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ASTHMA MEDICINE UTILIZATION IN CHILDREN

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LIST OF ABBREVIATIONS

ATC - Anatomical Therapeutic Chemical Classification

CDC - the Centers for Disease Control and Prevention

COPD – Chronic Obstructive Pulmonary Disease

EU – European Union

FDA - Food and Drug Administration

FEV1 - Forced Expiratory Volume

FVC - Forced Vital Capacity

GBD - Global Burden of Disease

GDP – Gross Domestic Product

GINA – Global Initiative for Asthma

ICS – Inhaled corticosteroids

LABA – Long-acting beta2-agonists

LTRA – Leukotriene Receptor Antagonists

NCD - Noncommunicable Disease

NF-κB - Nuclear Factor-κB

NHIF - The National Health Insurance Fund

pMDIs - Pressurized metered-dose inhalers with valved holding chambers

SABA – Short-acting beta2-agonists

WHO – World Health Ogranization

SUMMARY

Background: Asthma is a prevalent respiratory condition that impacts both children and adults worldwide. Numerous studies have investigated medication utilization to enhance the understanding of pediatric asthma management. However, there is limited information regarding asthma medication use among Lithuanian children. This study aims to elucidate the trends in asthma medication utilization among Lithuanian pediatric patients, ultimately contributing to improved asthma management strategies.

Aim: To investigate the prevalence and incidence of Asthma medicine use in children and adolescents between 0 and 17 years in Lithuania from 2014 to 2019.

Research objectives:

1. To assess the incidence of asthma medications among boys and girls in different age groups.
2. To assess the prevalence of asthma medications among boys and girls in different age groups.
3. To assess how the incidence and prevalence of different asthma medicines have changed from 2014 to 2019.
4. To assess frequency of different asthma medicine combinations dispensed.

Methodology: In this study, the annual asthma medicine utilization trends were calculated and expressed using prevalence and incidence per 1000 inhabitants per year and in percentages. Dispensing data of anti-asthmatic drugs were collected from the Compulsory Health Insurance Information System "Sveidra".

Results and conclusions: Throughout the study period of 2014 -2019 in Lithuania the incidence and prevalence decreased. The incidence of asthma medication was the highest in 0-5 male and female groups throughout the study period of 21 and 14 per 1000 inhabitants per year, respectively and moving to adolesence years asthma medication inidence got lower in both, males and females. Incidence of asthma medication from to 2015 to 2019 decreased by 15.24% (from 15 down to 14 per 1000 inhabitants) and 7.11% (from 10 down to 9 per 1000 inhabitants). Prevalence of asthma medication from to 2014 to 2019 decreased by 23.53% (from 51 down to 39 per 1000 inhabitants) and 25% (from 32 down to 24 per 1000 inhabitants) in males and

females, respectively. Moreover, SABA had the highest incidence in 2015 and prevalence in 2014 of 1.44% and 4.17%, respectively, however in 2019 the incidence and prevalence was the higest of LABA of 1.24% and 3.10%, respectively, in the youngest age group of males aged 0-5 years old. In 2014 the most dispensed asthma medications in combination were ICS+LABA fixed combination with SABA and LABA, however there were notable change throughout the study years and in 2019 the most dispensed asthma medications in combination were only SABA and LABA. In conlusion, this study results show that there is room for improvement in asthma medication utilization in children, as analysed trends show that in Lithuania asthma medication utilization does not reflect the ones in current international recommendations.

SANTRAUKA

Pagrindimas: Astma yra plačiai paplitusi kvėpavimo takų liga, nuo kurios kenčia ir vaikai, ir suaugusieji visame pasaulyje. Siekiant geriau suprasti vaikų astmos gydymą, atlikta daugybė tyrimų, kuriuose nagrinėtas vaistų vartojimas. Tačiau informacijos apie vaistų nuo astmos vartojimą tarp Lietuvos vaikų yra nedaug. Šiuo tyrimu siekiama išsiaiškinti Lietuvos vaikų pacientų vaistų nuo astmos vartojimo tendencijas ir galiausiai prisidėti prie geresnių astmos valdymo strategijų.

Tikslas: Ištirti vaistų nuo astmos vartojimo paplitimą ir dažnumą tarp 0-17 metų vaikų ir paauglių Lietuvoje 2014-2019 m.

Tyrimo uždaviniai:

1. Įvertinti astmos vaistų vartojimo dažnumą tarp berniukų ir mergaičių skirtingose amžiaus grupėse.
2. Įvertinti astmos vaistų vartojimo paplitimą tarp berniukų ir mergaičių skirtingose amžiaus grupėse.
3. Įvertinti, kaip keitėsi dažnumas ir paplitimas skirtingais vaistais nuo astmos nuo 2014 m. iki 2019 m.
4. Įvertinti išduodamų skirtingų vaistų nuo astmos derinių dažnį.

Metodika: Šiame tyrime apskaičiuotos metinės vaistų nuo astmos vartojimo tendencijos ir išreikštos naudojant paplitimą ir sergamumą 1000 gyventojų per metus bei procentais. Vaistų nuo astmos išdavimo duomenys buvo surinkti iš Privalomojo sveikatos draudimo informacinės sistemos "Sveidra".

Rezultatai ir išvados: Per visą 2014-2019 m. tyrimo laikotarpį Lietuvoje sergamumas ir paplitimas mažėjo. Per visą tiriamąjį laikotarpį didžiausias astmos vaistų dažnumas buvo 0-5 metų amžiaus vyrų ir moterų grupėse, atitinkamai 21 ir 14 atvejai 1000 gyventojų per metus, o pereinant į paauglystės amžių astmos vaistų dažnumas mažėjo tiek tarp vyrų, tiek tarp moterų. Nuo 2015 m. iki 2019 m. astmos vaistų dažnumas sumažėjo 15,24 % (nuo 15 iki 14 atvejų 1000 gyventojų) ir 7,11 % (nuo 10 iki 9 atvejų 1000 gyventojų). Vaistų nuo astmos vartojimo paplitimas nuo 2014 m. iki 2019 m. tarp vyrų ir moterų sumažėjo atitinkamai 23,53 % (nuo 51 iki 39 1000 gyventojų) ir 25 % (nuo 32 iki 24 1000 gyventojų). Be to, 2015 m. didžiausias dažnumas trumpo veikimo beta-2-agonistai ir paplitimas 2014 m. buvo atitinkamai 1,44 % ir 4,17 %, tačiau 2019 m. didžiausias dažnumas ir paplitimas buvo ilgo veikimo beta-2-agonistai - atitinkamai 1,24 % ir 3,10 % jauniausioje 0-5 metų amžiaus vyrų grupėje. 2014 m. daugiausiai išduodamų

vaistų nuo astmos derinyje buvo inhaliuojamų kortikosteroidų ir ilgo veikimo beta-2-agonistų fiksuotas derinys su trumpo veikimo beta-2-agonistais ir ilgo veikimo beta-2-agonistais, tačiau per visus tyrimo metus buvo pastebimų pokyčių ir 2019 m. daugiausiai išduodamų vaistų nuo astmos derinyje buvo tik trumpo veikimo beta-2-agonistais ir ilgo veikimo beta-2-agonistais. Apibendrinant galima teigti, kad šio tyrimo rezultatai rodo, jog vaikų astmos medikamentų vartojimą dar reikia tobulinti, nes analizuotos tendencijos rodo, kad Lietuvoje astmos medikamentų vartojimas neatspindi dabartinėse tarptautinėse rekomendacijose pateiktų.

1. INTRODUCTION

Asthma is a chronic lower respiratory tract inflammation. The definition and pathophysiology of asthma are becoming better understood scientifically, and it is crucial for healthcare professionals who treat upper or lower airway inflammation to be knowledgeable about these topics (1). According to the Global Burden of Disease (GBD) study, 339 million people worldwide were estimated to have asthma in 2016. Age-standardized prevalence has increased by 3.6% since 2006 (2). The prevalence of asthma is estimated to be 9.6% among children 5-11 years old and 10.5% among children 12-17 years old, according to the Centers for Disease Control and Prevention (CDC) 2016 report (3). A significant portion of children with asthma exhibit severe symptoms despite undergoing standard treatment, highlighting the need for more effective therapeutic options to address this issue. This phenomenon forms the basis for further research and investigation, with the aim of improving outcomes for these children (3). Through the use of low to moderate dosages of inhaled corticosteroids, the majority of children with asthma have effective symptom management. A subset of children with severe asthma may require greater doses of inhaled corticosteroids and extra controller medication to establish and maintain symptom control (2). Poor adherence of prescribed inhaled corticosteroids has been associated to increased morbidity and mortality. Efforts to promote drug adherence have met with modest success, but the efficacy of these interventions is uneven, even when identical approaches are employed (4). The improper use of medicine delivery systems is a significant factor in poor asthma symptom management. A study of children with asthma between the ages of 8 and 16 indicated that only a small percentage (8.1%) administered their metered dose inhaler correctly (3). For almost 10 years, tiotropium, a long-acting anticholinergic bronchodilator, has been prescribed for chronic obstructive pulmonary disease (COPD). Global initiative for asthma (GINA) guidelines recommend tiotropium mist inhaler at Steps 4 and 5 for individuals over 12 with uncontrolled asthma despite inhaled corticosteroids (ICS) and long-acting beta2-agonists (LABA) treatment (3).

Children from urban minority groups are more likely to develop health issues from poor asthma control compare to those who live in rural areas. This group is more susceptible to poorer asthma control and morbidity due to factors related to urban living, including exposure to urban stressors like violence, neighborhood stress, environmental irritants and allergens, poorer medication adherence, and cultural factors related to ethnic background (5). The occurrence of severe, early-life respiratory illnesses across populations have been linked strongly to the occurrence of childhood asthma or recurrent wheezing in epidemiological studies (6). Coughing, wheezing, and

pressure in the chest are common pediatric symptoms. Only 40% of preschoolers who exhibit these symptoms will continue to have asthma after the age of six, despite the fact that one third of all preschoolers do (7). An increased risk of asthma exacerbations is also strongly correlated with poor symptom control. At every opportunity, including during routine prescribing or dispensing, asthma symptom control should be evaluated (8). As with adults, evaluation of asthma symptom control in children is based on symptoms, activity restriction, and use of rescue medication. It's crucial to carefully assess how asthma affects a child's daily activities, such as sports, play, and social interactions, as well as school absences. Since many kids with poorly controlled asthma stay away from vigorous activity, their asthma may seem to be under control. This could result in inadequate fitness and an increased risk of obesity (8).

Over the past 20 years, studies conducted on general populations at the national and international levels have helped us better understand the burden of pediatric asthma on society. Epidemiological studies have used standardized questionnaires to define the prevalence of asthma rather than relying on physician diagnoses (9). This study will show asthma medication prevalence and incidence in Lithuania by analyzing data collected from compulsory health insurance information system "Sveidra"to get a better understanding of asthma in children in Lithuania as there is little information about this topic.

In this Master’s Thesis, the student independently reviewed the literature, with supervisors’ guidance formulated project’s aim and objectives, performed a descriptive statistical analysis, presented the results and compared them with previous similar studies, as well as made the conclusions.

2. LITERATURE REVIEW

2.1 Asthma disease

2.1.1 Definition

According to GINA, asthma is a heterogeneous disease that typically manifests as chronic airway inflammation. It is characterized by a history of respiratory symptoms, such as wheezing, shortness of breath, chest tightness, and cough, that vary in time and intensity, as well as variable expiratory airflow limitation (8).

