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ORIGINAL RESEARCH

Impact of Asthma Severity and Exacerbation Frequency on Burden of Disease Related Costs in Finland

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Purpose: Evaluating productivity loss and healthcare costs among working-aged individuals with asthma is critical for comprehending the economic burden and guiding healthcare policy decisions. An optimized care of asthma could result in substantial societal benefits by improving workforce participation and reducing healthcare resource use. Recent data on the impact of both asthma severity and exacerbation frequency on overall costs are scarce.

Patients and Methods: In this retrospective study from Finland, 89,606 working aged patients with asthma were followed from national registers for four years from 2017 to 2020 with the objective to assess the impact of asthma severity and exacerbation frequency on the overall costs arising from direct healthcare resource utilization (visits and drug purchases) and productivity loss (long term sick leaves and disability pensions) with gamma regression models.

Results: Severe asthma, noted in 10% of patients, increased healthcare resource utilization and productivity loss costs by 30% and frequent exacerbations, noted in 13% of patients, by 25%, independently of each other and of age, sex and Charlson comorbidity index. The annual overall cost per patient was € 14,359 for severe asthma with frequent exacerbations, followed by €11,802 in those with non-severe asthma and frequent exacerbations. Most costs were related to productivity losses (60%) compared to direct healthcare costs (40%). The prevalence of asthma increased from 2.7% to 3.0% over the four-year period, an increase was also observed in the subgroup of those with severe asthma.

Conclusion: A substantial disease burden associated with frequent exacerbations in both patients with asthma and severe asthma leads to increased productivity loss and direct healthcare costs. The estimated the total annual cost of working-aged patients with asthma was €715 million in Finland, with 25% of additional costs associated with frequent exacerbations, indicating the potential savings that could be achievable through improved disease control.

Plain Language Summary:

Why was the study done?

The study aimed to understand the economic burden of asthma in relation to disease severity and exacerbation frequency among working-aged individuals in Finland.

What did the researchers find?

The total annual cost of asthma for working-age patients in Finland was estimated at €715 million. Patients with severe asthma had 30% higher annual healthcare and productivity loss costs, compared to those with non-severe asthma. Frequent exacerbations also increased annual costs by 25%, irrespective of asthma severity. The annual cost per patient was highest for those with severe asthma and frequent exacerbations (€14,359), followed by those with non-severe asthma and frequent exacerbations (€11,802). Most costs (60%) were related to productivity losses, with direct healthcare costs making up the remaining 40%.

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What do the results mean?
The study highlights that the significant economic burden of asthma is driven by exacerbation frequency, suggesting that better disease control could lead to significant savings and enhance workforce participation.

Keywords: asthma, burden of disease, direct costs, exacerbations, productivity loss, severe asthma

Introduction

Studying productivity loss and healthcare costs among working-aged patients is essential for understanding the economic burden of diseases and informing healthcare policies. It helps in planning effective healthcare services and resource allocation, ensuring a sustainable and productive workforce.[1–4] The age standardized prevalence of asthma has been decreasing globally from 1990 to 2019.[5] However, in Finland the prevalence of asthma increased from 6.6% in year 1996 to 10.9% in year 2016. A levelling off in prevalence was observed between 2006 and 2016 at around 10%.[6] Depending on prevalence estimates, the affected population in Finland concerns 300 000–500 000 individuals.

While public health interventions targeting asthma and allergy have led to improved disease control and reduced healthcare resource utilization,[2–4] a proportion of patients still experience inadequate asthma control despite optimized inhalation therapy. These patients often face a high disease burden, which translates into increased healthcare costs and productivity losses.[1,7–10] Asthma, particularly more severe disease and the presence of comorbidities are associated with an increased risk of uncontrolled disease and therefore elevated risks of sick-leaves and disability pensions, further amplifying its societal impact.[7–9]

The challenges of asthma management extend beyond clinical outcomes. A critical yet underexplored dimension is the economic burden, especially among working-aged individuals. Currently, there is a lack of comprehensive information on how healthcare costs and productivity losses vary by asthma severity and exacerbation frequency among asthma patients of working-age. Addressing this gap, the aim of the study was to describe healthcare costs and productivity loss of asthma by severity and exacerbation frequency in Finland for the years 2017 to 2020 in working-aged asthma patients. Understanding the clinical and economic dimensions of asthma is crucial for shaping future interventions, especially in countries with high asthma prevalence.

