintenance and reliever therapy (SMART/MART). Several randomized clinical trials demonstrated that this approach was at least as effective as regular treatment with the previous concept to use ICS/LABA combinations and SABA as needed in preventing severe exacerbations. Additional benefit of SMART posology was the significant reduction of cumulative ICS exposure (32–34). Based on this evidence, the GINA guidelines adopted the SMART/MART approach as a preferred option to manage patients across STEP 3-5. In 2014, GINA executive committee made a significant revision. On the one hand the new guideline redefined the definition of asthma, which emphasized the various asthma phenotypes and endotypes requiring distinct management approaches (35). On the other hand, the new guideline differentiated symptom control and preventing exacerbation risk. In this new approach, it was explicitly emphasized that achieving both symptom control and reduction in future risk is essential goals of asthma management (35). Based on SYGMA studies, the 2019 update of the GINA document introduced another significant change in the management of mild asthma (36,37). The guideline recommended rescue ICS/FOR as the preferred option in STEP 1 and as an alternative to regular use of low-dose ICS in

STEP 2 (38). This change was based on the recognition that using short-acting β_2-agonists alone for as-needed treatment of mild asthma symptoms was associated with unfavourable outcomes, such as exacerbations and even deaths. The new guidelines emphasize the importance of using inhaled corticosteroids combined with formoterol, rather than relying solely on SABAs (35). This shift in management was done to reduce the risk of exacerbations and mortality (39). Interestingly the advantage of as-needed use of ICS plus β_2-agonist was proved 10 years before the SYGMA studies. Papi et al. with BEST study group found that symptom-driven rescue use of a combination of a short-acting β_2-agonist (albuterol, 100 μg per puff) and a corticosteroid (beclomethasone, 250 μg per puff) in a single inhaler was equivalent to regular treatment with inhaled beclomethasone (250 μg twice daily) in controlling mild persistent asthma (asthma symptoms and preventing exacerbation) (40). This finding suggested that mild persistent asthma may not require regular treatment with inhaled corticosteroids, but rather only as-needed use of an inhaled corticosteroid and an inhaled bronchodilator (40). In the GINA document 2022 the concept of using ICS/FOR as needed (without or with regular use of the same combinations) became the preferred option across all STEPs. Important to note that as needed concept legitimizes the presence of mild symptoms. Over the past 30 years, many studies have found that achieving full control remains a major challenge. Meanwhile the primary objective of asthma management has become the prevention of exacerbations because mild symptoms are usually manageable. However, avoiding the poorly controlled status is still an essential objective of asthma management. Since the first edition of GINA, the focus has shifted from primarily managing the day-to-day symptoms towards preventing exacerbations which is a substantial strategic change in asthma management.

1.2. Risk factors defined by GINA guideline

As mentioned earlier, the GINA guideline has been continuously evolving. The 2014 edition was the first to emphasize the importance of periodically assessing risk factors for poor outcomes in addition to symptomatic control. The next chapter introduces and evaluates these risk factors.

1.2.1. Potentially modifiable independent risk factors for flare-ups

1.2.1.1. Uncontrolled asthma symptoms

Regarding asthma symptoms, GINA guideline in 2014, referred to a study that was conducted as part of the Epidemiology and Natural History of Asthma (TENOR): Outcomes and Treatment Regimens study. It found that poorly controlled asthma compared to well-controlled increases the risk for future severe asthma exacerbations (41). The impairment domain of the EPR-3 guidelines included measures of asthma symptoms, use of rescue medications, and lung function. This study highlighted the importance of achieving and maintaining good asthma control (41). Later several other studies confirmed that the lower ACT scores at baseline were related to the higher probability of asthma exacerbations, unplanned visits, and emergency visits.

The key findings from these studies:

- Schatz et al. (2015): An ACT score of ≤15 was significantly associated with an increased 12-month risk of emergency hospital care, oral corticosteroid dispensing, and dispensing of more than six β_2-agonist canisters compared to a score of ≥20 (42).
- Bateman et al. (2010): Patients with a baseline ACQ-5 score ≥1.5 had a significantly higher exacerbation rate over a 12-month period compared to those with a score<0.5 (43).
- Meltzer et al.: For each one-point increase in ACQ score over 2 weeks, the risk of exacerbation increased by 1.5-fold (44).
- Guilbert et al.: Patients with asthma that was not well-controlled using an ACT score <20 at baseline had a three-fold greater risk of an any asthma-related visit and a ten-fold greater risk of an emergency department visit for asthma (45).

These studies demonstrate the importance of assessing and maintaining asthma control since the level of symptom control is a strong predictors of future asthma exacerbations.

1.2.1.2. Excessive SABA use (>1 x 200-dose canister/month)

This topic was generated initially in the 1960s when epidemics of asthma mortality occurred in six countries (New Zealand, Canada, Germany, England, Wales, USA) (46). The first epidemics were eventually linked to sales of the high-dose formulation of the non-selective beta-agonist isoprenaline forte (47). The death rate fell immediately after general warnings about the safety of inhaled beta-agonists were issued, and they were withdrawn from over-the-counter sale in the United Kingdom (48). A second epidemic occurred in New Zealand, commencing in 1976, and was eventually linked to fenoterol

in a case-control study published in 1989 (49). The initial case-control study findings were the subject of considerable controversy and criticism, but they have been confirmed by two further New Zealand case control studies (50,51), and a small cohort study of patients with chronic obstructive pulmonary disease in Germany also found an increased death rate in those prescribed fenoterol compared with those prescribed other beta-agonists (52). Fenoterol was marketed in a high dose 200 mcg/puff preparation, compared with salbutamol at 100 mcg/puff; there is some evidence that fenoterol is twice as potent as salbutamol (53), and that the 200 mcg/puff preparation is effectively a forte preparation at four times the strength of salbutamol. When taken repeatedly, fenoterol has similar adverse cardiac side effects to those observed with isoprenaline forte (54). The highest per capita sales of fenoterol in the world were in New Zealand; sales in most other countries were very low and it was not licensed in the USA (55). A dramatic fall in the death rate was observed in New Zealand immediately after the restriction of fenoterol in mid-1989 (56). Later, a series of studies underscored the need for caution in the use of inhaled beta-agonists in asthma management. In 1995, Suissa's cohort analysis revealed a significant increase in asthma death rates with the use of all beta-agonists (1.4 canisters per month), particularly fenoterol, and a drastic escalation in risk at high doses (57). Spitzer's case-control study further supported this, showing a 2.6-fold increase in asthma death risk per canister per month of beta-agonist use (58), while Anis et al. suggested that frequent use of these agents may worsen asthma control and increase the risk of death (59). Although salbutamol also increased the risk of death (57), it has maintained its role in symptom relief and without any other solution it was recommended to be used by the guidelines. During the 1990s, the usage of ICS based products started to grow rapidly, leading to a significant improvement in patients' asthma control and decreased mortality rates (60,61). In the early 2000s, the spread of fixed combinations promised an opportunity to reduce SABA use. In the last decade, the SMART/MART approach has become preferred by guidelines and popular in everyday practice, but SABA consumption has remained stable at very high level in European countries.

1.2.1.3. Inadequate ICS: not prescribed ICS; poor adherence; incorrect inhaler technique

Using inhaled corticosteroids is fundamental in managing asthma patients. Numerous studies demonstrated efficacy in improving asthma control (1,60,61). Furthermore, ICS

use is associated with a significant reduction in the frequency and severity of asthma exacerbations, including those requiring hospitalization or oral corticosteroid treatment (30). Long-term use of ICS has proved to slow the decline in lung function (30).

ICS is an unavoidable part of asthma therapy on all steps in the guideline and thus, avoiding or ignoring the use of ICS definitely undermine the therapeutic effect, worsen asthma control and trigger future risk for poor outcome.

1.2.1.4. Low FEV1, especially if <60% predicted

Although the role of lung function has changed in asthma management, since the inception of the guidelines, spirometry is essential for the assessment of patients with suspected chronic disease of the airways. The GINA guideline recommends that the lung function should be assessed at diagnosis or start of treatment; after 3–6 months of controller treatment to assess the patient's personal best FEV1; and periodically thereafter (1). When lung function parameters are assessed, we have to take into consideration it does not correlate strongly with asthma symptoms in adults or children (62,63). However, a deteriorated FEV1 correlates with another important outcome. Fuhlbrigge et al. analysed data from two longitudinal cohort studies conducted in the United States and the Netherlands. Participants were included if they reported ever having an asthma attack. For each observation, the report of an asthma attack in the past year was paired with the participant's FEV1% measured 1 year earlier. They found a progressive decrease in the proportion of individuals reporting an asthma attack with increasing deciles of FEV1%. In multivariate models, lower FEV1% was an independent predictor of a higher risk of asthma attacks over the subsequent year (64). Patients with lower FEV1 values are at significantly higher risk, underscoring the importance of spirometry in asthma care (65).

1.2.1.5. Major psychological or socioeconomic problems

Association between chronic diseases and psychiatric disorders (e.g. anxiety, and/or depression) has significant drawbacks on general health compared to either disease alone (66). Baiardini et al. reviewed the psychological factors which may have a burden on asthma management. They found that stress and perceived threat can increase inflammation and worsen asthma symptoms (67). Several studies support the idea that the presence of psychiatric and psychological symptoms is associated with increased severity of asthma symptomatology, health service use and costs, functional impairment and poorer asthma control (68–70). However, there is an important note in relation to

effective coping strategies which can improve asthma outcomes by reducing stress and anxiety (67). Regarding lower socioeconomic status, Sturdy et al. found a link to increased asthma prevalence, poorer asthma control, and higher rates of asthma-related hospitalizations (71). These findings support that both psychological factors and socioeconomic status can have significant impacts on asthma-related outcomes.

1.2.1.6. Exposures

Smoking triggers airway inflammation, increases airway epithelial permeability, modulates the immune system, and impairs normal repair processes (72). These mechanisms may contribute to the development of asthma (73). By triggering the inflammatory process smoking can worsen asthma symptoms such as coughing, wheezing, and shortness of breath and it can lead to more frequent and severe asthma attacks (74). Smokers with asthma generally have poorer asthma control compared to non-smokers with asthma (72). According to Polosa et al. smoking and asthma are dangerous liaisons because besides worsening symptoms smokers often have a reduced response to asthma medications, including inhaled corticosteroids and bronchodilators (74). The reduced effectiveness of asthma medication was also previously proved by Chalmers et al. (75). Moreover, smoking long-term accelerates the decline in lung function, leading to poorer future outcomes (72,74). Siroux et al. proved that smoking is associated with more severe asthma, increased risk of hospitalization, and higher rates of complications such as respiratory infections and chronic obstructive pulmonary disease (COPD) (76).

Allergen exposure if sensitized

Aetiology of asthma is multifactorial, among which sensitisation to allergens is a well-known risk factor for the development and exacerbation of asthma (77). Sensitization to indoor, inhaled aero-allergens is generally more important than sensitization to outdoor allergens for the presence of and/or development of, asthma (1). Indoor allergens (e.g. house dust mite, cockroach, pets, mould), especially in combination with viral infection can trigger allergic reactions in susceptible individuals, leading to worsening asthma symptoms and exacerbations (78).

1.2.1.7. Comorbidities

GINA guideline highlighted three clinical statuses as a comorbid risk factor:

Obesity

Association between obesity and asthma prevalence has been proven in many studies (79–83). Moreover, patients with obesity are more likely to have uncontrolled asthma compared to eutrophic patients (84). Additionally, an association between obesity and increased asthma severity in adults has been also demonstrated (85). The National Asthma Survey, one of the largest asthma surveys in the USA, showed that obesity is associated with several measures of asthma severity and control, including symptoms, missed workdays and medication use (86).

Rhinosinusitis

Rhinosinusitis is a frequent comorbidity of asthma and they can impact on each other's outcome (87). There are some well-known relations between them. Inflammation of the nasal passages can aggravate inflammation of the lower airways and vice versa, creating more severe symptoms in both conditions (88). Both diseases can be triggered by allergens, irritants and respiratory infections, and they can also worsen symptoms and cause exacerbation (89). Sinusitis can cause postnasal drip which can provoke asthma symptoms (90). Based on prospective studies comprehensive treatment of both conditions can lead to better overall outcomes (90).

Confirmed food allergy

Based on a survey in the United States, there is a 4-fold increased likelihood of having asthma among children with food allergy compared with children without food allergy (91). Although frequent association of food allergy was observed, food is rarely a trigger for asthma exacerbation (<2% of patients with asthma). However, Lui et al. found that sensitization to food allergens can provoke allergic reactions in the respiratory system, leading to asthma symptoms, besides the gastrointestinal tract (92). Despite the observation that foods are rarely important triggers of asthma exacerbation, Pumphrey et al. raised that coexisting asthma could be a risk factor for anaphylaxis, as well as for a fatal outcome (93). Therefore, based on US guidelines, epinephrine autoinjector is recommended to be prescribed in case of a history of a prior systemic allergic reaction; food allergy and asthma; or known food allergy to peanut, tree nuts, fish, or crustacean shellfish (94).

1.2.1.8. Sputum or blood eosinophilia

Mallah et al. published in 2021 a large meta-analysis including 1567 retrieved publications and 23 observational studies in those 155 772 patients met the inclusion criteria. They found that high blood eosinophil count was associated with higher risk of asthma exacerbation and emergency department visits. A significant association was observed starting from an eosinophils' cutoff value of 200 cells/μl (95).