2.1.2 Existing knowledge of asthma

Respiratory diseases are the leading cause of death and morbidity worldwide and a significant burden on health (8). Asthma is the most frequent chronic respiratory disorder. In 2015, these disorders were rated among the world's top 20 causes of disability (8). Northern and Western Europe, Brazil, and Australia have the highest prevalence of asthma in the worldwide, according to the 2018 Global Asthma Report (2). Asthma is estimated to have one of the greatest economic impact for the healthcare system among chronic diseases due to the substantial healthcare utilization associated with this condition (10). Described since Hippocrates, asthma affects people from all age groups. The term "asthma" derives from the Greek for "shortness of breath," indicating that every patient with shortness of breath had asthma (11). Asthma is often caused by various allergenic triggers such as house dust mites, molds, pets with fur, cockroaches, and rodents, and outdoor allergens, such as pollens and molds (12). This disorder is characterized by recurring episodes of shortness of breath and wheezing, especially at night or early in the morning, and chest tightness in susceptible patients (13).

2.1.3 Epidemiology

The World Health Organization (WHO) states that asthma is a significant noncommunicable disease (NCD) that affects both children and adults and is the most prevalent chronic illness in children (14). According to WHO in 2019, asthma affected an estimated 339 million people and was responsible for 450,000 deaths (14). A study performed in the United States showed that 46% of the children reported wheezing before the age of two, and 26% reported chronic wheezing through the age of eleven. Children born in neighborhoods with a higher proportion of low-income households, population density, and poverty had a higher incidence of asthma (15). Studies of both children and adults have indicated a broad difference in prevalence rates: low

prevalence rates (2–4%) in Asian countries (particularly China and India) and high prevalence rates (15–20%) in the United Kingdom, Canada, Australia, New Zealand, and other industrialized nations (16). Asthma is more prevalent in high-income nations, but the majority of asthma-related deaths occur in low to middle-income countries (17). Throughout the 20th century, a rapidly increasing trend of asthma prevalence has been observed in comparison to data from 50 years ago, when asthma was documented in 2% to 4% of the population, but modern data indicates that 15% to 20% or more of the general population has asthma (18). According to reports of Statista from 2019, Portugal and Sweden were the counties in European Union (EU) with the highest asthma prevalence, with around 9.9 percent and 8.2 percent of their respective populations affected. In contrast, Lithuania and Estonia had the lowest incidence rates, with 2.9% and 2.2% respectively. In the EU as a whole, the average prevalence was little over 6% (19). The incidence and prevalence of asthma vary between children and adults. Some people get asthma for the first time as adults, despite the fact that asthma is typically diagnosed during childhood. Although asthma is more prevalent in children, adult rates of healthcare consumption and mortality due to asthma are higher. In addition, the incidence and prevalence of asthma vary by gender and age among males and females (17). Females have a higher incidence of asthma compared to males until well into their fifth decade of life. However, this disparity in asthma burden between the sexes begins to diminish in the later stages of the fifth decade. Some studies even suggest a reversal in the asthma incidence differential, with a marked increase in the incidence of asthma among males around the fourth decade of life. The temporal relationship between the shift in asthma burden and major reproductive events provides evidence to suggest that hormones play a role in the etiology of asthma (17). The estimates of global asthma prevalence according to the GBD have shown significant fluctuations between consecutive reports: 334.2 million in 2010 (20), 220.4 million in the year 2000 (21), 241.7 million in 2013(22), and 272.7 million in 2017 (23). The reason behind the substantial differences, ranging up to 109 million, in the 2010 and 2017 data is unknown, but it is believed to stem from alterations in the analytical techniques as no standardized data of significant scale on asthma prevalence was obtained during this time frame.

2.1.4 Asthma classification

The GINA based on a person's symptoms, lung function, and responsiveness to treatment, they have devised a grading system for the severity of asthma. GINA classifies asthma severity into four categories: intermittent, mild persistent, moderate persistent, and severe persistent. The severity of an individual's asthma is defined by their symptoms and pulmonary function.

Intermittent asthma is the least severe form of the disease. Intermittent asthma is less severe than mild chronic asthma. People with mild chronic asthma may need to take a daily medicine to regulate their symptoms. The next severity category is chronic asthma with moderate severity. People with this form of asthma experience daily symptoms and may require many medications to control them. Additionally, they may need to utilize their rescue inhaler more frequently. This condition's most severe form is severe chronic asthma. Multiple drugs are ineffective in controlling the daily symptoms of those with severe chronic asthma. They may also experience frequent exacerbations, or spells of worsening symptoms, that necessitate immediate medical care.

It is crucial to remember that a person's asthma severity might alter over time. Patients with asthma must collaborate closely with their healthcare practitioner to manage their illness and prevent exacerbations (8).

2.1.5 Economic impact of asthma

The number of individuals suffering from asthma around the world increases, so do the economic consequences connected with the condition. For instance, the overall cost of asthma treatment in children and adults in the United States was estimated to be $56 billion in 2007, a 5.7% rise from 2002 (24)**.** The financial impact of asthma is considered to be significant, particularly in terms of the strain it places on healthcare services. Asthma is considered to be one of the most costly chronic conditions, in part because it requires ongoing medical care and treatment. This can put a strain on healthcare resources, resulting in higher costs for individuals, families, and the healthcare system as a whole (25)**.** A study that looked at the costs of asthma in children and adults found that the overall indirect costs of the condition were higher for children. This was due, in part, to the fact that parents of children with suboptimal asthma control often had to miss work in order to care for their child, which added to the economic burden of the condition. These findings suggest that better management of asthma in children could help reduce the economic costs associated with the condition (26)**.** In Western Europe, 43% of children diagnosed with asthma have missed school days because of their asthma (30). While there is no direct evidence that asthma impacts academic achievement, missing school can affect a child's social development and may indirectly impact their academic performance. These findings highlight the need for effective management of asthma in children to help prevent them from missing school and potentially impacting their education, however in this particular study it does not state how many days of school has been missed (27)**.** In the United States, 59% of children and 33% of adults who had an asthma attack missed school or work in 2008 because of their symptoms (28). In high-income countries, 1-2% of the healthcare budget is typically allocated to pediatric asthma

(29)**.** Reducing the global burden of asthma is challenging due to several barriers, such as limited healthcare resources and poor public education on asthma. Many governments do not prioritize asthma in their healthcare systems, and patients in developing countries often have limited access to care and essential medications. These challenges make it difficult to effectively manage asthma and improve outcomes for people with the condition (29)**.**

2.1.6 Diagnosis of asthma

The first step in diagnosing asthma is to obtain a thorough medical history, which includes details about the pattern of respiratory symptoms, triggers for coughing, wheezing, shortness of breath, and chest tightness, previous treatment and response to treatment, and family history of asthma or other respiratory conditions (30). As well, allergy testing is an important part of diagnosing asthma, and should include a review of the patient's medical history, skin prick tests, and blood tests. Other tests, such as measuring exhaled nitric oxide levels, may also be recommended in some cases (31). The evaluation of a patient's condition may include using spirometry to measure lung function, following standardized criteria established by the American Thoracic Society (ATS) (32). It is essential to recognize that children with severe asthma frequently exhibit normal lung function or may only exhibit mild airflow limitation in the absence of acute exacerbations. The spirometric index most likely to be abnormal in these cases is the ratio of forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) which the normal value for this ratio is above 0.75 (33). Therefore, in cases where the diagnosis of asthma remains uncertain, further testing such as bronchoprovocation with methacholine or exercise challenge may be indicated to assess for airway hyperresponsiveness and establish a definitive diagnosis. These tests can provide valuable information in challenging cases (34). Evaluating severe asthma should involve identifying triggers for the condition, such as aeroallergen sensitization and rhinosinusitis. It is uncommon for children with severe asthma to not be sensitized to aeroallergens. In most cases, more than 85% of patients with severe asthma are sensitive to at least one allergen, and most are sensitive to multiple allergens (35). However, despite the diagnostic options, underdiagnosis and undertreatment are prevalent among adolescents (36).

2.2 Pharmacological management of asthma

According to the GINA, the primary goals of asthma management are to establish adequate symptom control and lower the future risks of asthma-related mortality, asthma exacerbations, persistent airflow limitation, and treatment-related adverse effects (8).

GINA advocates a step-by-step strategy to controlling asthma with medication, increasing the dosage (stepping up) when necessary and decreasing it (stepping down) when practicable (8). The treatment of asthma is chosen by a comprehensive assessment that considers the amount of asthma control, modifiable factors (such as risk factors and comorbidities), lung function, and the patient's preferences (8).

According to GINA, the majority of patients with asthma require two types of medication: quick-relief (or "reliever") medications and long-term control (or "maintenance") medications (also known as "controllers"). Initial treatment decisions for asthma are based on the patient's symptoms, lung function, and modifiable risk factors; ongoing treatment decisions are based on the patient's reaction to treatment and any necessary changes (8).

In 2019, GINA undertook a comprehensive evaluation of the evidence regarding the adverse consequences of utilizing short-acting beta2-agonists (SABAs) as the sole treatment for asthma and the impact of ICS on asthma exacerbations and fatalities in individuals with moderate asthma. GINA determined, based on this analysis, that there is currently adequate evidence to recommend that adults and all children from 6 years old with asthma not be treated with SABAs alone. To lessen the likelihood of severe exacerbations, they should receive either symptom-driven treatment (in mild asthma) or daily ICS-containing medication (8).

The three main categories of pharmacological options for long-term treatment of asthma, as defined by GINA, are: controller medications, reliever (rescue) medications and add-on therapy (8). In the 1960s, the introduction of SABA revolutionized the way asthma symptoms were managed in the short term. These medications provide quick relief from acute symptoms and can be easily carried around in a portable device. Unlike previous systemic therapies, SABAs have fewer side effects, making them a safer and more effective treatment option for patients (8). The main aim of managing asthma over the long term is to reduce symptoms and prevent serious complications, such as death from asthma, worsening of symptoms (exacerbations), ongoing breathing problems, and negative effects from treatment (8).

According to GINA, the overarching goals of managing asthma are:

To ensure that patients experience minimal symptoms and can maintain their usual level of activity

- To reduce the risk of complications such as death from asthma, worsening of symptoms, ongoing breathing problems, and negative effects from treatment (8).

Many asthma patients can manage their symptoms and avoid exacerbations with regular use of controller medication, but some may not experience the same level of success, even with the most intensive treatment (37). This underscores the need for personalized care and ongoing monitoring to ensure that patients are receiving the most effective therapy for their specific needs. In certain individuals, inadequate symptom control and frequent exacerbations may be due to the presence of severe asthma. However, in other cases, the underlying cause may be related to comorbid conditions or ongoing exposure to environmental triggers (8). According to GINA, adolescents and adults with asthma should receive a combination of low-dose ICS and a long-acting beta-agonist (formoterol) as needed, to prevent serious exacerbations and control symptoms. GINA no longer recommends using SABA alone for asthma treatment. This recommendation is based on the evidence that a combination of ICS and formoterol is more effective at preventing exacerbations and controlling symptoms than SABA alone (38). The goal of managing asthma is to achieve symptom control and improve the patient‘s overall quality of life related to asthma (38). The ideal outcome of asthma management in children is to achieve a state of minimal or no asthma-related symptoms, a low dependence on rescue medications, few or no exacerbations, and the ability to engage in all daily activities, including physical exercise, without any limitations (8). Optimizing asthma control and quality of life in children should be pursued through the judicious use of medications, striving for the lowest possible dosage and frequency of use (39).