Methods

Data and Permission

This was a retrospective register-based study including nationwide data on diagnoses, primary and secondary healthcare contacts, drug purchases, causes of deaths, long term sick leaves (10th day onwards) and disability pensions with related diagnoses from four different registers [National Institute for Health and Welfare, Social Insurance Institution (SII), Statistics Finland, and Centre for Pensions]. Data were linked utilizing a unique personal identification number by the central permission authority Findata (permission number THL/2385/14.02.00/2021), in accordance with the Act on the Secondary Use of Health and Social Data in Finland. Per the Secondary Use Act, a separate ethical approval is not needed for retrospective non-interventional register-based studies.[11]

Cohort Formation

The cohort has been previously described[12] briefly adult patients with an asthma diagnosis (International Classification of Diseases, Tenth Revision (ICD-10) J45*/J46*) who had made at least one drug purchase for obstructive airway diseases [R03* anatomical therapeutic class (ATC)] and had received reimbursement from the national drug reimbursement system for asthma during 2015–2016 were included from a raw cohort of 2.38 million patients. Criteria for cohort formation and asthma reimbursement are presented in the Supplementary Methods (Supplementary Methods and Supplementary Figure 1). Exclusion criteria were: biologic treatment for asthma (N = 12 during follow-up, available from 2020 onwards), a diagnosis of chronic obstructive pulmonary disease (COPD), when registered 5 years before or at index (N = 19,278), or other conditions requiring corticosteroids (N = 26,370 inflammatory bowel disease (IBD),

rheumatoid arthritis, sarcoidosis, or polymyalgia rheumatica). After applying these criteria, the overall cohort included 144,013 patients, of which 89,606 were of working-age (<65 years).

The working-aged patients with asthma were followed for four years from 1 January 2017 to 31 December 2020 in the register data to assess healthcare resource utilization and productivity loss related costs. The costs were assessed in mutually exclusive subgroups of those with non-severe asthma and infrequent exacerbations, non-severe asthma and frequent exacerbations, severe asthma and infrequent exacerbations, and severe asthma with frequent exacerbations.

The definition of asthma severity and exacerbation frequency has been described elsewhere.[12] In brief, severe asthma was defined in line with the European Respiratory Society and American Thoracic Society (ERS/ATS) guidelines,[13] requiring a daily fluticasone propionate (FP) dose of ≥800 µg/day or equivalent (allowing 80% adherence to 1000 µg FP per day) and at least one other controller per sliding window of four consecutive purchases during a 2-year baseline. Patients not fulfilling this criterion were defined as having non-severe asthma.

Exacerbation status was determined based on healthcare contacts and oral corticosteroid (OCS) purchases. Frequent exacerbators were required to have at least two emergency room (ER) visits or one hospitalization during the 2-year baseline, with asthma (J45.x) as primary diagnosis, or secondary diagnosis if the primary diagnosis was a respiratory infection (J0.x-J22.x), or acute asthma (J46.x) as primary or secondary diagnosis. Patients who purchased >600 mg prednisolone equivalent (more than three bursts of prednisolone 40 mg per day for five days), per rolling 365 days during the 2-year baseline were also determined as frequent exacerbators. Patients not fulfilling either of these criteria were classified as having infrequent exacerbations.