1.2.1.9. Pregnancy

Pregnancy with asthma is a significant challenge for the specialists. Since asthma influences the outcome of pregnancy and vice versa, to manage this period successfully close cooperation are needed between gynaecologist and asthma specialists. Breton et al. investigated the association between asthma during pregnancy and perinatal mortality. In a relatively large database cohort based on 13 100 pregnant asthmatics and 28 042 non-asthmatics, they observed 35% increased risk of perinatal mortality among pregnant women with asthma (96). During pregnancy asthma clinical outcome could change towards any direction. Regarding asthma control one-third of patient worsen, one-third improve and one-third remain unchanged (97,98). Immunological changes were investigated by Tamasi et al. They found signs of pregnancy-induced attenuation of allergic responses in asthmatic pregnant women that can affect asthma symptoms and severity (99). Moreover, we know that the more severe a pregnant woman's asthma, the more frequent the asthma exacerbation: 12.6% in mild asthmatic pregnancies, 25.7% in moderate asthmatic pregnancies and 51.9% in severe asthmatic pregnancies (100).

1.2.2. Other major independent risk factors for flare-ups

1.2.2.1. Ever intubated or in intensive care unit for asthma

One of the most serious and critical situations of an asthma patient is being intubated due to severe asthma exacerbation (101). Some studies have shown that those who have been intubated or admitted to the intensive care unit due to asthma are particularly vulnerable to future exacerbations (102,103). These asthma patients require more intensive monitoring and management to prevent exacerbation and maintain asthma control.

1.2.2.2. ≥1 severe exacerbation in last 12 months

Severe exacerbations are potentially life threatening and their treatment requires careful assessment and close monitoring. Miller et al. published a 3-year observation regarding

the role of severe exacerbation. Their analysis has found that recent severe asthma exacerbations are strongly associated with future exacerbations, demonstrating a high risk (OR of 6.33) (104). Severe exacerbations were defined as either an asthma-related emergency department visit or night of hospitalization in the 3 months prior to study visit. Later several other studies confirmed it in different settings. Nakwan et al. found that patients with a history of 1-2 exacerbations or more than 2 exacerbations in the previous 12 months had a 95% and 132% higher risk of future exacerbations, respectively, compared to those with no prior exacerbations (105). Severe asthma exacerbations are a strong independent factor predicting future exacerbations.

1.2.3. Risk factors for developing fixed airflow limitation

Fixed airflow limitation refers to persistent and irreversible airflow obstruction that does not improve with bronchodilator therapy. The key factors contributing to fixed airflow limitation include chronic airway inflammation and airway remodelling.

1.2.3.1. Lack of ICS treatment

O'Byrne et al. investigated the association between severe asthma exacerbations and the decline in lung function. Their study aimed to determine whether severe asthma exacerbations are linked to a persistent decline in lung function and to assess the potential effects of inhaled corticosteroids, specifically budesonide, on exacerbation-related decline in patients with asthma. They found that severe asthma exacerbations are associated with a more rapid decline in lung function, as measured by the change in post-bronchodilator FEV1 % predicted and proved that treatment with low doses of inhaled corticosteroid (budesonide) was associated with an attenuation of the decline in lung function in patients who experienced severe exacerbations, compared to those who did not receive ICS. In the placebo group, the change in post-bronchodilator FEV1 % predicted was significantly greater in patients who experienced a severe exacerbation compared to those who did not (-6.44% vs. -2.43%, respectively) (30). This significant difference in lung function decline was seen in both children and adults.

1.2.3.2. Exposures: tobacco smoke; noxious chemicals; occupational exposures

The Copenhagen City Heart Study (conducted between 1976 and 1994), a community-based, prospective study found that people who identified themselves as having asthma had greater declines in FEV_1 over time than those who did not. Stratification according

to smoking status showed that smoking is an additional factor which significantly accelerated the decline in lung function in both subjects with asthma and those without asthma. Decline in FEV_1 among subjects with asthma was 38 ml per year, as compared with 22 ml per year in those without asthma. At the age of 60 years, a 175-cm-tall nonsmoking man without asthma had an average FEV_1 of 3.05 Liters, as compared with 1.99 Liters for a man of similar age and height who smoked and had asthma (106). Occupational exposures are also a significant risk factor for the development of asthma and are associated with airflow limitation and decreased lung function. Torén et al., based on 21 studies, found 17.6% of all adult-onset asthma is caused by occupational exposures (107).

1.2.3.3. Low initial FEV1; chronic mucus hypersecretion; sputum or blood eosinophilia

Patients with initial low FEV1 and persistent airflow limitation had a more severe and advanced stage of asthma compared to those with normal lung function or reversible airflow obstruction (108). Lange et al. proved that fixed airflow limitation was associated with poorer asthma control, increased symptoms, and a higher risk of exacerbations (106). **Chronic mucus hypersecretion**, defined as daily sputum production for ≥3 months/year in at least two consecutive years (109). Although chronic mucus hypersecretion may be related to the outcome of chronic obstructive pulmonary disease (COPD) (110) but it is also found in a substantial proportion of never-smokers with asthma (111,112). From a 6-year follow-up study of a population sample from Connecticut, involving 1 303 Caucasian residents aged ≥7 years, Schachter et al. reported not only a positive association between asthma and chronic mucus hypersecretion, but also an association between worsening asthma during the years of follow-up and the presence of cough and phlegm which might suggest an association between chronic mucus hypersecretion and the outcome of asthma (113). This assumption is supported by two population studies. Ulrik et al. and Lange et al. observed that chronic mucus hypersecretion in adults with self-reported asthma was significantly related to an increased annual decline in FEV1 compared with the decline in nonsmokers without mucus hypersecretion who reported asthma (106,114). Furthermore, Postma et al. reported from their longitudinal population study that individuals with chronic mucus hypersecretion combined with asthma had

greater declines in FEV1 than those who only had asthma, an association not abolished by adjustment for the initial level of FEV1 (115).

Airway infiltration by eosinophils and T-lymphocytes is recognized as being central to the pathophysiology of asthma, and peripheral eosinophilia is found in a large proportion of subjects with current asthma (116). Longitudinal studies of adult asthmatics have revealed a borderline significant association between eosinophil count at enrolment and subsequent decline in FEV1 (115,117). Elevated blood eosinophil counts were correlated with lower FEV1 and FVC, indicating airflow limitation and decreased lung function (118). Patients with higher blood eosinophil counts had more severe airflow obstruction and poorer asthma control compared to those with lower eosinophil counts.

1.2.4. Risk factors for medication side-effects

1.2.4.1. Systemic: frequent OCS; long-term, high dose and/or potent ICS; also taking P450 inhibitors

Decision regarding any medication use must be based on the balance of benefit and risk. ICSs have few adverse events at low and medium doses, when those are used appropriately (119). However frequent use of systemic corticosteroid or high dose ICS used long term could cause serious adverse effects (119,120). Prolonged use of systemic corticosteroids can have a couple of adverse effect including Cushing syndrome, osteoporosis, increasing the risk of fractures, cataracts, dermal thinning and bruising, growth suppression in children, increased susceptibility to infections through suppressing the immune system, and psychological complications (e.g. anxiety, depression) (16,119). Cushing syndrome and associated adrenal insufficiency have been reported as a result of drug interaction with CYP3A4 inhibitors (121,122). Due to these potential adverse effects it's essential to weigh the benefits of systemic corticosteroid therapy against the potential risks and to use the lowest effective dose for the shortest duration possible, especially in chronic asthma management.

1.2.4.2. Local: high-dose or potent ICS; poor inhaler technique

Local side effects of inhaled corticosteroids in asthma are primarily associated with the deposition of the active substances in the oropharynx. Common local side effects include hoarseness, oropharyngeal candidiasis, cough, dysphonia (119). These local side effects are usually mild and can often be minimized by proper inhaler technique, such as using a

spacer device or rinsing the mouth after inhalation. However, if these side effects persist long-term the patient may not use the drug according to the prescribed posology which can cause risk in clinical outcomes (120).

1.3. Hypothesis

GINA guidelines, as well as the local national asthma protocols, help in effective clinical management of asthma, and propose therapeutic decisions to be made based on the level of asthma control. One of the most important aims of asthma treatment is to achieve a controlled condition and to maintain it on the long term. Since the goal to achieve asthma control was set in 1995, asthma management has improved substantially. It has happened because, on the one hand, plenty of new innovative drugs had become available, additionally successful new therapeutic approaches and posology were developed. On the other hand, international guidelines and national protocols have been worked out to provide recommendations for all existing clinical statuses and problems. In spite of these enormous efforts, satisfactory asthma control still remains an unmet need worldwide (123), many asthma patients experience persistent symptoms, poor disease control, and exacerbations (124,125). A European study of 8000 asthmatic patients treated in general practice showed that 45% of them were uncontrolled and 44% required at least 1 course of oral corticosteroids in the last year (126). To identify the key determinant factors of unsatisfactory control level would be a crucial first step, and then based on those to develop and implement tailored strategies aimed at the improvement of asthma clinical outcomes. The core hypothesis is that selecting the right medicine, posology and doses get high emphasis in everyday practice but several other important clinical features including risk factors and comorbidities fundamentally modify the final clinical outcome. Without focusing on these factors there is a ceiling of achievable control level which have several negative implications. Each risk factor has different prevalence among asthma patients and there is various order of magnitude regarding their impact on asthma control level. In our study we aimed, on the one hand, to provide data about the level of asthma control of the Hungarian asthma patients, and on the other hand to explore the importance and association of certain risk factors and comorbidities with uncontrolled status. These objectives were examine based on a representative, cross sectional, real-life study.

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2. Objectives

Our prior aims were:

2.1. To determine the level of asthma control in Hungarian adult asthma patients.

2.2. To explore the prevalence of risk factors and their association with uncontrolled asthma.

2.3. To identify and assess the most significant risk factors associated with uncontrolled asthma.

2.4. To identify the prevalence of comorbidities associated with asthma and their relationship to asthma control measures.

2.5. To examine the gender and age-specific patterns of comorbidities associated with asthma.

2.6. To investigate the association between BMI, asthma control, and comorbidities.

2.7. To measure aerosol concentrations in a PFT laboratory and model the potential viral load near the patient.

3. Methods

3.1. Study 1.

Design and ethics

To address the objectives, a non-interventional, cross-sectional, real-life study was designed and conducted, which was published in two articles (127,128). The design and implementation of the study adhered to good clinical practice (GCP) guidelines and the Declaration of Helsinki. Patients were included in the study on a voluntary basis after being provided with information and after signing a written contract, without any remuneration. National ethical approval was obtained (ad.7864–2/2015/EKU).

Patient and data source

Data collection was carried out among Hungarian patients. To collect more detailed information and ensure broader perspective, separate doctor and patient questionnaires were developed. Patient enrolment was carried out throughout an entire year (from May 11, 2015, to May 19, 2016) in order to mitigate the influence of seasonal variations. To ensure unbiased patient inclusion, each health institution could include a maximum of 15 patients on 5 predetermined consecutive workdays per month. Enrolment was conducted randomly, with consecutive asthma patients who agreed to participate being included. Given that pulmonologist and allergologist specialists have exclusive responsibility for diagnosing and treating asthma patients in Hungary, all examinations and data collection were performed solely by respiratory specialists. The study occurred at dispensaries, outpatient clinics specializing in pulmonology, and outpatient departments of hospitals across all regions of Hungary (127).

Inclusion and exclusion criteria

Patient inclusion and data recording were performed on a single occasion.

Inclusion criteria

Adult asthmatic patients (> 18 years)

Asthma diagnosis > 6 months

Maintenance therapy unchanged in the last month

Outpatient

No hospitalisation in the last month

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No prominent, untreated chronic disease

Exclusion criteria

Lack of patient consent

Inability to complete patient-related questionnaires

Permanent need for maintenance systemic corticosteroid treatment

Acute exacerbations at time of inclusion in the study

Active tuberculosis

Malignant disease in a palliative treatment phase

Recorded data

A comprehensive data collection form was used to record patient demographic characteristics, major medical history, smoking habits, comorbidities, risk factors, current asthma control status, medications, and all relevant physical assessments. Asthma control, treatment steps, and risk factor assessment were conducted following the Global Initiative for Asthma (GINA) guideline (Box 2–2 and Box 3–5) (35). Treatment steps were determined based on the prescribed maintenance therapy (Figure 4.).