2.2.1 Controller medication

Inhaled corticosteroids

Inhaled corticosteroids are by far the most effective asthma controllers and the only medications that can effectively suppress the characteristic inflammation in asthmatic airways, even at relatively low doses (40). The introduction of ICS in asthma management has led to significant improvements in both symptom control and lung function, as well as a reduction in exacerbations and asthma-related deaths (8). A substantial portion, 50-90% when inhalation technique is poor, of ICS dose may be deposited in the mouth and throat upon inhalation of a drug, which could induce local side effects if not eliminated by rinsing the mouth (41). In addition, this portion of the dose may be swallowed and absorbed in the gastrointestinal tract,whichch can lead to systemic side effects if the medication escapes the liver's first-pass metabolism (41). While the amount of the ICS dose that reaches the lungs has the desired therapeutic effect, a significant percentage of the dose can also be absorbed into the general circulation via the pulmonary

vasculature, resulting in the possibility for systemic adverse effects (41). The primary function of corticosteroids is to suppress the expression of various genes that produce inflammatory compounds such as cytokines, chemokines, adhesion molecules, and enzymes. These genes are activated in the airways by proinflammatory factors like nuclear factor-κB (NF-κB) and activator protein-1, which are commonly found in asthmatic airways and activate these genes by interacting with coactivator molecules like CREB-binding protein, which have the ability to modify histones (40).

It has been proven through short-term and long-term studies in both adults and children that ICS are effective, however, there are still concerns about potential side effects, particularly in children and when high doses are used. There are various side effects that have been identified such as dysphonia, cough, oropharyngeal candidiasis (40). As shown in other studies inhaled corticosteroids can have a negative effect of growth decline. In children with mild to moderate persistent asthma, utilizing ICS on a regular basis at daily doses that are low to medium results in a decline in linear growth velocity of about 0.48 cm per year and a change of 0.61 cm on average from the baseline height over the course of one year (42). There is growing evidence that vitamin D may play a role in the onset of allergic disorders and asthma, however it is unknown whether taking vitamin D supplements throughout childhood may enhance the outcome. The use of corticosteroids has been linked to a decrease in vitamin D levels (43).

Leukotriene receptor antagonists

Leukotriene receptor antagonists (LTRAs) constitute a class of pharmaceutical agents employed as a prophylactic treatment for asthma. These medications are typically prescribed as supplementary therapy for patients in whom acute symptoms and exacerbations of asthma remain inadequately controlled through the use of inhaled corticosteroids (44). In Lithuania, montelukast is the only LTRA that has been officialy approved. This drug functions by attaching to the cysteinyl receptor for leukotrienes D4 and E4, which play a crucial role in the inflammatory aspect of asthma (45). Montelukast has been shown to effectively reduce beta2-agonist use, asthma symptoms, blood eosinophils and increase morning peak expiratory flow in controlled studies. This suggests that the drug lowers eosinophilic airway inflammation and improves clinical symptoms in chronic asthma patients (46). The recommended dosage regimen according to the summary of product characteristics for montelukast in the treatment of asthma is as follows: for pediatric patients between the ages of 1 and 5 years, a 4 milligram chewable tablet, administered once daily. For pediatric patients between the ages of 6 and 14 years, a 5 milligram chewable tablet, administered once daily. For adult patients, a 10 milligram tablet, administered once daily (47). Long-term asthma management is regarded to be safe and effective with

montelukast, but United States Food and Drug Administration (FDA) and other agencies introduced a boxed warning on the montelukast packaging in March 2020 because to the possible severity of adverse events, particularly serious neuropsychiatric problems in children (48).

Long-acting beta2-agonists

LABA, have a longlasting bronchodilator effect. Due to the increased risk of severe asthma exacerbations, hospitalizations and fatalities associated with the use of LABA as a single therapy, it is only recommended to be used in conjunction with ICS (49). While the combination of ICS and LABA improves lung function, it does not decrease the number of asthma exacerbations. Additionally, no additional adverse effects have been observed except for better growth when using the combination therapy as compared to higher doses of ICS alone (50). There is limited knowledge about the effectiveness and safety of the use of LABA in children under the age of 5, and more research is necessary to understand how it works in this population (8). A fixed ICS+LABA combination may boost adherence, simplify asthma management, improve control, and reduce exacerbations, potentially preventing emergencies (8). However, ICS and LABA combination therapy may not yield optimal efficacy for all patients with asthma or COPD. Individuals presenting with severe asthma or exhibiting inadequate response to ICS+LABA treatment may necessitate alternative or adjunctive therapeutic approaches, such as biologic agents. While these biologics entail a higher financial burden, they have the potential to deliver superior clinical outcomes for this subset of patients (51,52).

2.2.2 Add-on therapy

Add-on therapy is used when a condition cannot be treated by a combination of controller drugs (8). The two biological treatments now available for children aged 6 and older are omalizumab and mepolizumab, which was recently approved for this age range by the European Medicines Agency (EMA). Gupta‘s et al. open-label uncontrolled research is the only source of information regarding the benefit-risk profile of mepolizumab in children aged 6 to 11 years (53). Omalizumab is suggested as a first-line add-on therapy for children with severe allergic asthma that is not properly managed (8). Omalizumab is a monoclonal antibody that prevents free IgE from connecting to receptors on the surface of immune cells by binding to free IgE (54).

2.3 Delivery methods for inhaled asthma medication therapy

There are three primary delivery devices utilized for administering inhaled therapy to the airways in children: pMDIs, dry powder inhalers, and nebulizers. While each of these methods has its own advantages and disadvantages, they remain the mainstay of treatment for this patient population (38).

Holding chambers can be used by children as young as 2 years old who have been taught how to use the mouthpiece (55). However**,** According to guidelines, it is recommended that children under 4 years old use a mask with a holding chamber (38)**.** The accumulation of electrostatic charge can significantly decrease the effectiveness of drug delivery through a holding chamber (56). Although dry powder inhalers are small and discreet, they can only be used effectively by children who are able to inhale at a rate of 30 to 60 liters per minute through the inhaler (57). Therefore, dry powder inhalers are often used in children from 6 years of age and above (38)**.**

Nebulizers, which are large and bulky, require frequent cleaning and take a longer time to deliver medication, offer little to no clinical benefit compared to other delivery systems. They are not recommended or commonly used for delivering asthma preventer medications and should not be considered as the first choice of delivery device (39).

Proper use of the delivery device and proper inhalation technique are essential for maximizing the effectiveness of aerosolized medication. However, even after receiving instruction, children often have suboptimal inhalation technique (58). It is important to note that children up to 6 years of age may not possess the necessary respiratory capacity to perform a single maximal inhalation upon request (59).

2.4 Previous studies on utilization of asthma medication in children

As explained by the CDC, incidence is the measurement of new cases of a disease or injury within a specific population over a specific period of time while prevalence, also known as the prevalence rate, is the measurement of the proportion of people in a population who have a specific disease or attribute at a particular point in time or over a specific period of time. It is different from incidence, as it takes into account all cases of the disease or attribute, including both new and existing cases in the population, whereas incidence only considers new cases (60). These measures can also be applied using drug dispensing data, with incidence being the proportion of people starting to purchase a specific drug and prevalence the proportion being dispensed the drugs during a certain time-wondow (61). A Norwegian study conducted by Karlstad et al. has shown that the annual prevalence of anti-asthma medication increased slightly during a three-year period, from 5.6% to 5.9% in males and 4.9% to 5.0% in females. The increase was most notable in children 12 years and younger, and the highest increase was in 2-5 year old males. The highest prevalence was found in 2-year-olds at 13% for males and 9% for females, but decreased by half by age 10. The prevalence dropped further in males during adolescence, stabilizing above 3% from age 20. In contrast, females had a rising prevalence during adolescence and had a higher prevalence than males from age 16 onward, the incidence

was 1.5% for both males and females, however, females had a higher incidence than males from age 14. Using shorter run-in periods (a phase in clinical trials where participants receive the same treatment to establish a baseline, stabilize conditions, and exclude non-adherent individuals), the incidence increased to 2.3% and 1.7% for 1 and 2 year run-in periods, respectively (62). These findings suggest that incidence and prevalence of anti-asthma medications varies with age and gender. A Belgian study has shown that in 2018, Salbutamol, the most commonly dispensed asthma medication for children in Belgium, was prescribed to 6% of children in the database. Ipratropium and Budesonide were the second most commonly prescribed medications, both at 4% (63). The reason for the higher incidence and prevalence of asthma medication usage in younger children could be due to the use of these medications for other conditions such as bronchiolitis, wheezing, or cough (64). Multiple studies have revealed a consistent trend that boys are more commonly affected by asthma. A meta-analysis for instance has demonstrated that boys are more likely to have asthma (65). This could be explained by the diameter of the airways of young boys in relation with their lung volume, which is smaller than for girls. Due to this, young boys are more likely to present airway obstruction (66). Previous studies on the utilization of asthma medications in children have found that, in a sample of 331 adolescents with asthma, 53% (n = 176) experienced fully controlled asthma, while 47% (n = 155) suffered from uncontrolled asthma (67). A study conducted to investigate sex differences in factors associated with childhood and adolescent-onset wheeze. The study found that boys were more likely to develop wheezing in early childhood, while girls had a higher risk of developing wheezing during adolescence. Importantly, the study observed that girls with asthma were more likely to have uncontrolled symptoms compared to boys. These findings suggest that sex differences exist in the development and control of asthma symptoms in children and adolescents, highlighting the importance of considering gender in the management of pediatric asthma (68). The Lithuanian Sveidra database provides a valuable resource for conducting longitudinal assessments of dispensed medications. Despite its potential, there have been no studies to date that specifically analyze patterns of asthma medication use among children in Lithuania.

Aim: To investigate the prevalence and incidence of Asthma medicine use in children and adolescents between 0 and 17 years in Lithuania from 2014 to 2019.

Research objectives:

1. To assess the incidence of asthma medications among boys and girls in different age groups.

2. To assess the prevalence of asthma medications among boys and girls in different age groups.
3. To assess how the incidence and prevalence of different asthma medicines have changed from 2014 to 2019.
4. To assess frequency of different asthma medicine combinations dispensed.

3. METHODS

3.1 Study design

This was a cross-sectional study researching the asthma medication prevalence and incidence in children of different age and sex groups and the frequency of different asthma medicine combinations.

3.2 Setting

The study was conducted in the Republic of Lithuania, a Baltic country of Northeastern Europe with a population of 2.8 million permanent residents. According to the data of the Lithuanian Institute of Hygiene, from 2014 to 2019, in total 164,817 children of which 103,625 were male and 61,165 were female were diagnosed with an asthmatic condition (69). The prevalence of asthma increased significantly in the population of people between the ages of 15 and 24 in Lithuania between the years of 2014 and 2019. In males, the prevalence was 1.7% in 2014, compared to 2.6% in 2019, and in females, it was 2.2% in 2014, compared to 3.6% in 2019, meaning that there was a 0.9% increase for men and a 1.4% increase for women in this population (70).

The total population of Lithuanian children age from 0 to 17 years old during the study period from 2014 to 2019 (Table 1) reveals fluctuations in population size within each age and sex group, with the Male 0-5 group showing a decline from 92,232 in 2014 to 90,561 in 2019, and the Female 12-17 group decreasing from 93,851 in 2014 to 75,241 in 2019.