High short-acting beta-2 agonist (SABA) use was defined as purchasing over 450 actuations (irrespective of dose) per 12 months.[14]

Direct Healthcare Costs

Primary and specialized healthcare contacts, and medication purchases of ATC classes R* (respiratory system), A10* (diabetes), C* (cardiovascular system), H02* (systemically used corticosteroids), J* (anti-infectives for systemic use), N06A* (antidepressants), M05* (drugs for the treatment of bone diseases) during follow-up were included in direct healthcare costs, and assessed and reported as events per patient year (PPY). Unit costs were applied for the healthcare contacts accounting for the contact type (physician, nurse, home care, in person visits, phone call), specialty and duration. Medication costs were based on wholesale prices. All costs were index adjusted to year 2023, calculated based on unit prices from 2017 and index adjusted by multiplying with 1.10852.

Productivity Loss

Productivity loss was based on the lost working days due to long term sick leaves (10^{th} day onwards) reimbursed from the national social insurance (SII) and disability pension related days, or premature mortality if the person died before turning 65 years. SII reimburses losses of earnings if a person is unable to participate in the workforce due to illness or injury for a period of under one year, considering a 9-day deductible period. If the illness or injury lasts more than a year, partial or full disability pension is funded by SII or the Centre for Pensions in Finland. The application for disability pension is evaluated nationally by medical insurance specialists. The median salary cost from 2023 of 153.10 euro per working day, assuming 21 working days per month, was used to calculate the lost productivity costs.

For all analyses in the asthma cohort, a new COPD diagnosis after index was used as a censoring event, as was the date of a person turning 65 years in the analyses on the working-aged patients. Both healthcare resource utilization and productivity loss were classified as respiratory related if there was a respiratory main diagnosis (J*) and cardiovascular related if there was a cardiovascular main diagnosis (I*).

Statistical Analysis

Asthma prevalence was calculated by applying the cohort formation and asthma severity/exacerbation frequency criteria annually to the raw cohort (Supplementary Figure 1), and reported per 100,000 persons based on the annual adult population size from Statistics Finland, restricted to persons <65 years for the prevalence in working-aged patients. The significance for the change in prevalence over time was calculated with a linear regression model.

Kruskal–Wallis test followed by Dunn's test was used for continuous variables and Chi-squared test or Fisher's exact test for categorical variables. For pair-wise comparisons between groups, p-values were adjusted using the Holm method for controlling family-wise error rate. P-values less than <0.05 were considered statistically significant.

The healthcare resource utilization and productivity losses were assessed using mean cumulative functions (MCF) via the reda R package.[15] The MCFs were fitted to direct healthcare- and productivity loss events and costs separately and combined. Per patient year estimates with 95% confidence intervals (CI) were computed using the method by Lawless & Nadeau,[16] as implemented in the reda R package.

The impact of asthma severity and exacerbation frequency on direct healthcare costs and productivity loss was assessed using gamma regression models with a log link function, as it effectively handles skewed, non-negative, continuous variables such as medical expenses and costs. A model was created for total costs (direct healthcare costs and productivity loss combined) and for direct healthcare costs alone. For productivity loss costs including zero values, the analyses were performed in two parts: a Cox proportional hazards model to assess the impact of asthma severity and exacerbation frequency on the risk of having any productivity loss costs during follow-up, and a gamma regression model with a log link function for accumulated costs including only subjects with lost productivity.

In the gamma regression models, per patient-year costs were dependent on asthma severity, exacerbation frequency, Charlson comorbidity index, sex, age, and their interaction. In the Cox model, having any indirect costs were assessed with the same variables. The interaction of asthma severity and exacerbation frequency was excluded from final models due to lack of significance.

Patient characteristics, prevalence, direct healthcare costs, and the impact of asthma severity and exacerbation frequency on direct healthcare costs in the overall cohort of 144,013 patients, including also those aged over 65 years are presented in Supplementary Table 1, Supplementary Figure 1, Supplementary Figure 3, and Supplementary Table 2. The main analyses focused on the patients with asthma of working-age. Data processing and statistical analysis were performed using R version 4.0.3.[17]

Results

Out of all the 144,013 patients fulfilling the eligibility criteria of the study for asthma, 89,606 (62%) were of working-age (<65 years) (Supplementary Table 1). The proportion of subjects fulfilling these criteria showed a significant increase between 2017 and 2020 in those of working-age from 2736 to 2984 per 100,000 persons ($p < 0.001$), and the increase was also significant for those fulfilling the criteria of severe asthma and frequent exacerbations ($p = 0.001$) (Figure 1). A corresponding trend was also observed in the overall cohort (Supplementary Figure 1). All further results concentrated on the patients of working age.