Table 2. GINA 2014 assessment of asthma control in adults, adolescence and children 6-11 years (35)

Asthma symptom control	Levels of asthma symptom control		
	Well controlled	Partly controlled	Uncontrolled
In the past 4 weeks has the patient had: • Daytime asthma symptom nore than twice/week? Yes □ No □ • Any night waking due to asthma? Yes □ No □ • Reliever needed more than twice/week? Yes □ No □ • Any activity limitation due to asthma? Yes □ No □	None of these	1-2 of these	3-4 of these

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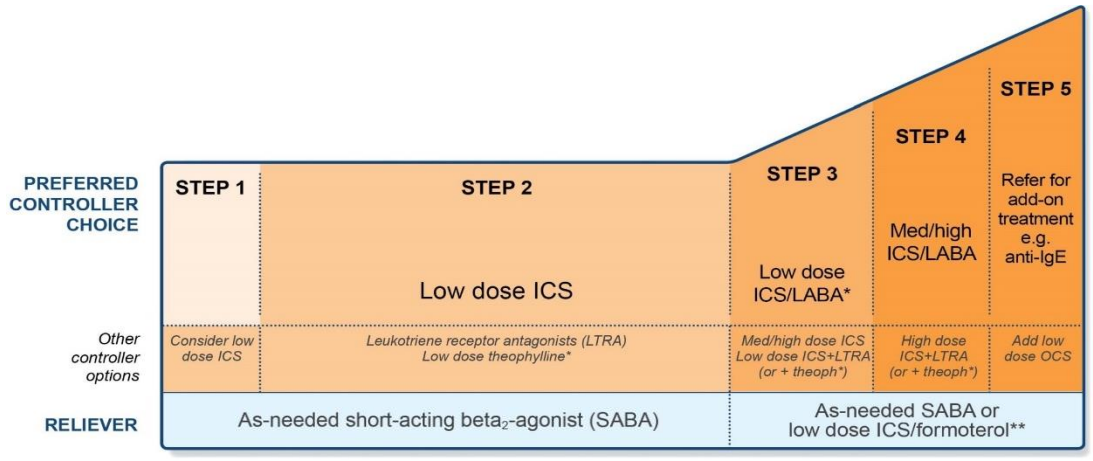

Figure 4. Stepwise approach to control symptoms and minimize risk in GINA 2014 (35)

The clinical records were used to collect information regarding allergen history, hospitalization, previous intubation, initial forced expiratory volume in 1 second (FEV1) at the time of diagnosis, the time of asthma diagnosis and comorbidities. Body Mass Index (BMI) was calculated using the patient's measured height and weight at the time of examination. Poor adherence was determined by the physician based on the patient's data. Additionally, data from patient surveys were collected. If spirometry was performed during the patient's medical visit, FEV1, FVC, and FEV1/FVC were recorded (127).

Evaluated comorbidities included:

Seasonal and perennial rhinitis

Gastroesophageal reflux disease (GERD)

Chronic obstructive pulmonary disease (COPD)

Hypertension

Atrial fibrillation

Other arrhythmias

Ischemic heart disease (IHD)

Acute myocardial infarction (AMI)

Other cardiac events

Cerebrovascular events

Osteoporosis

Diabetes mellitus (DM)
Impaired fasting glucose (IFG)
Prostate hyperplasia
Glaucoma
Other comorbidities (encompassing all other comorbidities not specifically listed in the questionnaire)

Since cardiovascular diseases are prevalent in the general population and are the leading cause of mortality in Hungary, they were evaluated thoroughly. Alongside examining their individual prevalence, a combined comorbidity index ('cardiovascular diseases') was created, including hypertension, atrial fibrillation, other arrhythmias, IHD, AMI, and other cardiac events. Laboratory tests were not conducted.

Statistical analysis

In the data analysis phase, descriptive statistics, graphical outputs, and Fisher's exact tests were employed. Odds ratios were reported along with their corresponding 95% confidence intervals (CI). Statistical analyses were conducted using Python 2.7.12 on a MAC operating system (Anaconda Inc., Austin, TX) and R for Windows 3.4.2 (R Core Team 2017) (127). Regarding smoking history, patients were categorized based on smoking exposure (measured in pack-years) and smoking status (nonsmoker, active smoker, and past smoker), as well as the combination of these parameters. Propensity scores are commonly utilized to stratify patients into groups with similar characteristics, thereby reducing the confounding effects of baseline parameters in observational studies where randomization is not feasible. Propensity scores were generated, taking into account gender, age group, BMI, time since asthma diagnosis, and smoking history. Comparing the asthma control of patients with or without a particular comorbidity within the same propensity score group allows for a comparison of the comorbidity's effect on asthma control, minimizing the confounding influence of baseline characteristics such as BMI and age, etc. This method ensures a more accurate analysis of the relationship between comorbidities and asthma control in observational studies (128).

3.2. Study 2.

Design and technical background

A single-centre observational study was conducted in the whole-body plethysmography box in the PFT laboratory at the Department of Pulmonology, Semmelweis University, Budapest, Hungary on 28 July 2020. The plethysmography box (PDT-111/pd, Piston Medical) had dimensions of 0.7x0.9x1.7 m and it was located in a room with dimensions of 5.6x3.5x3.0 m.

The study participants were volunteers and provided written consent. The study was completed based on ethical approval (no. SE RKEB 212/2020).

Two optical particle counters (OPCs; Grimm Aerosoltechnik, Portable Aerosol Spectrometer, model 1.109) were used to sample the background concentration and the concentration of particles near the patient's mouth in a whole-body plethysmography box. The size distributions were recorded in 31 size bins between 0.25 and 32 μm. Statistical evaluation of the measured particle concentration time series was completed. The particle exhalation rate was assessed based on the measured particle concentration data by applying the near-field/far-field theory. The number of exhaled viruses by an infected patient during the test was compared with the emission of viruses during quiet breathing and speaking.

Statistical analysis

Statistical evaluation of the measured particle concentration time series was performed using OriginPro 2021 Version 9.8.0.200. Background concentration and near-patient concentration time series were compared using two-sample t-tests. Concentration time series measured outside and inside the box were compared by correlation analysis (Pearson coefficient). The agreement between the two devices (OPC-A and OPC-B) sampling the same environment at the same time was verified using the BlandeAltman test.

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4. Results

4.1. Main clinical characteristics of patients and the level of asthma control

A total of 12 743 patients were enrolled by 187 pulmonology centres, representing 35% of the pulmonologists practicing in outpatient medical clinics in Hungary. During the 1-year inclusion period, an average of 68 patients were enrolled per investigational site.

The seasonal distribution of patients was well-balanced, 54.3% of the patients were examined from April to September, while 45.7% were examined from October to March. Patient inclusion also reflected population densities across geographical regions.

Regarding age distribution, it is important to note that 70% of patients were over 46 years old. Patients diagnosed with asthma for more than 5 years represented 66.9% of the cohort.

The proportion of men and women was in line with the national distribution, with 68.1% of participants being women. There was a statistically significant difference in the mean age of female compared with male patients (55.2 vs 51.5 years; $p < 0.0001$).

Based on the actual maintenance therapy 95.26% of patients were treated at GINA STEPs 2, 3, or 4. 13.1% were active smokers at the time of examination, 20.3% was ex-smoker and 66.6% was non-smoker.

The mean forced expiratory flow in 1 second (FEV1) value was 84.29% (2.34 L), mean forced vital capacity (FVC) was 94.18% (3.13 L). Regarding FEV1, 38.2% of the patients had values lower than 80% predicted, and 11.5% had values lower than 60%.

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Table 3. Demographic data and main clinical characteristics of the patients (127)

		Study population	
		N	%
Number of patients		12743	100
Number of cases in regions of Hungary	East	5149	40.4
	West	3984	31.3
	Central	3610	28.3
Examined patients according to seasonality	April–September	6923	54.3
	October–March	5820	45.7
GINA based treatment categories	STEP 1	274	2.15
	STEP 2	990	7.77
	STEP 3	4759	37.35
	STEP 4	6390	50.14
	STEP 5	330	2.59
Gender	Male	4059	31.9
	Female	8684	68.1
Age distribution	18–30	1261	9.9
	31–45	2466	19.4
	46–65	5687	44.6
	>65	3329	26.1
FEV_1 (forced expiratory volume in 1 s, % predicted) distribution	>80%	7527	59.1
	60–80%	3399	26.7
	<60%	1461	11.5
	No data	356	2.8

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The actual level of asthma control was an important parameter in the study, and these results are summarized in Figure 5.

Of all the patients, 36.0% had well-controlled asthma; however, 34.7 % had uncontrolled asthma, and 29.3 % had partially controlled asthma.

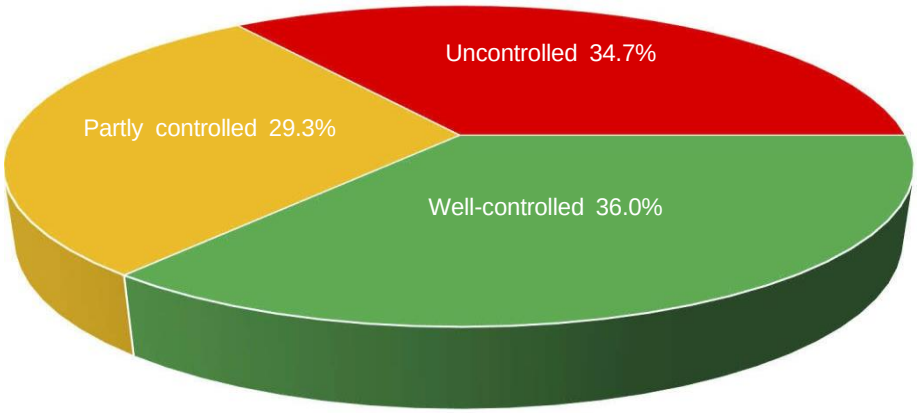

Figure 5. Proportion of patients with different levels of asthma control according to GINA guideline (127)

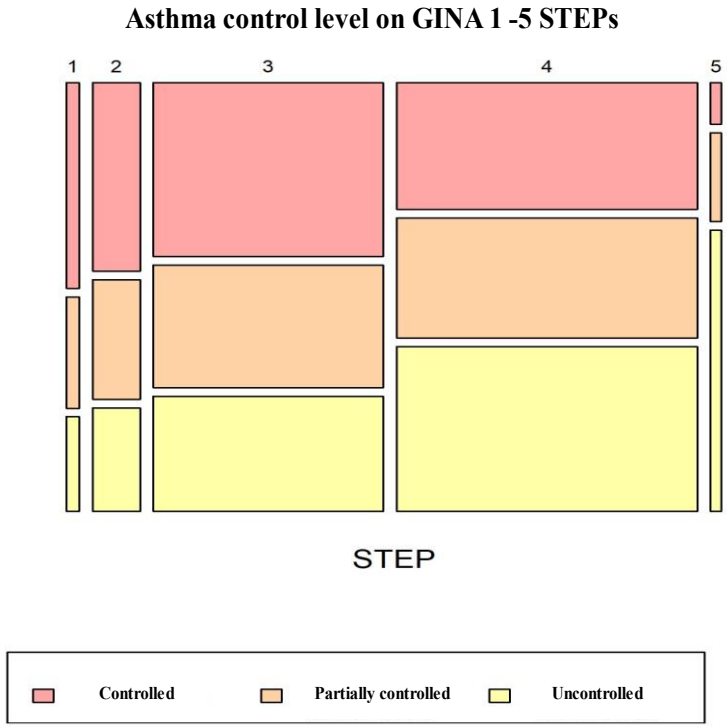

Figure 6. Asthma control level across GINA treatment steps.

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Patients' asthma control levels show significant differences across the GINA steps, as illustrated in Figure 6. In the first three steps, the percentage of controlled patients ranged from 42.2% to 50%, in the fourth step it was 30.7%, while in the fifth step it was only 10.1%.

Besides assessing asthma control according to GINA recommendations, several questions in the patient questionnaire addressed the patients' actual condition. They were asked to rate how they were feeling at the moment of the visit, with 5 types of answers: very bad, quite bad, bad, good and very good. Although less than 5% of patients responded ‘very bad’, together with the categories ‘quite bad’ and ‘bad’, it reached 40% of patients. An interesting result emerged regarding age groups. It was an expected outcome that patients in the 18-40 age group report feeling the best, with less than 30% indicating negative feelings. However, the 41-60 age group felt significantly worse than those over 60. More than 50% of aged 41-60 reported feeling 'very bad,' 'quite bad,' or 'bad’. In terms of BMI, comparing to the normal BMI, the higher the BMI of the patients, the greater the proportion of patients who reported feeling 'bad,' 'quite bad,' or 'very bad’.

48% of patients reported that their physical activity had been limited by their asthma in the past 4 weeks, and 38% of patients experienced daily symptoms and were forced to use extra reliever therapy to manage these symptoms. Nocturnal symptoms were experienced by 22% of patients in the last 4 weeks. Figure 7. visualizes the result for the question how well you are able to keep your asthma under control and live without symptoms and limitation. We can observe that only 44% of patients felt capable of controlling their asthma. In relation to BMI, a similar trend to the previous question emerged: the higher the patient's BMI, the less capable they were of controlling their disease, except for underweight patient whose results were similar to those of obese patients.