Table 1 Lithuanian children population stratified in different age and sex groups (2014-2019)

Age group	2014	2015	2016	2017	2018	2019
Male 0 - 5	92232	92587	92882	92437	91403	90561
Male 6 - 11	81787	82339	83334	84245	85339	86720
Male 12 - 17	99102	94040	89625	85084	81193	78690
Female 0 - 5	87727	88141	88198	87532	86716	85962
Female 6 - 11	77948	78623	79738	80388	81139	82401
Female 12 - 17	93851	88743	84424	80702	77225	75241

Lithuania has a single-payer compulsory health insurance system - The National Health Insurance Fund (NHIF), which essentially covers the entire resident population, provides most of the funding for the healthcare system. The program is built on mandatory contributions that are

primarily based on employment. Through five regional branches, the NHIF makes healthcare purchases on behalf of its contributors (71). Lithuania has the lowest life expectancy in the EU, six years lower than the EU average (74.6 years in 2015), and its life expectancy is rising. Additionally, there is a sizable gap between men and women, with Lithuanian men's life expectancy (69.2 years) being more than 10 years lower than women's (79.7 years), the largest gender gap in the EU (71). According to self-reported data, approximately one in six adults (17%) in Lithuania are obese today, which is slightly higher than the EU average (16%). Despite being the second lowest in the EU among 15-year-olds, the prevalence of overweight and obesity more than tripled (from 4% to 13%) between 2001-02 and 2013-14. Given that becoming overweight or obese as an adult is strongly predicted by being overweight or obese as a child or adolescent, this trend is especially concerning, therefore, a person can develop an asthma as obesity is a risk factor for the development of asthma (71). Genetic predisposition plays a significant role in asthma development, with individuals who have a family history of asthma or allergies being more susceptible. Atopy, which is a genetic tendency to develop allergic reactions, is also associated with a higher risk of asthma. Environmental factors, such as exposure to allergens like pollen, dust mites, animal dander, and mold, can trigger asthma symptoms or increase the likelihood of developing the condition. Viral respiratory infections, particularly during early childhood, can damage the airways and contribute to the development of asthma later in life (72,73). In Lithuania, asthma management varies compared to other European countries, with a lower density of respiratory specialists at 4.4 per 100,000 population compared to the European Union average of 6.6 per 100,000 population (74). Additionally, Lithuania's total expenditure on health as a percentage of its gross domestic product (GDP) was 6.7% in 2017, lower than the EU average of 9.8% in the same year (75). A study conducted in 2012 found that Lithuania had the lowest rate of inhaled corticosteroid use among 16 European countries, with only 18.7% of asthma patients using these medications (76).

3.3 Data collection

In this study anti-asthma medication utilization was defined as dispensed prescriptions of antiasthmatic drugs in Lithuania.

Prescription statistics were obtained from the compulsory health insurance information system "Sveidra" for the study period of 2014-2019. Population size of the study was 115,138 participants of the study period from 2014 to 2019. The data collected spanned from 2014 to 2019, as our objective was to analyze the pre-COVID period within the Lithuanian children population.

Retrieved asthmatic patient prescription data included:

- Patient ID
- Year of dispensing
- Patient age
- Patient sex
- Diagnose at the time of first prescription
- Drug class dispensed

Study participants were children from ages 0-17 years old. Participants were stratified into three age groups: preschool children (0-5 years old), school-age children (7-11 years old) and adolescents (12-17 years old). Due of the disease's considerable heterogeneity, treatment and management throughout childhood, these age groupings were selected (77).

In this study, asthma medications were classified according to the ATC (Anatomical Therapeutic Chemical Classification) group R03. However, it is important to note that this research specifically focuses on the utilization of asthma medications in pediatric populations, and thus, not all medications within the R03 ATC classification were included in the analysis. This study analysed the following anti-asthmatic medicines:

Table 2 Medication group, ATC code of anti-asthmatic grugs included in this study.

Medication group	Abbreviation	ATC codes	Substance names
Inhaled short-acting beta2-agonists	SABA	R03AC02 R03AC03	Salbutamol Terbutaline
Inhaled long-acting beta2-agonists	LABA	R03AC12 R03AC13	Salmeterol Formoterol
Inhaled corticosteroids	ICS	R03BA01 R03BA02 R03BA05	Beclometasone Budesonide Fluticasone
Fixed therapy	ICS and LABA	R03AK06 R03AK07	Salmeterol and Fluticasone

		R03AK08 R03AK10 R03AK11	Formoterol and Budesonide Formoterol and Beclometasone Vilanterol and Fluticasone Furoate Formoterol and Fluticasone
Leukotriene receptors antagonists	LTRAs	R03DC03	Montelukast
Biological drugs		R03DX05 R03DX07 R03DX08 R03DX09 R03DX10	Omalizumab Roflumilast Reslizumab Mepolizumab Benralizumab

3.4 Method of analysis

In this study, the dataset including dispensed asthma medication prescriptions was analyzed and visualized using Microsoft Excel. In this study, children were selected for inclusion based on the criterion of having at least one dispensation of an anti-asthmatic medication. This approach enables the broad identification of all children with asthma within the dataset. A 12-month wash-out period with no dispenasations was implemented in analyses of incidence.

The annual prevalence (per 1000 inhabitants) among different age and sex groups of population of asthma medication use was calculated by dividing the number of children with at least one dispensed prescription per calendar year by the gender and age-specific population of that year, as determined on January 1st of each year.

The annual incidence (per 1000 inhabitants) among different age and sex groups of population was determined by dividing the number of children who filled their first prescription by the gender and age-specific population of each year. It should be noted that for the purpose of this

analysis, children were considered as new users if they had a minimum of 12 months wash-out period without any dispensed asthma medication.

To visually represent how asthma prevalence per 1000 inhabitants varies across municipalities in Lithuania, a map was created using Microsoft Excel. Each municipality was color-coded according to its corresponding prevalence value from 0 to 75, allowing for a quick and easy comparison of rates between regions.

The prevalence of asthma medication use was calculated by dividing the number of individuals with at least one prescription for a particular medication by the total number of individuals in the total Lithuanian children population.

The annual incidence use was calculated by dividing the number of incident individuals with at least one prescription for a particular medication by the total number of individuals in the total Lithuanian children population. It should be noted that for the purpose of this analysis, children were considered as new users if they had a minimum of 12 months wash-out period without any dispensed asthma medication.

UpSet plots were applied to effectively illustrate the distribution patterns of various asthma medication combinations in Lithuanian children aged 0-17, comparing data from 2014 and 2019. These plots were created using the Python programming language, enabling a clear and comprehensive portrayal of the frequency of each medication combination for the specified age group and time frame.

3.5 Ethical considerations

In this study we have used individual level data as we had datasets containing records with individual study participants. However, the data that we have received from the Compulsory Health Insurance Information System "Sveidra" have been depersonalized before-hand, therefore, the risk of identifying a specific individual is very low and it will not lead to confidentiality problems and permit was granted to obtain this data. Datasets already have been collected before the study so there was no need to have an informed consent from individuals whose data has been used in this study. The potential benefits of this study include early identification and intervention for better asthma management, development of tailored treatment and prevention strategies, and improved awareness and education for parents, caregivers, and educators. On the other hand, potential risks encompass stigmatization or discrimination faced by children with asthma or higher risk, increased anxiety and stress for parents and caregivers, and unintended

consequences or adverse effects from interventions. Balancing these ethical considerations involves maintaining data confidentiality and using the findings to inform evidence-based approaches to asthma management, ultimately maximizing benefits while mitigating risks.

4. RESULTS

4.1 Lithuanian children population with at least one asthma medication prescribed

In this study, which investigates asthma medication utilization among children in Lithuania from 2014 to 2019, a total of 115,138 participants were examined. These participants, aged 0 to 17 years, consisted of 42,205 females and 72,933 males, all of whom had been dispensed at least one asthma medication during the specified time frame of 2014 to 2019 (Figure 1).

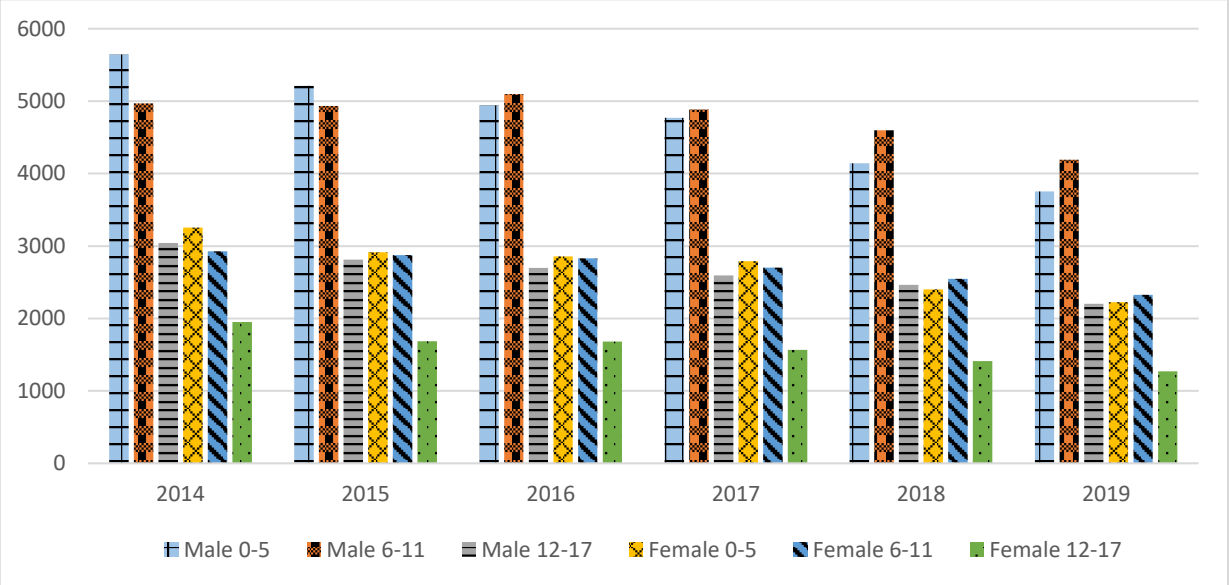

Figure 1 Study population including all children in Lithuania with atleast one dispensed asthma medication stratified by sex and different age groups (2014-2019)

Several trends can be observed when comparing the years 2014 and 2019. A general decline in the number of children receiving asthma medication across all age groups and both genders is apparent. The most significant decrease is observed in the Male 0-5 age group, with numbers dropping from 5,644 in 2014 to 3,754 in 2019. The Male 6-11 and Male 12-17 age groups also experienced notable reductions in asthma medication users, decreasing from 4,969 to 4,190 and from 3,041 to 2,203, respectively.

Similarly, the Female 0-5 age group showed a decline in asthma medication users, decreasing from 3,255 in 2014 to 2,224 in 2019. The Female 6-11 age group exhibited a decline as well, with the number of asthma medication users dropping from 2,926 in 2014 to 2,325 in 2019. Lastly, the Female 12-17 age group experienced a reduction in asthma medication users, with numbers decreasing from 1,949 in 2014 to 1,268 in 2019.

4.2 Prevalence of asthma medication

The annual prevalence of asthma medication (per 1,000 patients) among different age and sex groups in Lithuania decreased from 2014 to 2019 in every age and sex group (Figure 2).