Among those of working-age at the index year 2017, most patients had non-severe asthma and infrequent exacerbations (79.8%, N = 71,493), followed by non-severe asthma and frequent exacerbations (10.0%, N = 8967). In total, 10.2% of the included working-aged patients had severe asthma in combinations with infrequent exacerbations (6.8%, N = 6118) or in combination with frequent exacerbations (3.4%, N = 3028). In all four patient groups, the majority of patients were female with a median age of 46–52 years (Table 1).

Among patients with severe asthma and frequent exacerbations, 82% met the criteria based on OCS use, while 6% met the criteria based on ER visits or hospitalizations. Additionally, 12% fulfilled both criteria. In comparison, among those with non-severe asthma and frequent exacerbations, 88% met the OCS criteria, 7% met the ER visit or hospitalization criteria, and 5% fulfilled both. Patients with severe asthma and frequent exacerbations had the highest use of asthma medication before index (Table 1). The median (25^{th}, 75^{th} percentile) use of ICS was 821 (636, 1004) µg of FP equivalent daily, 2.46 (1.64, 3.56) mg prednisolone equivalent OCS daily, and 71% of patients had used at least two additional controllers (leukotriene receptor antagonist, LTRA; long-acting beta agonist, LABA; long-acting muscarinic antagonist, LAMA). Of those with severe asthma and frequent exacerbations 97.6% had at least one OCS purchase during baseline, and all patients had ICS purchases per definition. Further, 39% of patients with severe asthma and frequent exacerbations had more than 450 SABA doses dispensed and in 74%, the use of respiratory antibiotics was observed.