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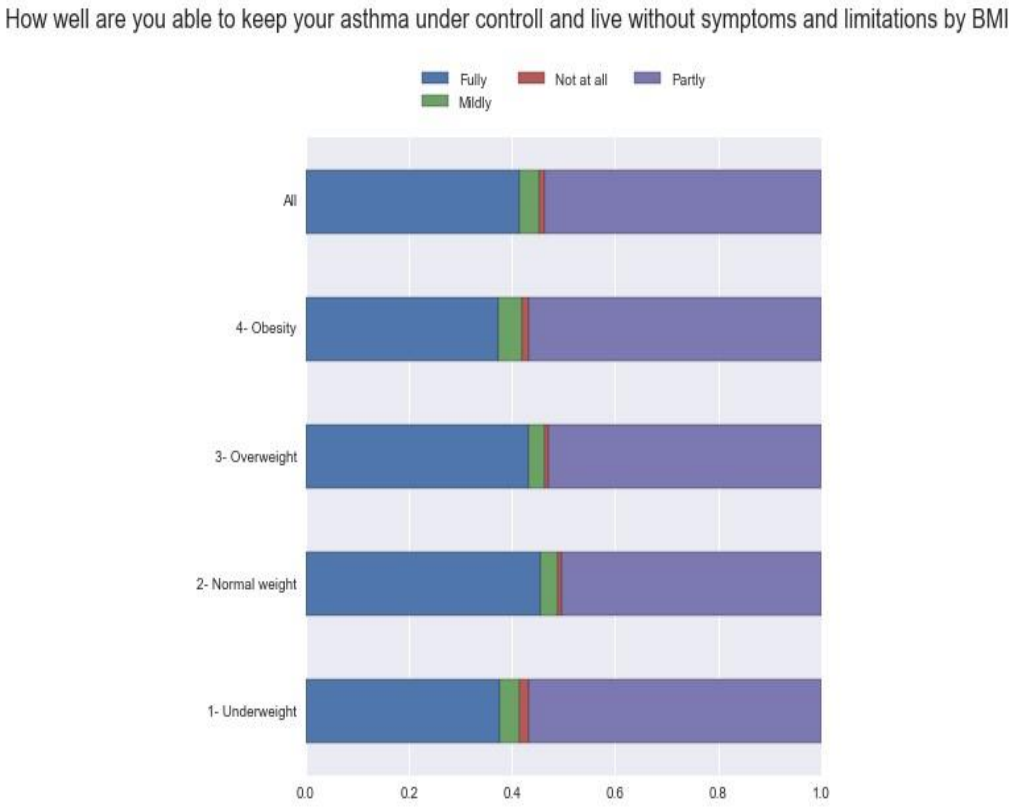

Figure 7. Patient questionnaire - How well are you able to keep your asthma under control and live without symptoms and limitation? (All, and according to BMI categories)

The order of frequency of symptoms was the following: dyspnoea, cough, limited exercise capacity, wheezing and chest tightness. In terms of triggers, 58% of patients reported stress, 31% cited air pollution or other inhaled agents, 22% reported tobacco smoke, 18% reported cold air, the same number of patients reported weather changes, and fewer than 10% reported fatigue or physical activity. These findings confirm that a significant proportion of patients were unable to achieve well-controlled asthma, and their asthma limited their daily activities with deteriorating quality of life.

4.2. Prevalence of risk factors and their association with uncontrolled asthma

In our study, we recorded the risk factors for poor asthma outcomes as outlined by the GINA document, which include exacerbation, fixed airway obstruction, and medication side effects. In addition to measuring the prevalence of risk factors, it was also important

to determine the proportion of patients with a given risk factor who had uncontrolled asthma.

Among the investigated risk factors, improper inhaler technique leading to side effects showed the strongest association with uncontrolled state (OR 4.86, CI 3.51–6.8), with 71.58% of affected patients being uncontrolled.

The patients who had at least 1 severe exacerbation in the last 12 months were also in very poor status because 70.05% of them were uncontrolled (OR 4.79, 4.02-5.72).

In third place was the excessive SABA use, with almost two-thirds (64.5%) of patients had uncontrolled asthma (OR 4.46, CI 4.03–4.93).

Patients with incorrect inhaler technique associated with an exacerbation had the fourth highest OR (3.91, CI 3.06–5.03), while poor adherence to inhaled corticosteroids (ICS) showed also a strong relation to uncontrolled disease, with 55.11% being uncontrolled (OR 2.51, CI 2.21–2.86).

In terms of FEV1, the actual low FEV1 had stronger relation to uncontrolled asthma (OR 3.14, CI 2.8–3.52), meanwhile low FEV1 at diagnosis also showed high level of uncontrolled asthma (OR 2.21, CI 2.01–2.44).

4 253 patients were affected by smoking including current and ex-smokers, 40.58% of them were uncontrolled (OR 1.47, 1.36–1.59).

Chronic rhinosinusitis was the most common risk factor. While a history of allergies showed similar disease control as the whole cohort, patients with allergic conditions at the time of examination had 44.62% uncontrolled asthma, demonstrating an OR of 1.63 (1.47–1.81) for loss of asthma control.

The need of systemic corticosteroid treatment was also associated with high level of uncontrolled state, almost half of these patients were uncontrolled (47.23%) which ratio was very close to the frequent use of oral corticosteroids (OCS) related to systemic side effects (47.46%, OR 1.83, 1.64–2.05).

Additionally, in 4575 cases, BMI was >30 kg/m2, with 39.04% of these patients being poorly controlled (OR 1.34, CI 1.24–1.45). Table 4 and Figures 8–10 present the control levels of patients alongside specific risk factors.

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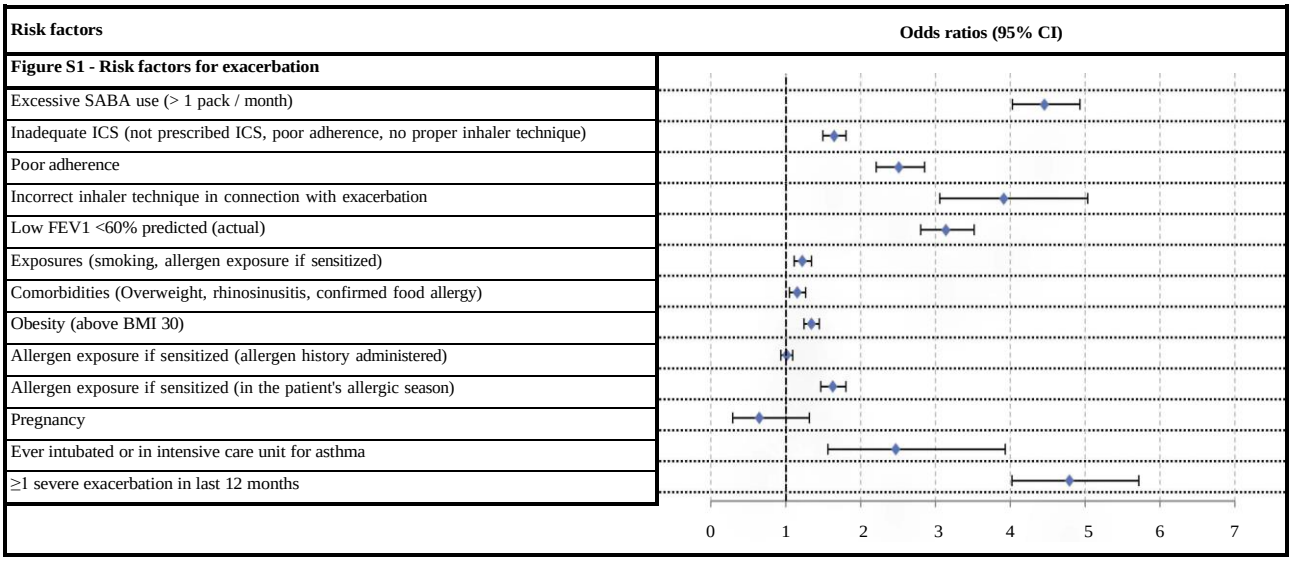

Figure 8. Risk factors for exacerbation (127)

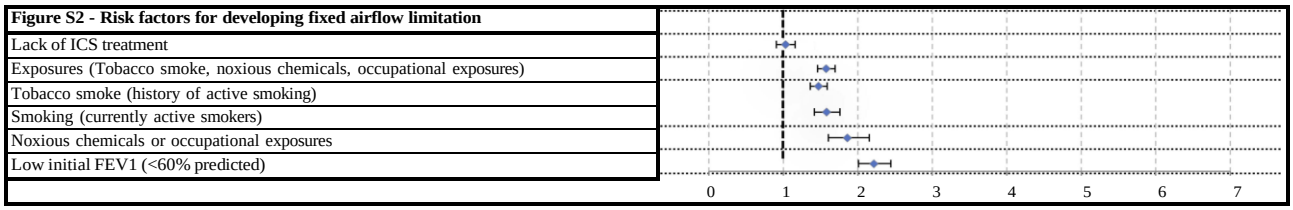

Figure 9. Risk factors for developing fixed airflow limitation (127)

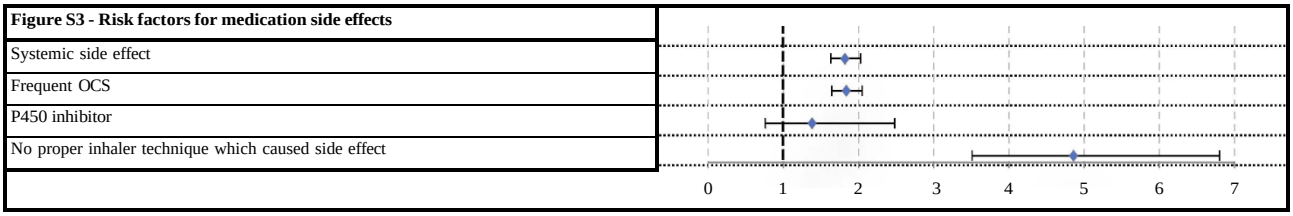

Figure 10. Risk factors for medication side effects (127)

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Table 4. Prevalence of risk factors, control levels of affected patients, and relationship between the risk factor and uncontrolled status (Fisher's exact test odds ratio) (127)

	Risk factors	Number of patients affected by the risk factor	Prevalence of risk factor	Ratio of uncontrolled patients	Number of uncontrolled patients	Number of partly controlled patients	Number of well-controlled patients	Odds ratios (95% CI)	*p*-value
Risk factors for exacerbation									
1	Excessive SABA use (>1 pack/month)	2045	16.05%	64.55%	1,320	460	265	4.46 (4.03-4.93)	*p*<0.001
2	Inadequate ICS (not prescribed ICS, poor adherence, no proper inhaler technique)	2250	17.66%	44.36%	998	679	573	1.64 (1.50-1.81)	*p*<0.001
2a	Poor adherence	1076	8.44%	55.11%	593	332	151	2.51 (2.21-2.86)	*p*<0.001
2b	Incorrect inhaler technique in connection with exacerbation	304	2.39%	66.78%	203	69	32	3.91 (3.06-5.03)	*p*<0.001
3	Low FEV_1<60% predicted (actual)	1461	11.47%	59.14%	864	327	270	3.14 (2.80-3.52)	*p*<0.001
4	Exposures (smoking, allergen exposure if sensitized)	10,210	80.12%	35.57%	3632	2991	3587	1.22 (1.11-1.35)	*p*<0.001
5	Comorbidities (Overweight, rhinosinusitis, confirmed food allergy)	10,193	79.99%	35.34%	3602	3007	3584	1.15 (1.05-1.27)	*p*=0.002
5a	Obesity (above BMI 30)	4575	35.90%	39.04%	1786	1353	1436	1.34 (1.24-1.45)	*p*<0.001
5b	Allergen exposure if sensitized (allergen history administered)	8517	66.84%	34.79%	2963	2462	3092	1.01 (0.94-1.09)	*p*=0.767
5b1	Allergen exposure if sensitized (in the patient's allergic season)	1786	14.02%	44.62%	797	561	428	1.63 (1.47-1.81)	*p*<0.001
6	Pregnancy	43	0.34%	25.58%	11	13	19	0.65 (0.29-1.32)	*p*=0.261
7	Ever intubated or in intensive care unit for asthma	83	0.65%	56.63%	47	15	21	2.47 (1.56-3.93)	*p*<0.001
8	≥1 severe exacerbation in last 12 months	651	5.11%	70.05%	456	115	80	4.79 (4.02-5.72)	*p*<0.001
Risk factors for developing fixed airflow limitation									
9	Lack of ICS treatment	1331	10.44%	35.24%	469	418	444	1.03 (0.91-1.16)	*p*=0.67
10	Exposures (Tobacco smoke, noxious chemicals, occupational exposures)	4736	37.17%	41.22%	1952	1423	1361	1.58 (1.46-1.70)	*p*<0.001
10a	Tobacco smoke (history of active smoking)	4253	33.38%	40.58%	1726	1292	1235	1.47 (1.36-1.59)	*p*<0.001
10a1	Smoking (currently active smokers)	1669	13.10%	42.30%	706	512	451	1.58 (1.42-1.76)	*p*<0.001
10b	Noxious chemicals or occupational exposures	793	6.22%	48.68%	386	227	180	1.86 (1.60-2.15)	*p*<0.001
11	Low initial FEV_1 (<60% predicted)	1999	15.69%	50.73%	1,014	508	477	2.21 (2.01-2.44)	*p*<0.001
Risk factors for medication side effects									
12	Systemic side effect	1550	12.16%	47.23%	732	369	449	1.82 (1.63-2.03)	*p*<0.001
12a	Frequent OCS	1513	11.87%	47.46%	718	353	442	1.83 (1.64-2.05)	*p*<0.001
12b	P450 inhibitor	52	0.41%	42.31%	22	17	13	1.38 (0.76-2.48)	*p*=0.247
13	No proper inhaler technique which caused side effect	190	1.49%	71.58%	136	33	21	4.86 (3.51-6.80)	*p*<0.001

4.3. The most significant risk factors associated with uncontrolled asthma

These risk-factors have outstanding association with poor asthma control:

1. Incorrect inhaler technique
2. Exacerbation history
3. Excessive SABA use
4. Persistently low FEV1
5. Poor adherence to treatment

In terms of prevalence, obesity and smoking pose the greatest challenge.