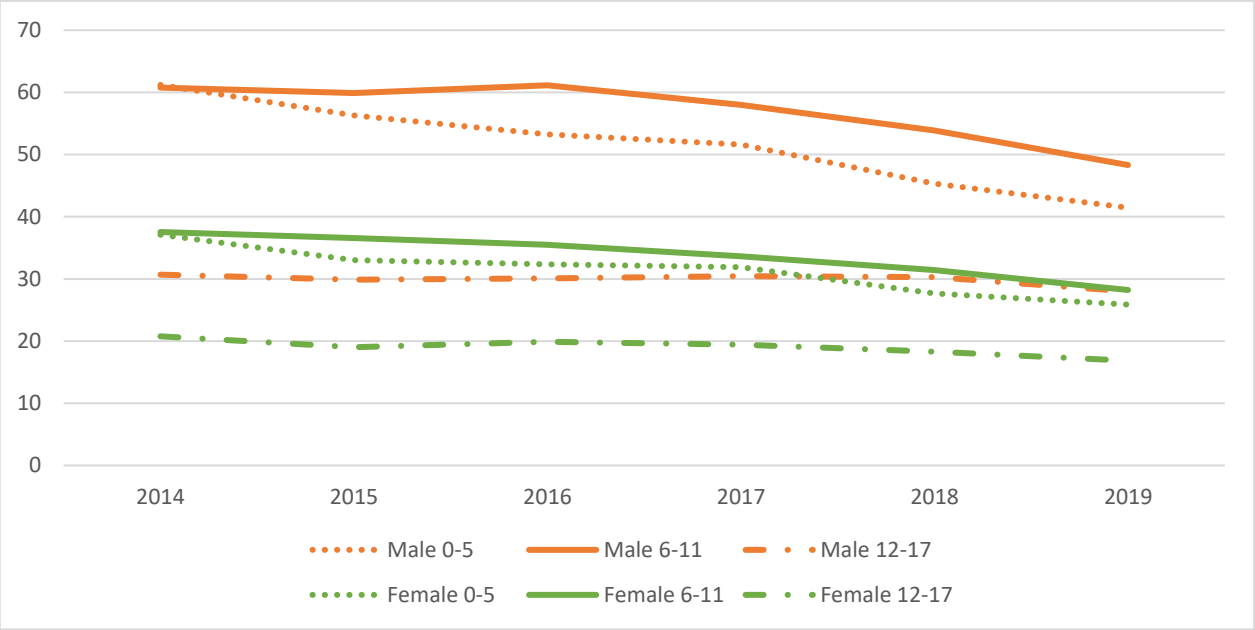

Figure 2 Asthma medication prevalence*: Age and Sex Comparisons (2014-2019) (per 1000 inhabitants)*

The prevalence of asthma medication in the 0-5 age group was higher across both sexes when compared to the other age groups (6-11 and 12-17). In 2014, the prevalence was 61 per 1,000 patients for both male 0-5 and 6-11 age groups, while the male 12-17 age group had a prevalence of 31 per 1,000 patients. In 2019, the male 0-5 age group had a prevalence of 41 per 1,000 patients, while the male 6-11 and 12-17 age groups had a prevalence of 48 and 28 per 1,000 patients, respectively. This trend suggests that children in the 0-5 age group may experience more severe asthma symptoms or have a higher prevalence of asthma.

Males in each age group (0-5, 6-11, and 12-17) consistently exhibited higher asthma medication usage than their female counterparts. In 2014, the prevalence of asthma medication for the male 0-5 age group was 61 per 1,000 patients, while the female 0-5 age group had a prevalence of 37 per 1,000 patients. In 2019, the male 0-5 age group had a prevalence of 41 per 1,000 patients, while the female 0-5 age group had a prevalence of 26 per 1,000 patients.

From 2014 to 2019, there has been a general decline in the prevalence of asthma medication use across all age and sex groups. For the male 0-5 age group, the prevalence decreased from 61 per 1,000 patients in 2014 to 41 per 1,000 patients in 2019, representing a 32.8% decrease. Similarly,

the female 12-17 age group showed a decrease in prevalence from 21 per 1000 inhabitants in 2014 to 17 per 1,000 patients in 2019, representing a 19.0% decrease.

Upon examining the data representing asthma medication prevalence per 1000 inhabitants in Lithuanian children aged 0-17 years in 2019, several patterns and differences between males and females can be observed (Figure 3).

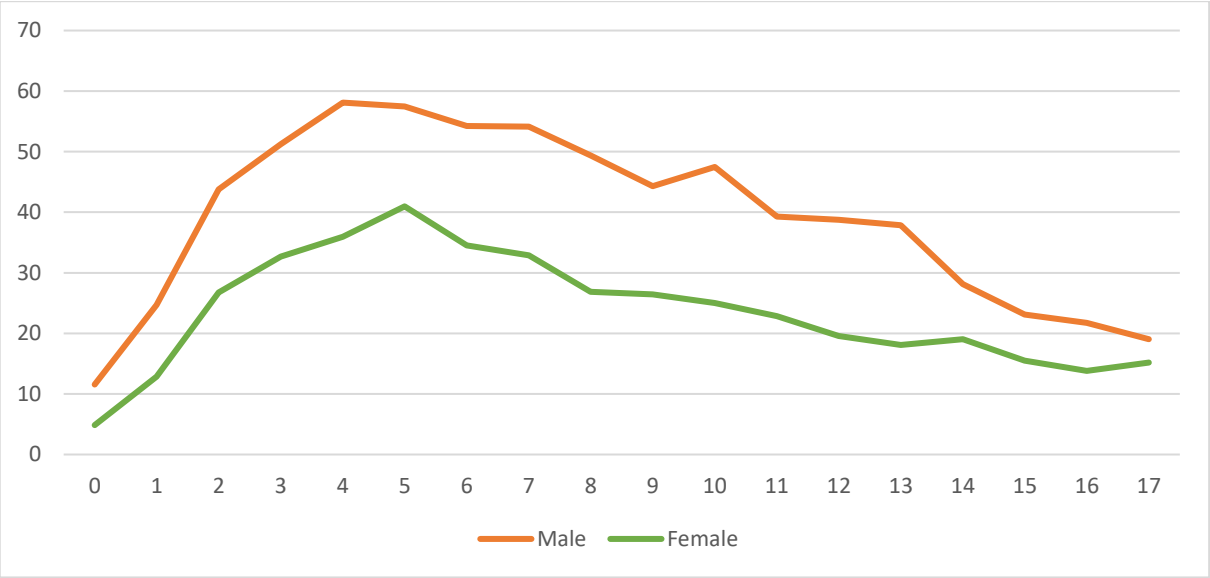

Figure 1 Gender-specific Asthma medication Prevalence Trends in Lithuanian Children Aged 0-17 Years (2019) (per 1000 inhabitants)

A consistent trend is evident, with asthma medication prevalence being higher in males than in females across all age groups. The disparity between the genders is most pronounced during the early years of life. For example, at age 0, there are 12 cases of asthma medication use per 1000 male inhabitants, while there are only 5 cases per 1000 female inhabitants. This trend continues as the children grow older, with the gap between males and females reaching its largest at age 2, where the prevalence of asthma medication in males is 44 cases per 1000 inhabitants, compared to 27 cases per 1000 inhabitants in females.

As children progress into school-age years, the difference in asthma medication prevalence between males and females narrows. By age 7, the gap has significantly lessened, with male prevalence at 54 cases per 1000 inhabitants and female prevalence at 33 cases per 1000 inhabitants. From this age onwards, the overall asthma medication prevalence appears to gradually decrease in both genders. Male prevalence declines from a peak of 58 cases per 1000 inhabitatns at age 4 to 19 cases per 1000 inhabitants at age 17. Similarly, female prevalence decreases from a peak of 41 cases per 1000 inhabitants at age 5 to 15 cases per 1000 inhabitants at age 17.

The data demonstrates that asthma medication prevalence in Lithuanian children aged 0-17 years in 2019 is higher in males than females, with the most significant differences occurring during early childhood.

When examining the asthma medication prevalence within multiple municipalities throughout Lithuania in 2019, there were notable disparities in the data between certain areas, highlighting the considerable variation in the occurrence of this respiratory condition across regions (Figure 4).

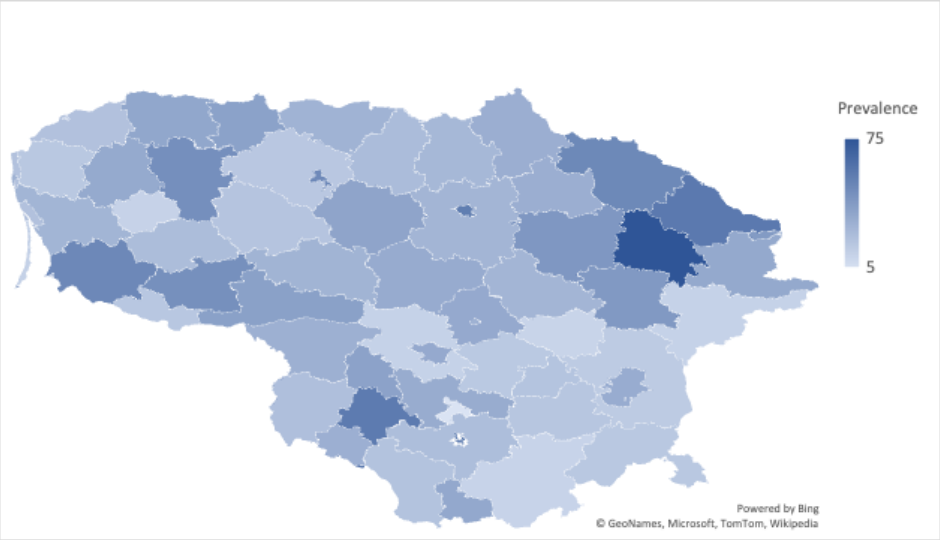

Figure 2 Prevalence of Asthma medication per 1000 children aged 0-17 in Lithuanian Municipalities in 2019

There was a large variation in prevalence of asthma medication use between the different municipalities.

Utena County had the highest asthma medication prevalence, with 75 cases per 1000 inhabitants. Birštonas Municipality exhibited the lowest asthma medication prevalence, with only 5 cases per 1000 inhabitants.

Asthma medication prevalence rates in other municipalities varied widely, with Širvintos District Municipality and Skuodas reporting 12 cases per 1000 inhabitants, and Alytus and Marijampolė reporting 57 cases per 1000 inhabitants.

Comparison of years 2014 and 2019 reveals a general decline in asthma medication prevalence rates across most municipalities. For example, in Akmenė District Municipality, the prevalence

of asthma medication decreased from 56 per 1000 inhabitants in 2014 to 37 per 1000 inhabitants in 2019.

Similarly, in Alytus, the asthma medication prevalence dropped from 103 per 1000 inhabitants in 2014 to 57 per 1000 inhabitants in 2019. However, there are a few cases where the prevalence of asthma medication increased between 2014 and 2019.

Notably, in Molėtai District Municipality, the prevalence of asthma medication rose from 37 per 1000 inhabitants in 2014 to 42 per 1000 inhabitants in 2019. Furthermore, in Neringa Municipality, the prevalence of asthma medication increased from 9 per 1000 inhabitants in 2014 to 14 per 1000 inhabitants in 2019.