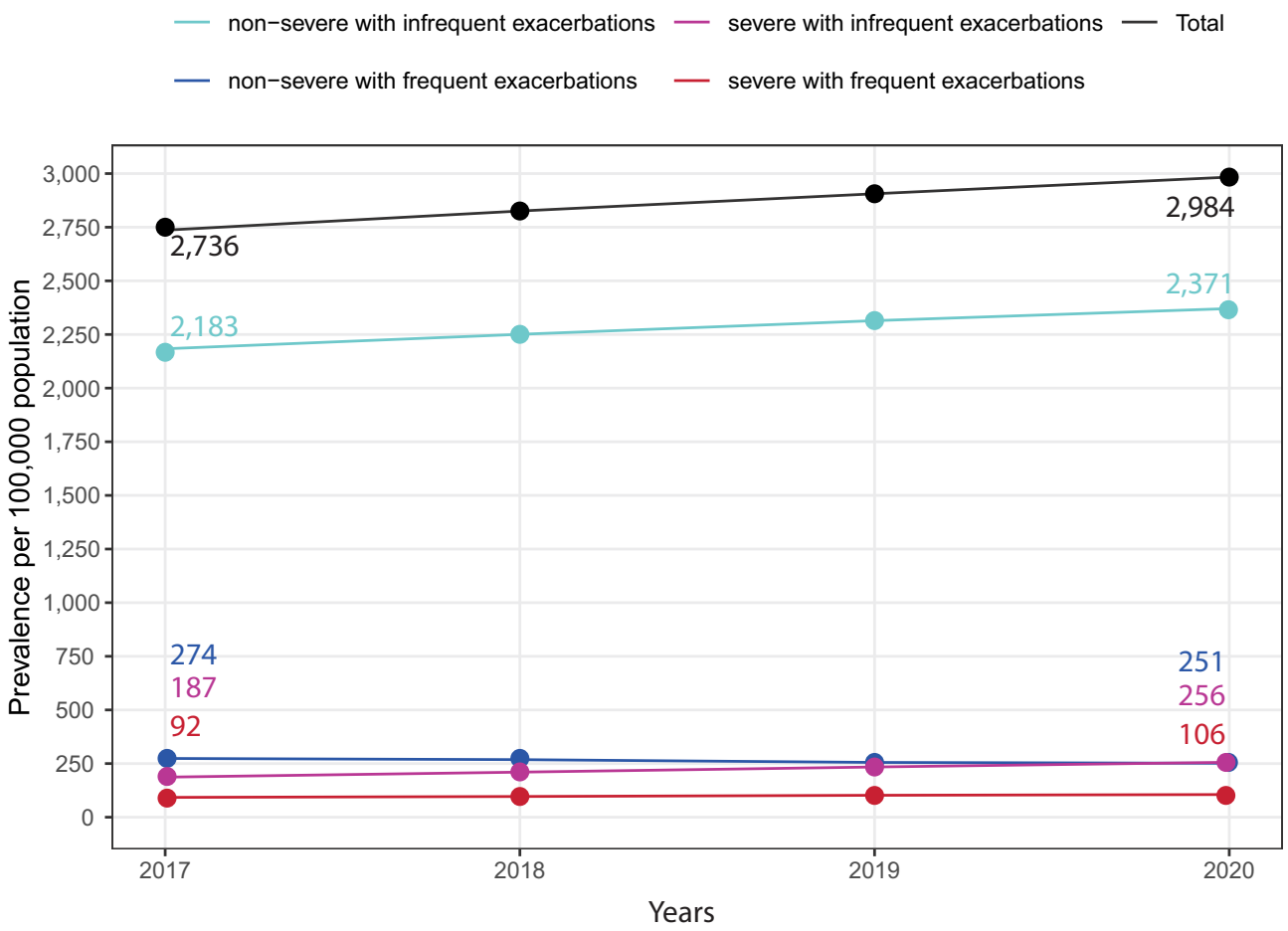

Figure 1 Prevalence of patients with asthma fulfilling the eligibility criteria per 100 000 persons, stratified by asthma severity and exacerbation frequency in patients of working-age (<65 years). The change in prevalence was significant for the total (black, $p < 0.001$), non-severe asthma and infrequent exacerbations (light blue, $p < 0.001$), and severe asthma with infrequent (purple, $p < 0.001$) and frequent exacerbations (red, $p=0.004$) groups. Prevalence was calculated by applying the cohort and subgroup criteria to the raw cohort, see Supplementary Methods.

Direct Healthcare and Productivity Loss Related Costs

All patients had contacts to public healthcare as well as drug purchases during follow-up that cumulated direct healthcare costs. These costs were 2.3 times higher in those with severe asthma and frequent exacerbations compared to non-severe asthma and infrequent exacerbations (€5618 (96% CI: €5328, €5908) vs €2418 (€2379, €2457) per patient-year) (Figure 2). Indirect costs from lost productivity were observed in 42–62% of patients depending on asthma severity and exacerbation frequency (Table 2). In severe asthma patients with frequent exacerbations, 62% had lost productivity during the follow-up. The corresponding proportion was 57% in those with non-severe asthma but with frequent exacerbations (Table 2). In all subgroups, productivity loss due to long term sick leaves was most common, observed in 32–43% of patients, followed by disability pensions in 12–23% of patients. Both sick leaves and disability pensions were the highest in those with severe asthma and frequent exacerbations, and 1.3–1.9-fold higher compared to those with non-severe asthma and infrequent exacerbations. The proportion of patients with lost productivity due to mortality, ie, those who died before turning 65 years, varied between 0.8% and 2.2% across subgroups, and was 1.5–2.7-fold higher in those with frequent exacerbations compared to patients with infrequent exacerbations, regardless of asthma severity.