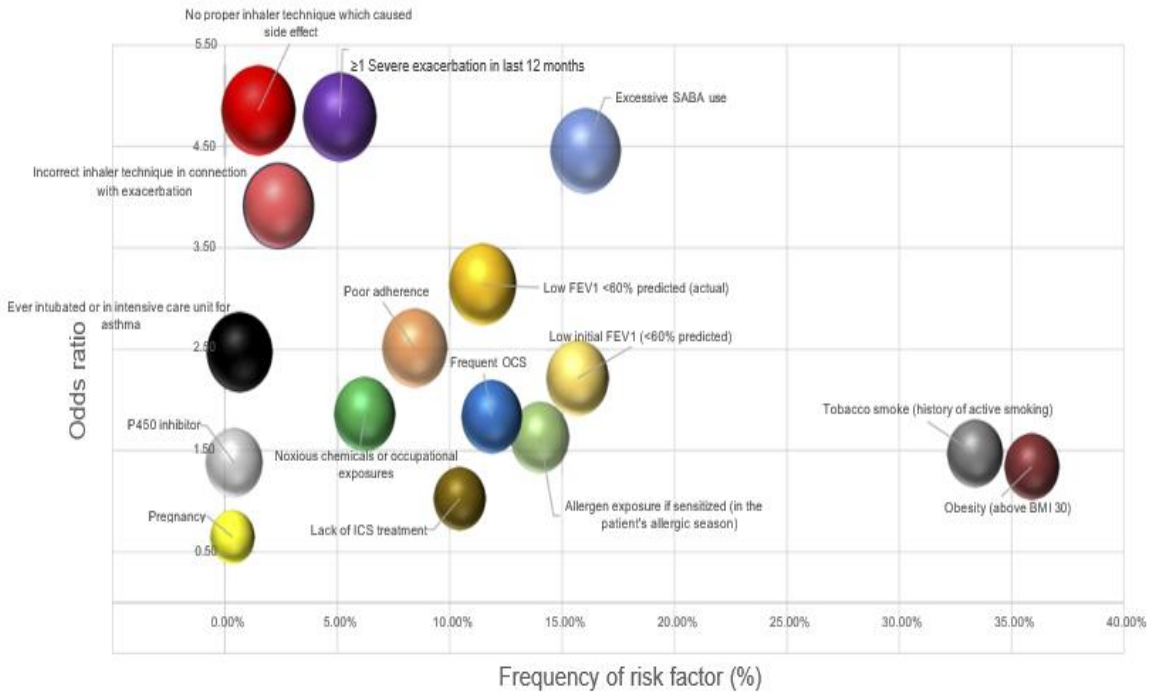

Figure 11. The prevalence of specific risk factors and the odds ratio of its relationship with uncontrolled status. Note: Size of bubbles represent the ratio of uncontrolled patients (127).

4.4. Prevalence of comorbidities associated with asthma and their relationship to asthma control measures

In parallel with risk factors, we studied the prevalence of common noncommunicable diseases coexisting with asthma. In our patient population, perennial rhinitis and cardiovascular disease were the most prevalent comorbidities.

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Table 5. Numbers and proportions of patients with controlled and uncontrolled asthma in each demographic parameter (128)

		Controlled	Uncontrolled	p values *
Gender	Male (n = 4059)	2858 (70%)	1201 (30%)	0.0000
	Female (n = 8684)	5462 (63%)	3222 (37%)	
Age group	18–30 (n = 1261)	931 (74%)	330 (26%)	0.0000
	31–45 (n = 2466)	1812 (73%)	654 (27%)	
	46–65 (n = 5687)	3437 (60%)	2250 (40%)	
	> 65 (n = 3329)	2140 (64%)	1189 (36%)	
BMI	Underweight (n = 228)	145 (64%)	83 (36%)	0.0000
	Normal (n = 3475)	2419 (70%)	1056 (30%)	
	Overweight (n = 4465)	2967 (66%)	1498 (34%)	
	Obese (n = 3009)	1900 (63%)	1109 (37%)	
	Severely obese (n = 1566)	889 (57%)	677 (43%)	
Smoking amount	< 10 pack-years (n = 2077)	1356 (65%)	721 (35%)	0.0000
	≥10 pack-years (n = 2234)	1205 (54%)	1029 (46%)	
Smoking status	Active smoker (n = 1669)	963 (58%)	706 (42%)	0.0000
	Ex-smoker (n = 2588)	1568 (61%)	1020 (39%)	
	Non-smoker (n = 8486)	5789 (68%)	2697 (32%)	
Time since diagnosis	0–5 years (n = 4222)	2915 (69%)	1307 (31%)	0.0000
	6–10 years (n = 3174)	2047 (64%)	1127 (36%)	
	11–20 years (n = 3617)	2326 (64%)	1291 (36%)	
	> 20 years (n = 1702)	1014 (60%)	688 (40%)	
	no data (n=28)			

Regarding comorbidities our primary objective was to evaluate their potential impact on asthma control and treatment outcomes. By using propensity scores, we aimed to minimize the impact of basic patient characteristics on both comorbidity prevalence and treatment outcomes. This involved categorizing patients into five groups, where the sole distinction was the presence or absence of the assessed comorbidity, resembling a randomized distribution.

We evaluated the impact of the presence of the given comorbidity and each component of the propensity score on asthma control, and calculated odds ratios. Asthma control was assessed as controlled, which included both well-controlled and partially controlled

patients (n = 8320), versus uncontrolled (n = 4423). Within the controlled group, patients were further categorized as well-controlled (n = 4588) or partially controlled (n = 3732). Concerning the first comparison (Figure 13.), every comorbidity, with the exception of prostate hyperplasia, showed a statistically significant impact on asthma control levels (OR = 1.24, 95% CI 0.97– 1.59).

We observed the strongest association on treatment outcome for the concomitant COPD (OR = 2.06, 95% CI 1.80–2.36). In the presence of COPD, 55% of patients were uncontrolled. IHD showed the second strongest association with poor control, with 51% of patients having poor control (OR = 1.86, 95% CI 1.64–2.10). Cerebrovascular events had the third highest odd ratio (OR = 1.85, 95% CI 1.47–2.32).

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Table 6. A and B Numbers and proportions of patients with controlled and uncontrolled asthma in each comorbidity (128)

		Controlled	Uncontrolled
A			
Cardiovascular diseases	Not present (n = 7160)	5084 (71%)	2076 (29%)
	Present (n = 5583)	3236 (58%)	2347 (42%)
Seasonal rhinitis	Not present (n = 10,957)	7331 (67%)	3626 (33%)
	Present (n = 1786)	989 (55%)	797 (45%)
Perennial rhinitis	Not present (n = 4226)	2766 (65%)	1460 (35%)
	Present (n = 8517)	5554 (65%)	2963 (35%)
GERD	Not present (n = 10,180)	6847 (67%)	3333 (33%)
	Present (n = 2563)	1473 (57%)	1090 (43%)
COPD	Not present (n = 11,741)	7869 (67%)	3872 (33%)
	Present (n = 1002)	451 (45%)	551 (55%)
Ischaemic heart disease	Not present (n = 11,493)	7704 (67%)	3789 (33%)
	Present (n = 1250)	616 (49%)	634 (51%)
Hypertension	Not present (n = 7517)	5285 (70%)	2232 (30%)
	Present (n = 5226)	3035 (58%)	2191 (42%)
AMI	Not present (n = 12,533)	8211 (66%)	4322 (34%)
	Present (n = 210)	109 (52%)	101 (48%)
Atrial fibrillation	Not present (n = 12,583)	8233 (65%)	4350 (35%)
	Present (n = 160)	87 (54%)	73 (46%)
B			
Other arrhythmias	Not present (n = 12,119)	7999 (66%)	4120 (34%)
	Present (n = 624)	321 (51%)	303 (49%)
Other CV	Not present (n = 12,528)	8215 (66%)	4313 (34%)
	Present (n = 215)	105 (49%)	110 (51%)
Cerebrov. events	Not present (n = 12,432)	8171 (66%)	4261 (34%)
	Present (n = 311)	149 (48%)	162 (52%)
Osteoporosis	Not present (n = 11,662)	7715 (66%)	3947 (34%)
	Present (n = 1081)	605 (56%)	476 (44%)
Impaired fasting glucose	Not present (n = 11,685)	7765 (66%)	3920 (34%)
	Present (n = 1058)	555 (52%)	503 (48%)
Diabetes mellitus	Not present (n = 11,614)	7726 (67%)	3888 (33%)
	Present (n = 1129)	594 (53%)	535 (47%)
Prostate hyperplasia	Not present (n = 12,437)	8131 (65%)	4306 (35%)
	Present (n = 306)	189 (62%)	117 (38%)
Glaucoma	Not present (n = 12,516)	8196 (65%)	4320 (35%)
	Present (n = 227)	124 (55%)	103 (45%)
Other	Not present (n = 11,423)	7607 (67%)	3816 (33%)
	Present (n = 1320)	713 (54%)	607 (46%)

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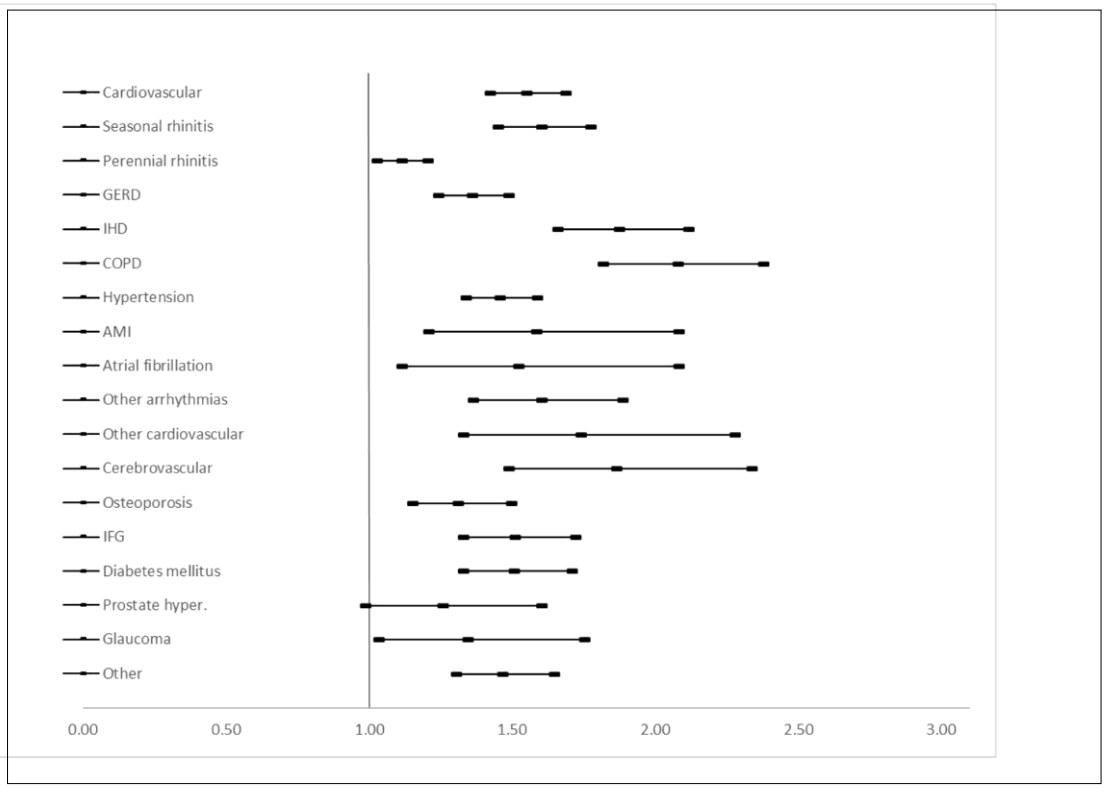

Figure 12. Risk of having uncontrolled asthma if the given comorbidity is present (128)

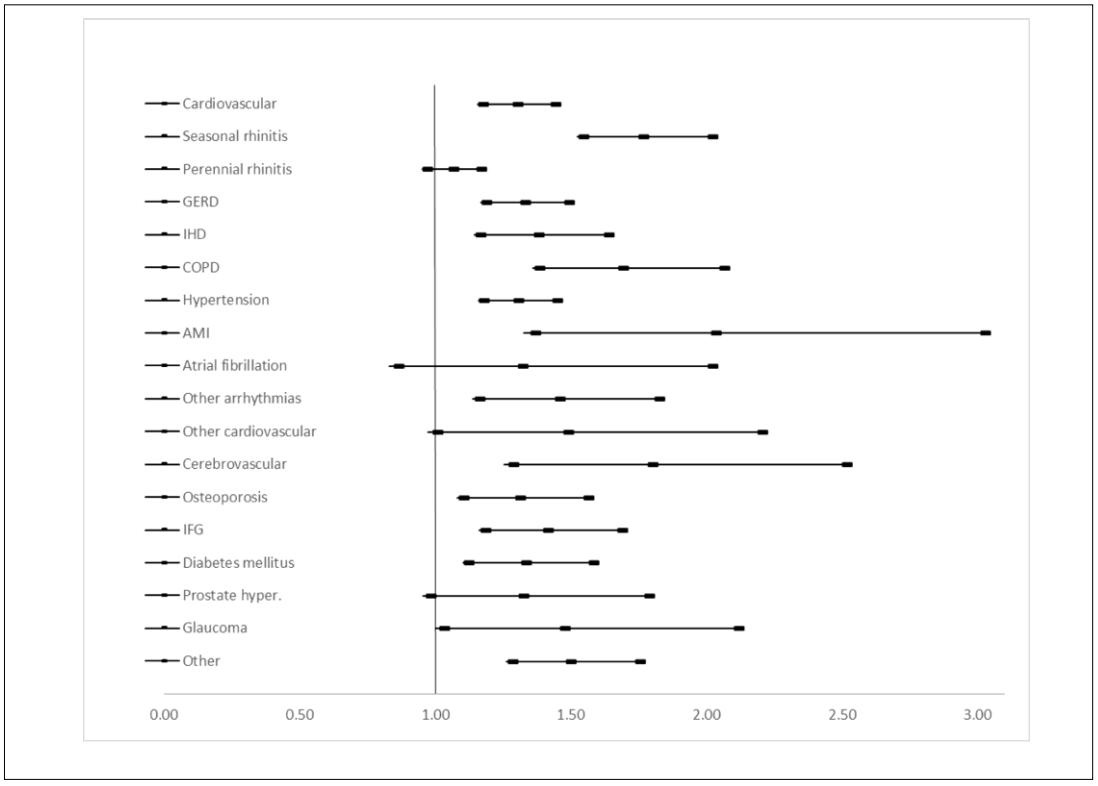

Figure 13. Risk of having partially controlled asthma if the given comorbidity is present (128)

Besides IHD, other cardiovascular diseases such as arrhythmias, AMI, atrial fibrillation, and hypertension also demonstrated a highly significant association with poor control. Comparing well versus partially controlled asthma (Figure 14), prostate hyperplasia (OR = 1.31, 95% CI 0.97–1.77), atrial fibrillation (OR = 1.31, 95% CI 0.85–2.01), perennial rhinitis (OR = 1.05, 95% CI: 0.96–1.16) and other cardiovascular events (OR = 1.48, 95% CI 0.99–2.19) had a significant effect on asthma control level. AMI (OR = 2.02, 95% CI 1.35–3.01), cerebrovascular events (OR = 1.79, 95% CI 1.27–2.50) and seasonal rhinitis (OR = 1.75, 95% CI 1.53– 2.01) had the strongest effect on the control level in this comparison (128).