4.3 Asthma medication prevalence by drug class

This section presents the results of the analysis of the prevalence of asthma medication use among three male and three female age groups (0-5, 6-11, 12-17) in Lithuania from 2014 to 2019. The data encompasses the usage of five types of asthma medications: SABA, LABA, ICS, ICS+LABA and LTRA. During the period from 2014 to 2019, no biological asthma medications were prescribed to children aged 0-17 in Lithuania (Table 3)

Table 3 Prevalence of different asthma medication groups among Lithuanian children of different and sex groups from 2014 to 2019. (n = 115,138)

Year	Age sex/group	SABA	LABA	ICS	ICS+LABA	LTRA
2014	Male 0-5	4.17	4.06	0.16	3.93	0.00
	Male 6-11	4.08	3.37	0.64	3.47	0.04
	Male 12-17	2.09	1.42	0.64	1.07	0.10
	Female 0-5	2.46	2.43	0.13	2.46	0.00
	Female 6-11	2.48	2.05	0.36	2.15	0.01
	Female 12-17	1.43	0.95	0.43	0.77	0.07
2015	Male 0-5	3.88	3.94	0.16	3.40	0.00
	Male 6-11	4.13	3.43	0.58	3.08	0.03
	Male 12-17	2.14	1.38	0.66	0.99	0.05
	Female 0-5	2.19	2.24	0.11	2.08	0.00
	Female 6-11	2.45	2.06	0.32	1.85	0.02
	Female 12-17	1.31	0.87	0.39	0.64	0.04
2016	Male 0-5	3.71	3.74	0.07	3.20	0.00

	Male 6-11	4.40	3.65	0.35	2.87	0.03
	Male 12-17	2.18	1.34	0.60	0.88	0.04
	Female 0-5	2.19	2.19	0.05	2.02	0.00
	Female 6-11	2.39	2.07	0.21	1.72	0.02
	Female 12-17	1.46	0.92	0.36	0.59	0.02
2017	Male 0-5	3.62	3.67	0.09	2.84	0.00
	Male 6-11	4.10	3.50	0.44	2.61	0.02
	Male 12-17	2.20	1.44	0.61	0.82	0.02
	Female 0-5	2.12	2.19	0.06	1.94	0.00
	Female 6-11	2.31	1.97	0.20	1.53	0.00
	Female 12-17	1.38	0.88	0.35	0.55	0.01
2018	Male 0-5	3.16	3.32	0.08	2.05	0.00
	Male 6-11	3.75	3.28	0.41	2.17	0.01
	Male 12-17	2.22	1.35	0.65	0.71	0.01
	Female 0-5	1.84	1.93	0.06	1.39	0.00
	Female 6-11	2.14	1.86	0.16	1.28	0.00
	Female 12-17	1.31	0.76	0.38	0.48	0.01
2019	Male 0-5	2.83	3.10	0.10	1.72	0.00
	Male 6-11	3.40	3.04	0.37	1.67	0.01
	Male 12-17	2.04	1.28	0.60	0.59	0.01
	Female 0-5	1.69	1.92	0.07	1.13	0.00
	Female 6-11	1.93	1.81	0.18	1.00	0.00
	Female 12-17	1.18	0.74	0.36	0.38	0.00

Overall, the prevalence of asthma medication use decreased from 2014 to 2019 across all age and sex groups. The prevalence of SABA use among the male 0-5 age group decreased from 4.17% in 2014 to 2.83% in 2019, a reduction of 32.14%. Similarly, the female 12-17 age group experienced a decrease in SABA use from 1.43% in 2014 to 1.18% in 2019, a decline of 17.48%.

The male 0-5 age group consistently had the highest prevalence of SABA, LABA, and ICS+LABA use. In 2014, the prevalence was 4.17% for SABA, 4.06% for LABA, and 3.93% for ICS+LABA. By 2019, the prevalence had decreased to 2.83% for SABA, 3.10% for LABA, and 1.72% for ICS+LABA.

The female 12-17 age group consistently had the lowest prevalence of SABA, LABA, and ICS+LABA use. For instance, in 2014, the prevalence was 1.43% for SABA, 0.95% for LABA, and 0.77% for ICS+LABA. By 2019, these numbers had decreased to 1.18% for SABA, 0.74% for LABA, and 0.38% for ICS+LABA.

The youngest age group (0-5) consistently had higher asthma medication usage across both sexes when compared to the other age groups (6-11 and 12-17) throughout the years from 2014 to 2019. In 2014, the male 0-5 age group had a SABA use of 4.17%, while the male 6-11 and 12-17 age groups had 4.08% and 2.09% SABA use, respectively. Similarly, in 2019, the male 0-5 age group had a SABA use of 2.83%, while the male 6-11 and 12-17 age groups had 3.40% and 2.04% SABA use, respectively. Conversely, the 12-17 age group consistently exhibited the lowest prevalence of asthma medication use among both sexes. In 2014, female 12-17 age group had a SABA use of 1.43%, while in 2019, it decreased to 1.18%, indicating better asthma control or a lower disease prevalence in this group.

4.4 Asthma medication incidence

Throughout the study period, the incidence of asthma medication in male children consistently surpasses that of female children across all age groups (Figure 5). The incidence of asthma medication within the age group of 0-17 years throughout 2015 to 2019 in this study is 10,35 per 1000 inhabitants, for males aged 0-17 the incidence is 12,57 per 1000 inhabitants and for females aged 0-17 the incidence is 8,02 per 1000 inhabitants.

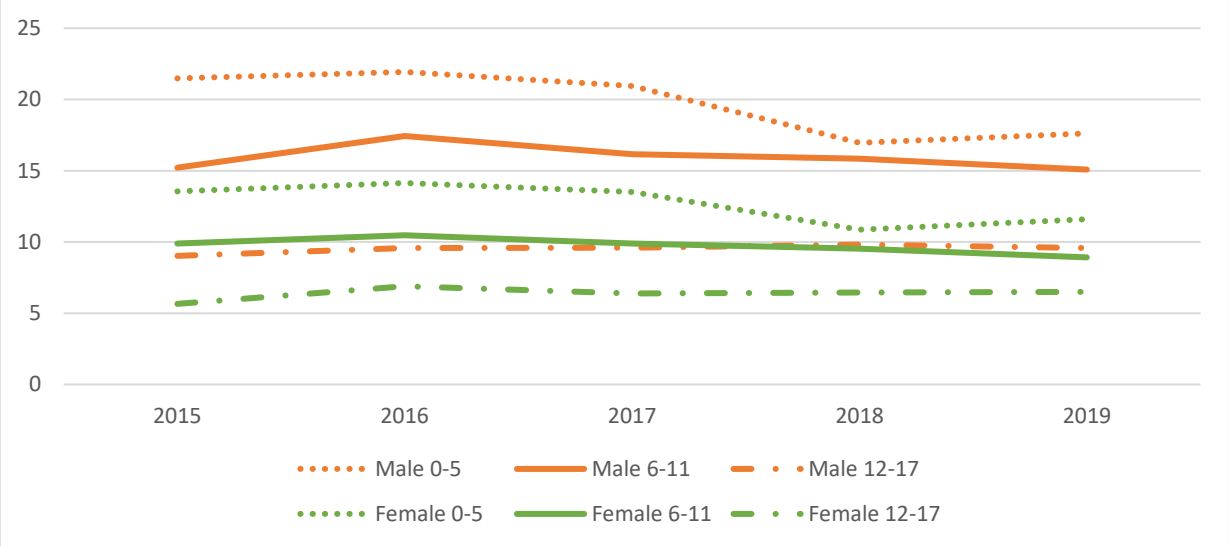

Figure 3 *Asthma medication incidence: Age and Sex Comparisons (2014-2019) (per 1000 inhabitants)*

The incidence of asthma medication is generally higher in the younger age groups (0-5 and 6-11) for both males and females. In 2015, the incidence rate for males aged 0-5 was 21.48 per 1,000 patients, while for those aged 6-11, it was 15.21 per 1,000 patients. Similarly, for females, the incidence rate for the 0-5 age group was 13.56 per 1,000 patients, while for the 6-11 age group, it was 9.90 per 1,000 patients. This indicates that younger children might be more susceptible to developing asthma. In contrast, the 12-17 age group consistently exhibits the lowest incidence rates among both sexes, with males at 9.03 per 1,000 patients and females at 5.66 per 1,000 patients in 2015.

The sex differences in asthma medication incidence vary across age groups. In 2015, the gap between male and female incidence rates in the 0-5 age group was 7.92 per 1,000 patients (21.48 for males vs. 13.56 for females). In the 6-11 age group, the gap was 5.31 per 1,000 patients (15.21 for males vs. 9.90 for females), and in the 12-17 age group, it was 3.37 per 1,000 patients (9.03 for males vs. 5.66 for females).

While the incidence of asthma medication has generally decreased for both sexes across all age groups between 2015 and 2019, the rate of decline is not equal between males and females. For instance, the male 0-5 age group experienced a 17.9% reduction in asthma medication incidence, while the female 0-5 age group saw a slightly smaller decrease of 14.4%.

When examining the data on asthma medication incidence per 1000 inhabitants in Lithuanian children aged 0-17 in 2019, it is evident that there are notable differences between males and females (Figure 6)

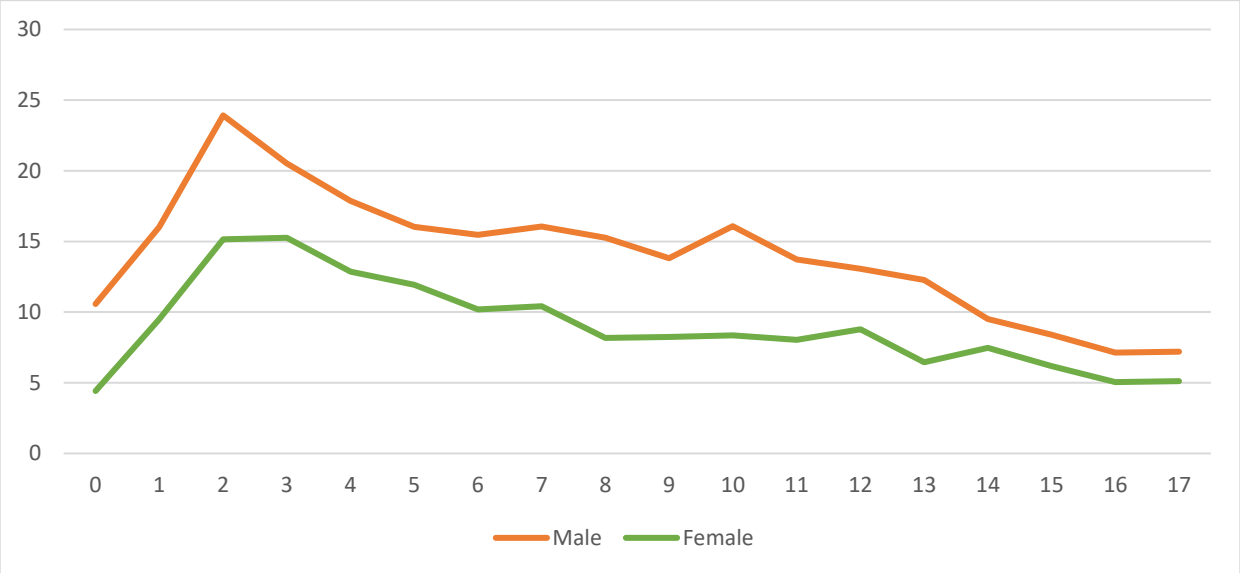

Figure 4 Gender-specific Asthma medication Incidence Trends in Lithuanian Children Aged 0-17 Years (2019) (per 1000 inhabitants)

It is apparent that the incidence of asthma medication is consistently higher in males compared to females across all age groups. The most pronounced difference is observed in the younger age groups, particularly between ages 0-5, where the asthma medication incidence rates for males are more than double those of females. For instance, in the 2-year-old age group, there are 24 males with asthma per 1000 inhabitants compared to 15 females, while in the 5-year-old age group, the respective figures are 16 and 12.