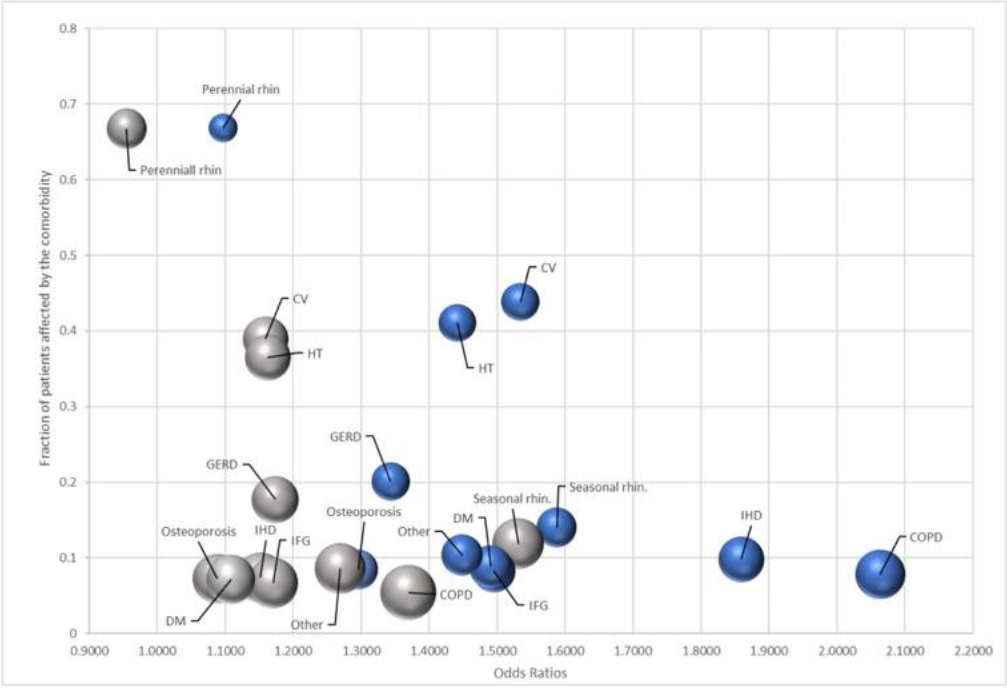

Figure 14. The prevalence of specific comorbidities (prevalence of at least 10%) and the odds ratios of their relationship with uncontrolled (blue) and partially controlled (grey) asthma. The size of the bubbles represents the ratio of uncontrolled asthma (of all patients who suffer from that specific comorbidity) (128).

4.5. Gender and age-specific patterns of comorbidities associated with asthma

We found significant differences in the prevalence of comorbidities between male and female patients. Cardiovascular diseases (46.7% vs 37.7%; $p < 0.0001$), GERD (22.2%

vs 15.6%; p < 0.0001), hypertension (43.9% vs 34.9%; p < 0.0001), other arrhythmias (6.1% vs 5%; p = 0.0034), osteoporosis (11.5% vs 2.1%; p < 0.0001), IFG (8.7% vs 7.5%; p = 0.0210), glaucoma (2.1% vs. 1.2%; p = 0.0004) and 'other comorbidities' (11.9% vs 7.1%; p < 0.0001) were significantly more prevalent in female patients compared to male patients. Three diseases were found to be more prevalent in men: concomitant COPD (9.3 vs 7.2%; p = 0.0001), AMI (2.3 vs 1.4%; p = 0.002) and atrial fibrillation (1.6 vs. 1.1%; p = 0.0208). The proportion of uncontrolled asthma was significantly higher in females (37.1% vs 29.6%; p < 0.0001).

Older patients tended to have more comorbidities than younger ones; however certain diseases showed a different distribution according to age. To aid understanding, we grouped comorbidities into three categories based on their age-related prevalence trends: diseases with increasing prevalence (Trend 1), decreasing prevalence (Trend 2), and diseases with a different age distribution pattern (Trend 3). Figure 12. shows an example of a comorbidity that follows each trend.

Trend 1

Cardiovascular diseases were present in 3.5% of all patients in group 1 while 70.4% of patients suffered from them in group 4, with a steep increase in prevalence starting at 50 years of age. A similar trend was observed for IHD (prevalence of 0.2% in group 1 and 20.4% in group 4), AMI (from 0.2 to 3.0%), atrial fibrillation (from 0.24 to 3.18%), other arrhythmias (from 0.6 to 8.4%), other cardiovascular events (from 0.4 to 3.2%), cerebrovascular events (from 0.1 to 4.7%) and hypertension (from 2.4 to 66.4%). Concomitant COPD showed an increase up to 12.6% in group 4 (vs 0.4% in group 1). Osteoporosis mostly occurred at the age of 40 and increased in prevalence, reaching 17.9% in group 4. Prostate hyperplasia (from 0.0% in group 1 to 6.8% in group 4), IFG (from 0.6 to 13.2%), DM (from 0.8 to 13.9%) and glaucoma (from 0.2 to 3.2%) also showed increased prevalence with age in asthmatic patients.

Trend 2

Contrary to the aforementioned diseases, the prevalence of perennial rhinitis (from 82.3% in group 1 to 55.5% in group 4) decreased with age.

Trend 3

The occurrence of GERD increased until the age of 55, when it reached 25% and stayed the same after, regardless of increasing age. 'Other comorbidities' showed a trend with a

similar plateau starting from the age of 50 years. Furthermore, there was a statistically significant difference in the mean age of patients with controlled asthma (53.1 years, 95% CI 52.4–53.4) and uncontrolled asthma (55.9 years, 95% CI 55.4–56.3; $p < 0.0001$). The proportion of patients with uncontrolled asthma was highest in age group 3 (39.6%).

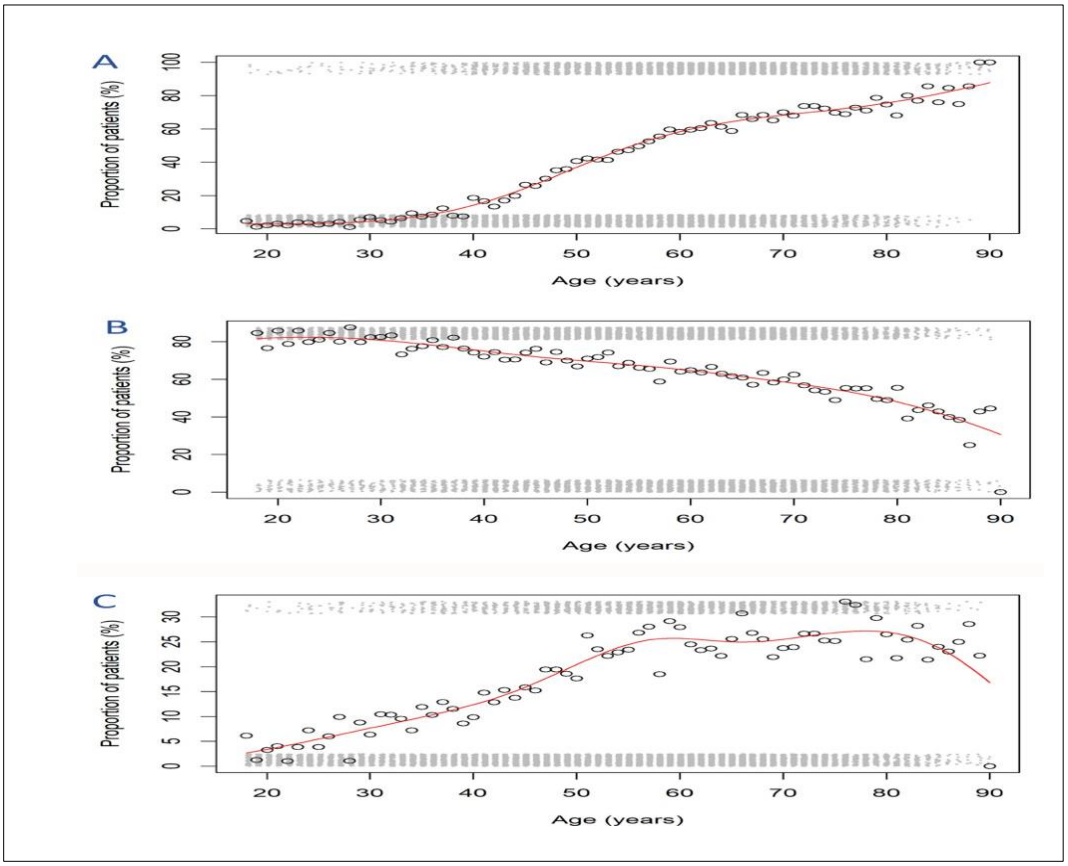

Figure 15. The distribution of patients with cardiovascular disease (age trend 1, A), seasonal rhinitis (age trend 2, B) and GERD (age trend 3, C) (128)

4.6. Association between BMI, asthma control, and comorbidities

Patients were categorised into five groups according to BMI values: underweight (BMI ≤ 18.5 kg/m2; 1.8%), normal (BMI 18.5–25 kg/m2; 27.3%), overweight (25– 30 kg/m2; 35.0%), obese (30–35 kg/m2; 23.6%) and severely obese (> 35 kg/m2; 12.3%).

The average BMI was significantly higher in patients with the following comorbidities: cardiovascular disease, hypertension, IHD, AMI, atrial fibrillation, other arrhythmias, DM, IFG, GERD and other comorbidities (in all cases, $p < 0.0001$); glaucoma ($p = 0.001$); other cardiovascular events ($p = 0.001$); cerebrovascular disease ($p = 0.004$); and prostate hyperplasia ($p = 0.049$). On the other hand, the average BMI was significantly lower in

patients with perennial ($p < 0.0001$) and seasonal ($p = 0.019$) rhinitis. The prevalence of most evaluated comorbidities increased with BMI, with the largest increase observed in the rate of hypertension (present in 8.3% of underweight and 62.1% of severely obese patients). A similar BMI related increase was seen in the prevalence of IHD, AMI, atrial fibrillation, other arrhythmias, other cardiovascular events, DM, IFG, and other comorbidities. There was a similarly increasing prevalence for GERD, with a plateau at a BMI of 30 kg/m2. There was a reversed trend for perennial and seasonal rhinitis, where the prevalence decreased as the BMI increased. In the case of the much more prevalent perennial rhinitis, 71.9% of underweight and only 61.9% of severely obese patients were affected. There was a trend for an increasing then decreasing prevalence for cerebrovascular events, prostate hyperplasia, and glaucoma. The prevalence of concomitant COPD and osteoporosis were independent of BMI values. Finally, there was a significant difference in the average BMI of the patients with controlled asthma (28.1 kg/m2, 95% CI 28.0–28.2) and uncontrolled asthma (29.1 kg/m2, 95% CI 29.0–29.3; $p < 0.0001$). The severely obese patients had the highest proportion of uncontrolled asthma (43.2%).

4.7. Aerosol concentrations in a PFT laboratory and the potential viral load near the patient

Twenty-five patients were involved in the study, suffering from different diseases: two asthmatics, eight transplant patients, four patients with chronic obstructive pulmonary disease, one patient with cystic fibrosis, two patients with idiopathic pulmonary fibrosis, two patients with interstitial lung disease, one smoker suspected of asthma, two subjects suspected of tuberculosis, one patient with lung cancer, one patient with sarcoidosis, and one patient with pulmonary hypertension (129). The total number of measurements was 27, as two measurements were made on two of the patients (reversibility test). One participant (with sarcoidosis) was excluded because the increase in aerosol concentration (almost two orders of magnitude higher than the average increase) was generated by cloth handling by the patient (129).

The 24 patients (12 males and 12 females) had a mean age of 57.7 [standard deviation (SD) 17.3] years and mean body mass index (BMI) of 24.1 (SD 5.8) kg/m2. Mean forced expiratory volume in 1 s (FEV1) was 2.0 (SD 0.9) L [70.5 (SD 29.4)%] and mean forced

vital capacity was 2.8 (SD 1.1) L [81.0 (SD 22.8)%] (129). The mean duration of the examinations was 2.6 (SD 1.1) min. Mean ambient room humidity was 37.9 (SD 2.3)% and mean temperature was 23.4 (SD 0.9)℃. Throughout the measurement period, the mean ambient levels of total concentration corresponding to the monitored daily routine were [144 (SD 1.2)]x10^3 L^{-1} and [142 (SD 1.1)]x10^3 L^{-1} in the laboratory and in the body box, respectively (129).

In eight cases (31% of the total number of measurements), the patient-specific total concentration values, calculated as the concentration of 0.25-32 μm particles measured by OPC-B averaged over the duration of patient stay in the cabin, were not significantly higher than the background concentration measured simultaneously by OPC-A (129). In 18 cases (69% of the total number of measurements), the total concentration increase was significant (p=0.05). The mean total concentration increase was 1910 (SD 1018) particles/L. No statistically relevant correlation could be demonstrated between the type of disease and particle concentration enhancement due to the measurement. The correlation between FEV1 and FVC and the increase in particle concentration was also weak (129).

Submicron particles dominated the number size distribution of the generated particles, but large particles represented a higher volume fraction in the generated particles compared with background. An average gene exhalation rate of 0.2/min was estimated from this data. This is one order of magnitude higher than the release rate for the same infected person during quiet breathing, and of the same order of magnitude as the release rate during normal speaking (129).

5. Discussion

The first GINA document in 1995 aimed to improve asthma management in response to the increasing prevalence of asthma and asthma-related mortality. Since the very beginning, achieving good asthma control has been a primary aim. However, despite the goal set by the GINA guidelines, there have been few studies in Hungary evaluating asthma control in a large patient population. The largest such study was conducted by Herjavecz and colleagues in 2003, which examined 711 adult patients and found that 50.7% of patients had good control, 36.6% had moderate control and 12.7% had poor control (130). During that period, several other European studies found that at least half of the patients continually suffer from symptoms, and researchers raised concerns about the challenges of achieving good asthma control in real-life clinical practice (24,25).

Between 2000 and 2010, new and more advanced medicines were developed and became available, and the objectives of the GINA guideline was used more widely and more intensively, furthermore standardized questionnaires were developed and validated. Alongside these advances, it was reasonable to expect that the level of asthma control should continue to improve.

In 2011, Müller et al. conducted a study in Hungary evaluating asthma control in 111 outpatients with moderate to severe persistent asthma in real-life situations. Despite the study design allowing the use of only the three original ICS/LABA fixed combinations, which were considered the most advanced therapies, asthma control was achieved by 45.9% of patients; 38.7% were partially controlled, and 15.3% were uncontrolled (131). As we can see, in spite of enormous efforts and advancements asthma control level remained more or less on the same level.

At the same time, we are aware that poor control has plenty of negative implications.

Therefore, our aim was, besides assessing asthma control on really large patient population, to identify the key determinant factors of unsatisfactory control level.

We used GINA's 2014 document as a framework to identify the prevalence and evaluate the risk of the most important factors. Additionally, patients' chronic comorbidities, as a potential factors for poor outcome, were collected to evaluate their associations to uncontrolled status.

5.1. Clinical status and asthma control level of the Hungarian adult asthma patients

Our current study, based on 12 743 involved patients, confirmed that achieving high level of asthma control on large population remains a challenge: 36% of the patients were well controlled, 29.29% were partially controlled, and 34.71% were uncontrolled. In comparison to a specialist-based cross-sectional study of adult asthma in Japan conducted by Adachi et al., our investigation demonstrated a nearly equivalent result, with only 35.1% of patients achieving controlled asthma despite receiving treatment from an allergy and/or respiratory specialist (132). Similarly, Gemicioglu et al. observed the same rate of controlled patients in Turkey, the percentage of patients with total control in the elderly and young groups was 33.9% and 37.1% at the first visit, respectively (133).

Through the patient questionnaire, we learnt that 40% of patients reported feeling bad rather than well, while 48% reported limitations in physical activity due to asthma in the past 4 weeks. Additionally, 38% of patients experienced daily symptoms and required extra reliever therapy to manage them. These findings are somewhat surprising, considering that asthma patients in Hungary are managed by specialists who are familiar with guideline requirements and have access to medications with a high level of reimbursement.

Our study revealed that despite escalating treatment, the rates of uncontrolled asthma increased with higher GINA treatment STEPs. In everyday practice, specialists pay great attention to the selection of the right drug, posology and dosage and when needed, they intensify therapy, but nevertheless at higher GINA STEPs, the level of control deteriorates further.

Now we know that several other important clinical features including risk factors and comorbidities fundamentally modify the final clinical outcome. Our expectation is that without focusing on these factors there is a ceiling of achievable control level which have several negative implications. However, each risk factor has different prevalence among asthma patients and there is various order of magnitude regarding their impact on asthma control level.

5.2. Prevalence and impact of risk factors

These considerations triggered our second objective which aimed to assess the prevalence of risk factors and evaluate which risk factors pose the greatest challenge and to what extent in achieving well-controlled status.

Our study confirmed our hypothesis that the frequencies and associations of listed risk factors with poor control vary widely.

The frequency of specific risk factors and the odds ratio of its relationship with control loss are visualized in Figure 11.

In our study, besides excessive SABA use, yearly exacerbating disease pattern, improper inhaler technique, and low FEV1 (<60% predicted) were the most strongly related to suboptimal disease control. It was not surprising that high SABA use had an especially high OR. Of the patients who used more than 1 pack of salbutamol a month, 64.55% were uncontrolled at the time of the survey, and in total only 13% of them were well controlled. This result clearly shows that overuse of salbutamol is related to uncontrolled disease. Similarly to high SABA use, the chance of an uncontrolled status amongst patients who had at least 1 severe exacerbation per year was exceedingly high. This confirms the results of the TENOR Study Group that severe asthma exacerbations are a strong independent factor predicting future exacerbations (104). Although patients in acute exacerbation were excluded from our study, 5.11% of the patients had severe exacerbation within the last year, and 70.05% of them were poorly controlled at the time of the study. Incorrect inhaler technique was recorded in two aspects listed in the GINA guideline. In the present study, incorrect inhaler technique showed a strong relationship to uncontrolled status. Melani et al. discovered that between 12% to 43.5% of patients made at least one critical error in inhalation technique, resulting in hospitalizations or emergency department visits for 30% of them (134). The study revealed that various errors in device usage can affect the effectiveness of therapy differently. In real-life situations, incorrect inhaler technique could be a significant risk factor for losing asthma control and resulting exacerbations. This is because improper inhaler technique may lead to insufficient drug delivery, reducing the effectiveness of the medication.

On the other hand, improper inhaler technique may worsen drug adherence. Thus, educational programs, which are inexpensive and effective, may help in preventing the development of loss of asthma control (135,136).

GINA underlines the fact that low FEV1 is a strong independent predictor of future exacerbations. Our results are in concordance with these findings, both when low FEV1 is measured at the time of diagnosis or with maintenance therapy. However, our results suggest that patients are at higher risk of poor outcomes if their low FEV1 exists despite the use of maintenance therapy. Although we experienced low FEV1 in only 11.47% of our patients, it may be considered as a very strong predictor of uncontrolled status with an OR of 3.14. Interestingly, low initial FEV1 values also showed a significant relationship to loss of asthma control, with an OR of 2.21. Our results were consistent with those of Osborne and co-workers, who found that patients with low FEV1 at any time of their life are at a significantly higher risk of exacerbations, which underscores the importance of spirometry in asthma care (65). Notably in our study, the incidence of frequent OCS users was high, and despite the effective systemic effect of this medication, their control was significantly lower than average. In the CHAS study, González et al. observed a high level of uncontrolled asthma (63.9%) which was strongly associated with oral corticosteroid treatment (OR=6.55) (137). Patient adherence is essential in the management of all chronic disease. Our results still confirmed the well-established evidence of poor adherent patients having a high probability of an uncontrolled status (138–140). Three risk factors were identified in our study that affected a massive number of patients. The smoker group represented 33.38% of all the patients and was associated with suboptimal control, with an odds ratio (OR) of 1.47. Smoking is a common factor contributing to suboptimal asthma control and poses a risk for developing COPD. Among smokers, 13.1% were currently active smokers, with an OR of 1.58 (CI 1.42–1.76). Therefore, active smoking is considered a prevalent factor contributing significantly to suboptimal asthma control. Furthermore, for ex-smokers, the chance of poor outcome remains higher for a long time after quitting.

Many studies support an association between obesity and asthma prevalence (79–83,141). It has also been proved that patients with obesity are more likely to have uncontrolled asthma compared to eutrophic patients (84). Additionally, an association between obesity and increased asthma severity in adults has been demonstrated (85). The National Asthma Survey, one of the largest asthma surveys in the USA, showed that obesity is associated with several measures of asthma severity and control, including symptoms, missed

workdays, medication use, and GINA severity classification (86). In our study, the risk of an uncontrolled status was also higher due to obesity.

A history of rhinosinusitis or food allergy was especially prevalent amongst Hungarian asthmatic patients; however, it showed mild relationship with poor asthma outcomes. Inhaled allergens cause problems and symptoms at a specific time of the year. Therefore, we separately analysed the patient group who had seasonal allergies at the time of data registration. Out of 1786 patients who were examined in their sensitized allergen period, 44.62% had bad asthma control, which was higher compared to the rest of the patients and correlated significantly with a higher chance for bad asthma outcomes.

Finally, we identified infrequent risk factors as well which were less likely to worsen asthma control. Patients who had been pregnant in the last 12 months represented 0.34% of the cohort, but this condition had hardly any effect on current asthma control. At the time of enrolment, 43 patients were pregnant; however, due to the small number of participants, it was not possible to reliably determine what effect pregnancy had on current asthma state.

The risk of uncontrolled asthma was not associated with a lack of ICS. The reason for this may be that pulmonologists underestimate the lack of ICS resulting from non-adherence. On the other hand, there could be a patient population who used maintenance therapy as needed without losing control of their asthma. This hypothesis was supported by Papi et al., who found that patients with mild persistent asthma who have infrequent symptoms may not require regular treatment with inhaled corticosteroids (40).

As the results demonstrated, the presence of risk factors is associated with poor asthma control. The risk factors that appear more frequently than average and those which strongly linked to a poor outcome should be prioritized and monitored continuously.

5.3. Importance of pulmonary function test

While in everyday practice we focus heavily on symptoms, I think it is important to emphasise the importance of respiratory function parameters. Our study has shown that a low FEV1 at diagnosis is a risk factor for poor clinical outcome, and that if low FEV1 persists in spite of right choice of maintenance therapy, the likelihood of a non-controlled condition increases. For this reason, periodic follow-up pulmonary function tests (PFTs) are important and necessary tool in asthma management. However shortly after the onset

of the COVID 2019 pandemic, the number of PFTs was reduced drastically or even stopped in some places because there were concerns that forced breathing manoeuvres may increase the number of particles (droplet and aerosol) exhaled by the patient. In addition, atypical breathing can provoke coughing, which may also be associated with increased particle exhalation. As patients do not wear a facemask during PFTs, the chances of pathogen transmission may be increased. In order to assess this risk, we performed a real-life measurement of aerosol concentrations in a PFT laboratory to monitor the concentration of particles near the patient, and to model the associated potential viral load (129).

In our study two optical particle counters were used to sample the background concentration and the concentration of particles near the patient's mouth in a whole-body plethysmography box (129). Statistical evaluation of the measured particle concentration time series was completed. The particle exhalation rate was assessed based on the measured particle concentration data. The number of exhaled viruses by an infected patient during the test was compared with the emission of viruses during quiet breathing and speaking (129).

We found that PFTs are indeed aerosol-generating procedures. The number of viruses emitted during a PFT is approximately one order of magnitude higher than the number of copies emitted by quiet breathing, and of the same order of magnitude as the copies released during normal speaking. Therefore, the viral load of a PFT is only slightly higher than the viral load of a routine medical examination with the patient speaking without a mask (129).

Obviously, the risk of infection can be decreased by a series of preventive measures. All the relevant information on the examination and all the possible instructions, except coaching during the test to optimize the patient's effort, should be given before the test while the patient is wearing a facemask. Regular ventilation (ventilation systems providing fresh air are advised instead of recirculators), use of air sterilizers with high filter efficiency and air turnover, frequent disinfection of the body box and the laboratory, use of disposable nose clips and mouthpieces/filters, longer turnaround time between testing, greater distance between the technician and the patient, and the use of facemasks (preferably FFP2) will all contribute to minimization of infection in the PFT laboratory.

This study's results reveal that the excess risk associated with PFTs is not negligible. However, our previous data also demonstrated that PFT measurements provide essential information regarding the patient's status. Therefore, in our opinion, discontinuing PFTs is not recommended. It is essential that all activities related to PFTs are conducted with preventive measures, ensuring all possible safety protocols are followed (129).

With the rise of telemedicine, remote pulmonary function testing could open new opportunities to perform more tests at lower costs and in a safer manner.

5.4. Implication of excessive SABA usage

The overuse of short-acting bronchodilators is an important risk factor for exacerbations and death. Our research team recently published a study result, among the patients who died, the prevalence of SABA over-users (≥3/year) was much higher than in the general study population (142). The risk associated with high SABA use had been investigated also in the SABINA study, which found that 3–5 dispensation of SABA canisters a year was associated with a significant increase in mortality risk (143).