As children grow older, the gap between asthma medication incidence rates for males and females narrows. For example, in the 12-year-old age group, there are 13 males with asthma per 1000 inhabitants, while the number for females is slightly lower at 9. This trend continues into the teenage years, with the disparity between the two genders becoming less significant. In the 17-year-old age group, there are 7 males with asthma per 1000 inhabitants, and for females it is 5.

The data indicates that gender plays a significant role in asthma incidence among Lithuanian children, with males generally exhibiting higher rates than females. This gender difference is particularly evident in the early years of life and gradually diminishes as children age.

4.5 Asthma medication incidence by drug class

This section presents the incidence of asthma medication usage among Lithuanian children in various age and sex groups from 2015 to 2019. The data encompasses five main categories of medications: SABA, LABA, ICS, combination therapy of ICS+LABA, and LTRA. The findings reveal notable trends and differences in medication usage across age and sex groups, as well as changes in prescribing patterns over the years.

Table 4 Incidence of different asthma medication groups among Lithuanian children of different and sex group from 2015 to 2019. (n = 93,354)

Year	Age sex/group	SABA	LABA	ICS	ICS+LABA	LTRA
2015	Male 0-5	1.44	1.42	0.02	1.20	0.00
	Male 6-11	1.14	0.74	0.09	0.58	0.01
	Male 12-17	0.66	0.37	0.11	0.21	0.01
	Female 0-5	0.88	0.88	0.02	0.82	0.00
	Female 6-11	0.71	0.49	0.04	0.38	0.00
	Female 12-17	0.42	0.25	0.07	0.13	0.00
2016	Male 0-5	1.49	1.43	0.01	1.29	0.00
	Male 6-11	1.26	0.92	0.04	0.70	0.00

	Male 12-17	0.73	0.42	0.09	0.18	0.01
	Female 0-5	0.93	0.90	0.01	0.89	0.00
	Female 6-11	0.73	0.52	0.03	0.43	0.00
	Female 12-17	0.51	0.30	0.06	0.13	0.00
2017	Male 0-5	1.40	1.41	0.01	1.08	0.00
	Male 6-11	1.16	0.83	0.07	0.54	0.00
	Male 12-17	0.74	0.40	0.10	0.16	0.00
	Female 0-5	0.87	0.88	0.01	0.79	0.00
	Female 6-11	0.68	0.50	0.03	0.37	0.00
	Female 12-17	0.46	0.28	0.06	0.12	0.00
2018	Male 0-5	1.17	1.16	0.01	0.73	0.00
	Male 6-11	1.19	0.82	0.06	0.49	0.00
	Male 12-17	0.77	0.41	0.11	0.14	0.00
	Female 0-5	0.73	0.72	0.01	0.48	0.00
	Female 6-11	0.71	0.48	0.02	0.29	0.00
	Female 12-17	0.49	0.25	0.08	0.12	0.00
2019	Male 0-5	1.19	1.24	0.02	0.71	0.00
	Male 6-11	1.10	0.82	0.06	0.40	0.00
	Male 12-17	0.71	0.43	0.10	0.12	0.00
	Female 0-5	0.74	0.83	0.01	0.45	0.00
	Female 6-11	0.62	0.53	0.04	0.23	0.00
	Female 12-17	0.49	0.28	0.09	0.12	0.00

From 2015 to 2019, there was a general trend of increasing LABA use across most age and sex groups, while the use of SABA seems to be decreasing or remaining stable (Table 4). Males aged 0-5 showed an increase in LABA use from 1.42% in 2015 to 1.24% in 2019. In contrast, SABA use in the same group slightly decreased from 1.44% in 2015 to 1.19% in 2019.

There are noticeable differences in the dispensing patterns between males and females. For instance, in 2019, males aged 0-5 had a higher incidence rate of SABA use (1.19%) compared to females in the same age group (0.74%). Similarly, LABA use was higher in males aged 0-5 (1.24%) compared to females aged 0-5 (0.83%).

The use of ICS and ICS+LABA is lower compared to SABA and LABA. However, some age groups, such as males aged 6-11, showed a higher incidence of ICS+LABA use in 2019 (0.40%)

compared to 2015 (0.58%), which might indicate a shift towards combination therapy for asthma management. The use of LTRA is relatively low across all age and sex groups.

4.6 Asthma prevalence and incidence comparison

When examining the data on asthma incidence and prevalence among Lithuanian children aged 0-17 in 2019, it is essential to analyze the correlation between these two indicators to better understand the overall drug utilization in the population (Figure 7).

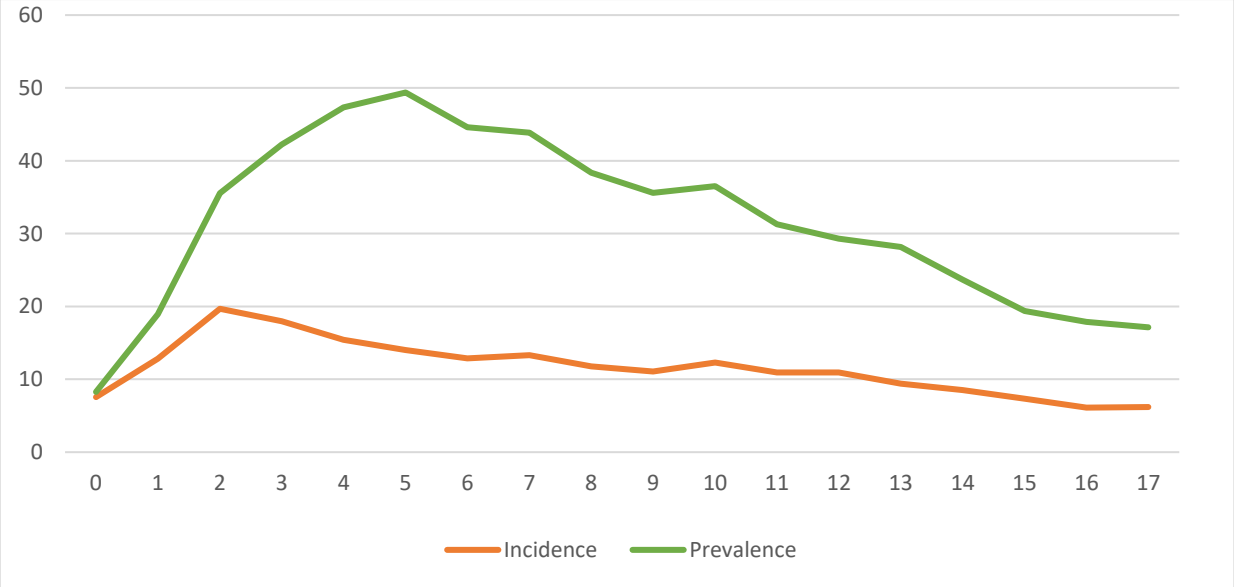

Figure 5 Asthma Incidence and Prevalence among Lithuanian Children Aged 0-17 in 2019 (per 1000 inhabitants)

There is a general trend of increasing prevalence with age, peaking at age 5 and then gradually decreasing. This trend suggests that as children grow older, they become more likely to be diagnosed with asthma, but the rate of new cases declines over time. The prevalence of asthma medication is generally higher than the incidence across all ages except at age 0 which had the same prevalence and incidence, which suggests that the rate of new cases diagnosed is the same as accumulated cases of asthma during these early years.

The incidence shows an initial increase, peaking at age 2 before gradually decreasing. This pattern indicates that there is a higher likelihood of developing asthma during the early years of life, particularly between ages 1 and 2. After the age of 2, the incidence begins to decrease, suggesting that as children grow older, the rate of new asthma cases declines.

4.7 Asthma medicine combination dispensation frequencies

The data on asthma medication combinations for the Lithuanian pediatric population reveals notable differences in dispensing trends between 2014 and 2019. This analysis highlights the major changes in the utilization of different asthma medication combinations over this period – from 2014 to 2019.

In 2014, the most common asthma medication combinations were SABA, LABA, ICS+LABA (4,238 prescriptions), followed by SABA, LABA (3,893 prescriptions) (Figure 8). However, in 2019, the numbers changed: the most common combination was SABA, LABA with 4,621 prescriptions, while the common combination, SABA, LABA, ICS+LABA, experienced a considerable decrease in prescriptions with 2,047 (Figure 9).

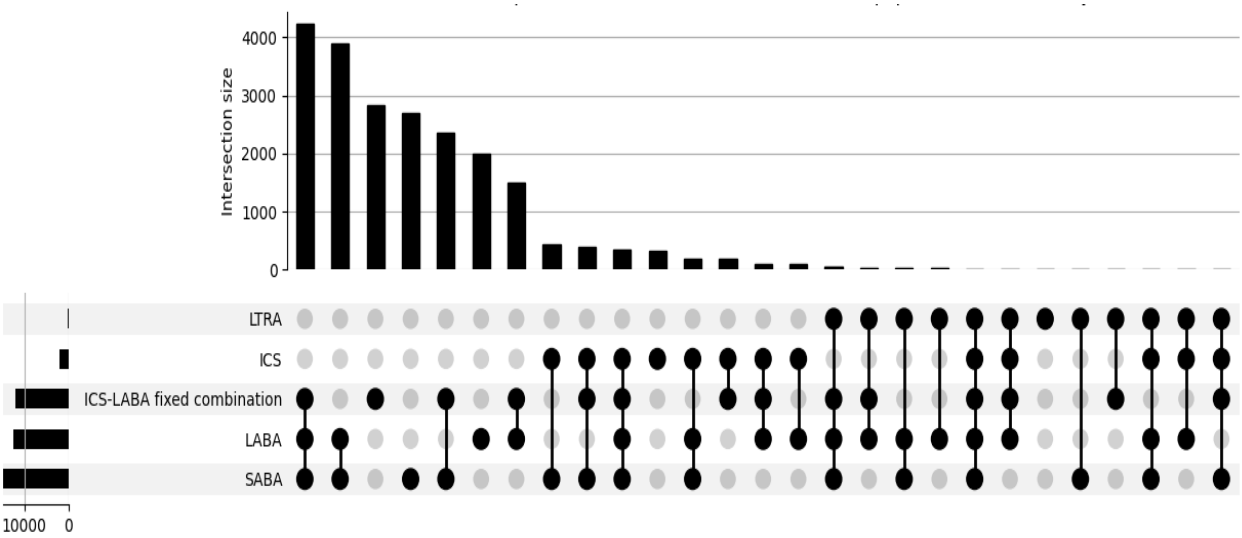

Figure 6 Asthma Medicine dispensation Combinations in Lithuanian children population from 0 to 17 years old (2014)