These results confirm that the overreliance on SABA by patients and the underestimation of its risks by healthcare professionals generate a serious problem for a certain patient population, which urges proactive steps to exclude SABA-only therapy.

5.5. Prevalence and association of comorbidities with poor asthma control

In addition to risk factors, comorbidities are also increasingly recognized as crucial determinants of asthma management and prognosis. This prompted us to analyse specific comorbidities relevant to Hungarian patients for their prevalence and their association with poor asthma control.

The presence of asthma might increase the risk of certain comorbidities (18,144) that may worsen asthma symptoms and provoke acute flare-ups, especially if they are not treated appropriately (18,144–146). Thus, the GINA guidelines recommend assessing comorbidities before treatment modification if asthma control worsens (1). However, neither the GINA nor other guidelines provide detailed recommendations on the assessment of comorbidities or provide information on only a subpopulation of all asthmatic patients (147). In our study, we evaluated the prevalence of 18 different comorbidities, their distribution in the population and their associations with asthma

control levels. Our aim was to provide a comprehensive data set of the most prevalent diseases that can affect asthmatic patients and, simultaneously, to compare their effect on asthma treatment outcomes. Our results suggest that the populations most affected by diseases are older, obese women with a history of heavy smoking, or who are still active heavy smokers. The correlation between age and multimorbidity is well-known—due to the ageing of world population, the proportion of elderly people has increased steadily and, consequently, the global burden of diseases has increased. The older a patient is, the more likely they will develop another disease, resulting in a clustering of diseases in elderly patients (148). Most of the comorbidities assessed in this study showed an age distribution that fits the described trend, but there were some exceptions. Perennial and seasonal rhinitis showed an inverse trend, which does align with the known age distribution of allergic diseases (149). The proportion of patients diagnosed with perennial rhinitis was more than two thirds of all our patients, which is much higher compared with the general population, and even to subsets of asthmatic populations examined in earlier studies (150). One of the reasons behind this finding could be that unlike all other comorbidities, the reporting of perennial rhinitis was based on symptoms and self-reporting, and not on exact detection of allergies. This approach could lead to an overestimation of the disease prevalence. The higher proportion of female patients and the different prevalence of certain comorbidities are both well-documented aspects of asthmatic populations (11,151–153). Veenendaal et al. (154) examined the prevalence of comorbidities of more than 32 000 asthmatic patients and showed that females are affected by overall comorbidities at a higher rate compared with males, with significant differences in certain disease categories. Other studies have also presented a significant gender related difference in certain comorbidities, including hypertension, cardiovascular diseases, depression, osteoporosis, and allergic diseases (151–153). Most of our findings correlate with these data; however, in our study the prevalence of perennial rhinitis did not differ between the genders. The prevalence of GERD was markedly higher in females, contrary to the general population, where there is no difference between the genders (155). On the other hand, COPD was more prevalent in males, an outcome that might be due to the higher prevalence of male active smokers (156). AMI and atrial fibrillation were the only cardiovascular diseases that affected a higher percentage of male patients,

but these diseases had the lowest prevalence in our population (1.65% and 1.26%, respectively). These low values could have affected the accuracy of the calculations.

5.6. Impact of BMI and smoking on asthma

Two modifiable lifestyle risk factors, obesity and smoking, which are closely associated with asthma clinical outcomes and comorbidity manifestations, warranted a separate analysis due to their high prevalence in our country. Therefore, we analysed the influence of body mass index (BMI) and smoking habits on coexisting diseases and the asthma clinical outcomes.

Obesity is an important and thoroughly studied risk factor for asthma and a plethora of other diseases, such as hypertension, DM, and IHD among others (18,153). A very high proportion of our patient population was overweight (70%), even compared with the general Hungarian population, which is in the top 10 most obese countries in Europe (157). Due to the cross-sectional design of our study, it was not possible to determine whether obesity or asthma developed earlier in our patients. However, as our results show, obesity by itself worsens asthma control, and it is a well-known risk factor of other diseases, which makes asthma treatment even more difficult. It is paramount for patients to understand that maintaining a healthy weight is an important aspect of asthma control.

Smoking is not just an important risk factor for developing asthma; it is also one of the leading causes of preventable deaths in Hungary. Active smoking not only increases the risk of developing asthma but is also an important contributor to uncontrolled asthma (158). We observed dose-dependency in our findings, with a higher proportion of uncontrolled patients in the active, heavy-smoker groups. Perhaps the most interesting findings of our study were the results of the analysis of the effect of smoking on comorbid conditions. The prevalence of some diseases (like COPD) showed a clear, dose- and exposure-dependent correlation, which meant that the more a patient smoked, the more likely they were to have COPD; this increased risk was mitigated by smoking cessation. On the other hand, the effect of smoking status and exposure on the prevalence of some conditions showed a different pattern: in some cases, different smoking habits (for example, starting age, time of cessation, intensity of smoking, and overall exposure) lead to different coexisting conditions. For example, both IFG and DM had a higher prevalence in heavy, ex-smokers compared with all other groups. These data could mean that

different smoking habits could lead to different comorbidities, however we have to highlight that the differences could be caused by confounding variables not assessed in our study.

Comorbidities can affect asthma control for two distinct reasons. First, some comorbidities have similar symptoms as asthma. Among others, COPD and IHD could cause coughing, shortness of breath, and decreased physical fitness, all of which could be attributed to asthma and, as such, could result in a patient being classified as uncontrolled. This change of status may lead to escalation of therapy, which would not decrease the symptoms, because these are not caused by asthma. Keeping this chain of undesirable outcomes in mind, even the 2014 GINA guidelines recommended that physicians should check the treatment of comorbid conditions before treatment escalation an important recommendation still present in the GINA 2023 guideline (1). The results of our study underline the importance of this recommendation. Another way to influence disease control is through the modification or enhancement of the disease pathogenesis, or the decrease of the response to otherwise adequate asthma treatment. Smoking and, consequently, COPD worsens asthma through decrease of lung function and increase of exacerbation risk and modification of the inflammatory reaction. GERD can also increase exacerbation risk and promote bronchoconstriction (144). Allergic airway diseases, obstructive sleep apnoea, and psychopathologic conditions have also been reported to worsen asthma pathophysiology and decrease responsiveness to treatment (18,144). The findings in our study correlated with these data but due to the study design, it was not possible to distinguish the reasons behind worsening asthma control based on the aforementioned effects.

In summary, a systematic evaluation and appropriate treatment of asthma-associated comorbidities should be an integral part of asthma management, particularly for severe disease. Identifying and managing comorbidities can improve asthma control and outcomes.

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5.7. Strengths and limitations

Strengths:

The strength of the first study was the high number of enrolled patients, notably it has been the largest asthma study examining asthma control in Eastern Europe. Its validity is enhanced by the fact that the cohort was evaluated by specialist and patients were enrolled from all regions of Hungary. Another strength of this study is the large number of different comorbidities assessed through a wide spectrum of disease categories.

Limitations:

There are limitations originate from cross-sectional nature of the first study, which did not allow the follow-up of patients and made it impossible to assess time-dependent relationships between parameters. Regarding the first study data recording of poor adherence to treatment was lower than in other specific adherence-focused studies. Our method had limitations in recognizing all non-adherent patients, which may be the consequence of deficiencies in the collection of adherence data by specialists in everyday clinical practice. Another limitation of our study is that some comorbidities such as depression, anxiety, obstructive sleep apnoea, and bronchiectasis etc were not actively screened, which could impact on control status of moderate to severe asthma patients.

6. Conclusions

Our study which has been the largest real-world study in Eastern Europe conducted by respiratory specialists found that 36% of patients have good control, while 34.7% have poor control. We observed that achieving high level of asthma control at the population level remains a challenge, with several negative implications for patients and significant economic and social impacts. The asthma control level hasn't improved since its launch, despite continuously advancing protocols and innovative therapeutic options. It is important to note that patients treated at higher treatment STEPs have a lower chance of achieving good control. Therefore, when clinicians increase the dose of ICS or add additional medications, it is worthwhile to intensify their efforts and monitor the patients more frequently. Our studies clearly demonstrated that the risk factors identified by GINA are closely associated with poor asthma control. Thus, it is of utmost importance to assess the full risk factor spectrum during specialist visits, in addition to assessing asthma control. The presence of any risk factors is associated with a higher proportion of patients with uncontrolled asthma, though these factors vary among patients. Among these, 5 risk factors should be taken more seriously and should receive special attention and proactive action during medical check-ups:

1. Incorrect inhaler technique 2. Exacerbation history 3. Excessive SABA use
4. Persistently low FEV1 5. Poor adherence to treatment

These risk-factors have outstanding association with poor asthma control. In order to further improve disease control, substantial attention might be paid to recognizing risk factors and address personalized interventions. Similarly to risk factors comorbidities also play important role in poor asthma outcome. COPD, IHD, DM, CVD, obese and smoker patients require a holistic approach, and their management needs close cooperation of relevant specialists. We have learned a lot and achieved significant success in the management of asthma patients over the past three decades. However, if we want to improve clinical outcomes further, we propose major strategic changes and see significant potential in the proactive introduction of digitalisation and telemedicine tools.

Based on these findings, there are suggestions for optimizing asthma management:

1. Labor force optimization: Respiratory specialists in Hungary, currently manage both challenging and straightforward cases, which create suboptimal allocation of time and resources. It is suggested that GPs are more involved in the management of non-

problematic patients (those who are controlled and lack of risk factors). This would allow GPs to become more familiar with asthma management, therapeutic choices, and patient education. By involving GPs in managing ‘easy to control’ patients, specialists would have more time and efforts to allocate on more complex uncontrolled patients who require more frequent, longer, and more detailed visits.

2. Structured analysis for uncontrolled patients: For uncontrolled patients, a structured analysis of risk factors and comorbid conditions is needed in everyday practice. The necessary digital and analogue tools should be developed and implemented.

3. Monitoring SABA prescriptions and banning SABA monotherapy: Due to the mortality risk, SABA prescriptions need to be monitored. For example, if a second SABA prescription is needed, the GP should refer the patient to a specialist. Further SABA prescriptions would require a specialist's recommendation. SABA therapy alone should be banned, and only SABA containing ICS should be available.

4. For patients with low FEV1 or high variability, frequent remote pulmonary function testing using portable spirometers is worth considering as it provides a new opportunity to follow up with these patients.

5. Monitoring adherence advanced way: Adherence can be partially monitored through the National eHealth Infrastructure (EESZT), as information on medication dispensing is available for each patient. However, information on the time distribution and frequency of use is not available. In the future, digitized inhalers (integrated in telehealth platforms) could be used to accurately monitor the amount of drug used.

6. Increase the rate of proper inhaler technique: Few substances are available for asthma management. The challenge is not the number of substances but the variety of available inhalation devices. The wide choice of devices is counterproductive because each device requires a different breathing manoeuvre to achieve sufficient lung deposition. Our research group is working on a diagnostic and educational tool to provide personalized recommendations to maximize lung deposition.

7. Involving asthma patients in rehabilitation programs: Rehabilitation could greatly contribute to better asthma control, as rehabilitation programs include breathing exercises, respiratory muscle training, learning controlled breathing techniques, sputum mobilization, ensuring proper oxygenation, endurance training, patient education, dietary counselling, psychosocial support, and, if applicable, assistance in smoking cessation.

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7. Summary

GINA guidelines and local national asthma protocols help in the effective clinical management of asthma. One of the most important aims of asthma treatment is to achieve and maintain long-term control of the condition. Since the goal to achieve asthma control was set in 1995, asthma management has improved substantially. Plenty of new innovative drugs had become available, additionally successful new therapeutic approaches and posology were developed. In spite of enormous efforts, satisfactory asthma control still remains an unmet need worldwide.

Our aim was to identify the key determinant factors of unsatisfactory control level. Our study provided data about the level of asthma control among Hungarian asthma patients on large patient population and investigated the prevalence, and association of certain risk factors and comorbidities with uncontrolled status. Our cross-sectional real-life study involved 12 743 Hungarian asthma patients, revealing that 36% had well-controlled asthma, 29.29% were partially controlled, and 34.71% were uncontrolled. The study confirmed that the frequencies and associations of the listed risk factors with poor control vary widely. Excessive SABA use, a yearly exacerbating disease pattern, improper inhaler technique, and low FEV1 (<60% predicted) were most strongly related to suboptimal disease control. Besides these risk factors, we evaluated the prevalence of 18 different comorbidities. Each comorbidity, with the exception of prostate hyperplasia, showed a statistically significant impact on asthma control levels. COPD, IHD, CVD, seasonal rhinitis, CV, and DM had very strong associations with poor asthma control.

Our observation is that in daily practice, selecting the right medicine, posology, and doses receives high emphasis. However, several other important clinical features, including risk factors and comorbidities, fundamentally modify the final clinical outcome. Without focusing on these factors there is a ceiling of achievable control level which have several negative implications. In our work, we identified the key determinant factors of unsatisfactory control levels, which is a crucial first step. Based on these results, we then created suggestions to develop strategies aimed at improving asthma clinical outcomes.

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9. Bibliography of the candidate's publications

Aggregate impact factor of the candidate: **84.699**
Aggregate impact factor of original publications on the subject of the thesis: **16.047**

Relevant publications grounding the thesis:

1. **Tomisa Gábor**, Horváth Alpár, Szalai, Zsuzsanna, Müller, Veronika, Tamási Lilla.
Prevalence and impact of risk factors for poor asthma outcomes in a large, specialist-managed patient cohort: a real-life study
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