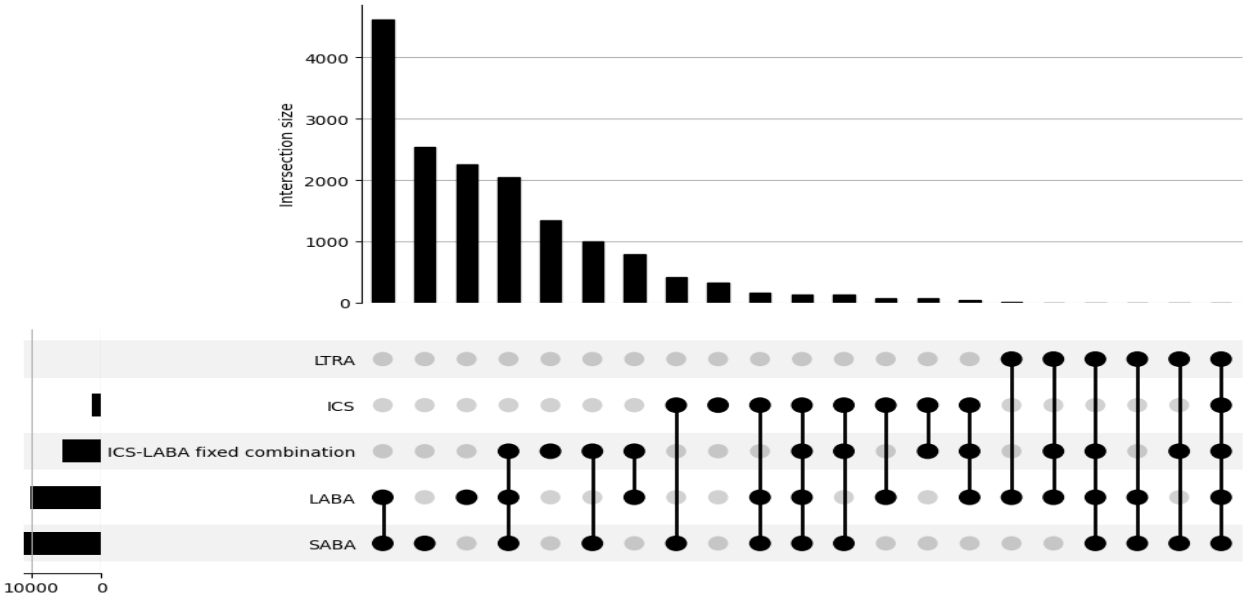

Figure 7 Asthma Medicine dispensation Combinations in Lithuanian children population from 0 to 17 years old (2019)

It is also important to notice that the use of ICS+LABA as a single medication dropped significantly from 2,835 prescriptions in 2014 to 1,339 in 2019. Similarly, the frequency of LTRA as a single medication decreased from 7 in 2014 to 0 in 2019.

The use of single medication regimens showed mixed changes. While the number of ICS prescriptions remained relatively stable (325 in 2014 and 327 in 2019), SABA prescriptions experienced a slight decline (2,700 in 2014 to 2,537 in 2019). Conversely, LABA prescriptions increased from 1,987 in 2014 to 2,263 in 2019.

5. DISCUSSION

This study aimed to investigate the utilization of asthma medications among children aged 0-17 years in Lithuania between 2014 and 2019. The main findings indicate a general decline in asthma medication use across all age and sex groups, with the most significant decrease observed in males 0-5 years. The observed differences between asthma medication incidence and prevalence among Lithuanian children aged 0-17 in 2019 underscore the importance of tailoring prevention and management strategies to address the unique needs of various age groups, ultimately improving asthma control and reducing the overall burden of this chronic condition on the population and healthcare system. The analysis of asthma medication incidence and prevalence by drug class has been conducted, revealing that SABA, LABA, ICS+LABA, ICS, and LTRA were identified as the drug classes with the highest prevalence and incidence rates, respectively, among Lithuanian children population aged from 0 to 17 years old.

5.1 Asthma medication incidence and prevalence in males and females

The prevalence of asthma medication was consistently higher among males and in the younger age groups (0-5 and 6-11 years), with the highest prevalence of 6.1% observed in male 0-5 and 6-12 year age groups throughout the study period. The results of this study align with those of a previous investigation conducted by Karlstad et al. that explored the prevalence of asthma medication use in children. In both studies, a similar prevalence of 6.8% was observed among males aged 6-12 years. However, there were notable discrepancies between the two studies in terms of the male 0-5 age group specifically, the prevalence of asthma medication usage reported by Karlstad et al. was higher, at 10.1%. Furthermore, the female populations in both studies exhibited similar findings, with a minor 1% difference in asthma medication prevalence, indicating a relatively low variation. However, a notable exception was observed in the female 12-17 age group, where a significant discrepancy was identified between the two studies. In this study, the prevalence of asthma medication usage was 1.7%, while the previous study reported a higher prevalence of 5.1% (62).

The difference in asthma medication prevalence between Lithuanian municipalities, notably, between Utena county and Birštonas municipality could be partly attributed to the disparity in the number of doctors per 10,000 people in 2019, with Utena county having only 28.2 and Birštonas municipality having 56.6 doctors. This variation in healthcare access might have affected asthma management and detection, leading to higher prevalence in Utena county and lower prevalence in Birštonas municipality (78). Similar results were found in a study conducted in Palestine in

which the lower prevalence of asthma and asthma medication was attributed to better healthcare access and management (79).

The male 0-5 age group exhibited the highest incidence of asthma medication usage at a rate of 2.1%. Intriguingly, this incidence declined during adolescence, reaching a low of 0.9% in the male 12-17 age group. This finding contrasts with the results of Karlstad et al., which reported an approximate 4% incidence in the male 0-5 age group. Nonetheless, both studies revealed similar outcomes for the male 12-17 age group, emphasizing a degree of consistency within this demographic. Similarly, the female 0-5 age group showed the highest incidence of asthma medication usage at 1.4%. As the female group progressed into adolescence, the incidence rate fell to 0.7%. While these results diverge from those of Karlstad et al. for the female 0-5 age group, both studies exhibit comparable findings for the female 12-17 age group, suggesting a consistent pattern in this age group (62).

From 2014 to 2019, the study population consisting of children aged 0 to 17 years old were not dispensed any biological asthma medications, likely because these treatments are typically administered in clinical settings and thus not included in this study because the data has not been received from the compulsory health insurance information system "Sveidra".

5.2 Different asthma medication class incidence and prevalence

It is evident that SABA had the highest prevalence of asthma medication for Lithuanian children across all age and sex groups throughout the study period. This observation aligns with the established role of SABA in providing immediate relief from asthma symptoms (8). Bianchi et al. carried out an extensive analysis of 12 studies from six countries - Italy, The Netherlands, Denmark, Norway, Canada, and the United States. The conclusions drawn from their review largely correspond with the results of this research, except for Italy. The findings indicate that SABA were the most commonly prescribed medications for asthma management, which is consistent with the results of the present study (80).

LABA saw a general decline in usage across most age groups, which indicate a shift in treatment preferences as of 2006 recommendations for LABA monotherapy has changed and should be prescribed in combination with ICS due to high risk for exacerbations and mortality (49). The relatively low and stable incidence of ICS usage suggests that these medications were primarily reserved for specific cases or more severe asthma conditions. Interestingly, a slight increase in ICS usage was observed in older children (12-17 years), potentially reflecting a more targeted approach to asthma management in this age group.

The utilization of ICS+LABA in combination experienced a decline in most age groups, especially in younger children aged 0-5 years. These findings stand in contrast to research conducted in the United Kingdom, where the incidence and prevalence of LABA and ICS+LABA in combination usage among children aged 0 to 15 years exhibited a significant increase (81). LTRAs were observed to be minimally prescribed and remained relatively stable throughout the study period. This indicates that LTRAs have a limited role in the overall management of pediatric asthma in Lithuania. These findings contrast with the previously mentioned study conducted in the United Kingdom, which reported a consistent increase in LTRA prevalence among children throughout the study period (81).

5.3 Asthma medicine combinations

The changes in asthma medication distribution over the study period showed a shift in dispensing practices towards more targeted and personalized asthma treatment. The most frequently prescribed asthma medications among Lithuanian children were SABA in combination with LABA. These findings partly concur with Phillips et al. study conducted in 2008 where period from 2002 to 2005 has been analysed and SABA was most prescribed antiasthmatic medication and LABA one of the least prescribed medications, throughout the study period there have been changes in LABA+ICS in combination prescriptions as there was a significant increase, which diverse from our findings where LABA+ICS in combination have decreased throughout the study period (81). This shift in prescribing practices may be attributed to the growing recognition of the potential risks associated with ICS+LABA combinations, such as increased risk of pneumonia and decreased growth velocity in children (8).

Furthermore, the incidence of ICS+LABA as a single medication decreased significantly. Previous studies conducted in British Columbia have shown an increased use of ICS+LABA over 6 years period, which differs significantly from this study results (82). These results align with current guidelines which recommend the use of ICS as a monotherapy for all children aged 6 and above, while highlighting the combination of ICS+LABA as a more effective alternative, particularly for children aged 12 years and older (8).

Additionally, the frequency of LTRA as a single medication decreased from 7 in 2014 to 0 in 2019, which concurs with recommendations that LTRA is no longer recommended as a first-line treatment for asthma in children (38).

The most common asthma medication combinations in 2014 and 2019 were SABA, LABA, and ICS+LABA, followed by SABA and LABA, respectively. These findings are consistent with

previous studies that have shown that combination therapy is more effective than monotherapy in improving asthma control and reducing exacerbations in children (83).

5.4 Strengths and limitations

This study has several strengths, including the use of a database of all Lithuanian children who have been prescribed at least one asthma medication, the investigation of a comprehensive range of asthma medications, and the examination of trends in asthma medication use over a six-year period. The study also provides valuable insights into the regional variation in asthma prevalence, incidence, number of dispensing across Lithuania.

However, there are also limitations to this study. The analysis is based on dispensing data, which might not accurately reflect actual medication use or adherence among children. Additionally, the study does not account for potential confounding factors, such as environmental triggers, healthcare access, or diagnostic practices, which could have influenced the observed trends in asthma medication use.

Another limitation, the exact combinations of asthma medications are not precise, as the available database only provides annual dispensing data without specifying the exact timing of dispensation. Consequently, two drugs may have been dispensed separately rather than simultaneously. A further limitation of this study is the absence of data on biological asthma medications, which precluded the analysis of their prevalence and incidence in the study population.

5.5 Implications for future research

Future research should aim to investigate the factors contributing to the observed trends in asthma medication use, as well as the disparities in asthma prevalence across different regions and adherence of asthma medications in Lithuania. Longitudinal studies and analyses incorporating environmental, socioeconomic, and healthcare access factors would be valuable in understanding the complex interplay of factors influencing asthma prevalence and management. Moreover, research focusing on effective interventions and management strategies for high-risk populations, such as younger children and males, may help to reduce the burden of asthma in these groups.

6. CONCLUSIONS

1. The incidence of asthma medication varied among different age and sex groups in Lithuania. SABA and LABA were the most used medications across all age and sex groups, while the use of ICS and ICS+LABA was relatively low. Notably, there was a general trend of increasing LABA use from 2015 to 2019, while the use of SABA remained stable or slightly decreased. Males aged 0-5 consistently had the highest incidence of SABA, LABA, and ICS+LABA use, while the female 12-17 age group consistently had the lowest incidence of these medications. Additionally, males aged 6-11 showed a higher incidence of ICS+LABA use in 2019 compared to 2015.
2. There were significant differences in the prevalence of asthma medication use between different age and sex groups in Lithuania. The youngest age group (0-5) had consistently higher usage of asthma medication, including SABA, LABA, and ICS+LABA, compared to the older age groups (6-11 and 12-17) throughout the study period from 2014 to 2019. In contrast, the 12-17 age group had the lowest prevalence of asthma medication use among both sexes. Additionally, the male 0-5 age group consistently had the highest prevalence of asthma medication use across all medication types.
3. We have found that the most common asthma medication combinations in 2014 and 2019 were SABA, LABA, and ICS+LABA, followed by SABA and LABA, respectively. However, it is important to note that the use of ICS+LABA in fixed combination dropped significantly over the study period.
4. There was a decline in the overall number of asthma medication prescriptions for Lithuanian children and adolescents from 2014 to 2019. However, it is important to note that despite the declining trend, asthma remains a significant public health issue in Lithuania, and continued efforts are needed to improve asthma control and management.

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