The annual overall costs including both direct and productivity loss costs were the highest for patients with severe asthma and frequent exacerbations (€14,359 [95% CI: €13,673, €15,044] per patient-year), followed by patients with non-severe asthma and frequent exacerbations (€11,802 [€11,427, €12,178] per patient-year) (Figure 2). Compared to the

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Table 1 Clinical Characteristics of Working-Aged Patients (<65 years of Age) with Asthma Stratified by Severity and Exacerbation Frequency

Characteristic		Non-Severe with Infrequent Exacerbations (NSIE)	Non-Severe with Frequent Exacerbations (NSFE)	Severe with Infrequent Exacerbations (SIE)	Severe with Frequent Exacerbations (SFE)	p-value	Significant Post-Hoc Tests
Number of patients		71,493	8967	6118	3028	-	-
Age, median (25^{th}, 75^{th} quartile)		46 (34, 56)	51 (41, 58)	51 (40, 58)	52 (43, 59)	<0.001	NSFE/NSIE NSFE/SFE NSIE/SFE NSIE/SIE SFE/SIE
Female, N (%)		44,025 (62%)	6253 (70%)	3766 (62%)	2122 (70%)	<0.001	NSFE/NSIE SFE/NSIE SIE/NSFE SFE/SIE
Years from first reimbursement, median (25^{th}, 75^{th} quartile)		8 (4, 15)	9 (4, 17)	8 (3, 15)	10 (4, 19)	<0.001	All
Age at reimbursement		35 (22, 46)	39 (27, 48)	40 (28, 49)	38 (28, 47)	<0.001	NSFE/NSIE NSIE/SFE NSFE/SIE NSIE/SIE SFE/SIE
Charlson comorbidity index[a]	0	33,767 (47%)	2104 (23%)	2147 (35%)	430 (14%)	<0.001	All
	1	34,127 (48%)	5788 (65%)	3563 (58%)	2264 (75%)		
	2	1437 (2.0%)	310 (3.5%)	143 (2.3%)	89 (2.9%)		
	3	1832 (2.6%)	593 (6.6%)	236 (3.9%)	204 (6.7%)		
	4	128 (0.2%)	61 (0.7%)	13 (0.2%)	15 (0.5%)		
	5+	202 (0.3%)	111 (1.2%)	16 (0.3%)	26 (0.9%)		
Median daily ICS dose, FP equivalent (μg)[b,c]		239 (123, 369)	287 (164, 433)	800 (616, 985)	821 (636, 1004)	<0.001	NSFE/NSIE NSFE/SFE NSIE/SFE NSFE/SIE NSIE/SIE
Patients with no ICS purchases, N (%)		3177 (4.4%)	167 (1.9%)	0 (0%)	0 (0%)		
Median daily OCS dose, prednisolone equivalent (mg)[b,c]		0.82 (0.41, 0.82)	1.78 (1.64, 3.02)	0.82 (0.68, 0.82)	2.46 (1.64, 3.56)	<0.001	All
Patients with no OCS purchases		57,772 (80.8%)	288 (3.2%)	3957 (64.7%)	73 (2.4%)		
Number of add on maintenance drug classes used (LTRA/LABA/LAMA)[b]	0	29,648 (41%)	1894 (21%)	0 (0%)	0 (0%)	<0.001	All
	1	31,721 (44%)	3903 (44%)	3091 (51%)	858 (28%)		
	2	9484 (13%)	2661 (30%)	2512 (41%)	1463 (48%)		
	3	640 (0.9%)	509 (5.7%)	515 (8.4%)	707 (23%)		
High SABA use, >450 doses per 12 months		8284 (12%)	2090 (23%)	1486 (24%)	1185 (39%)	<0.001	NSFE/NSIE SIE/NSIE SFE/NSIE SFE/NSFE SFE/SIE
Respiratory antibiotic use[b,d]		22,658 (32%)	5606 (63%)	2701 (44%)	2235 (74%)	<0.001	All

Notes: N (%), median (25^{th}, 75^{th} quartile); [a]5 years before index; [b]during the two-year baseline; [c]among patients with purchases; [d]at least one purchase of doxycycline, amoxicillin, amoxicillin clavulanate, azithromycin, or clarithromycin.

Abbreviations: ICS, inhaled corticosteroid; OCS, oral corticosteroid; LTRA, leukotriene receptor antagonist; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist.

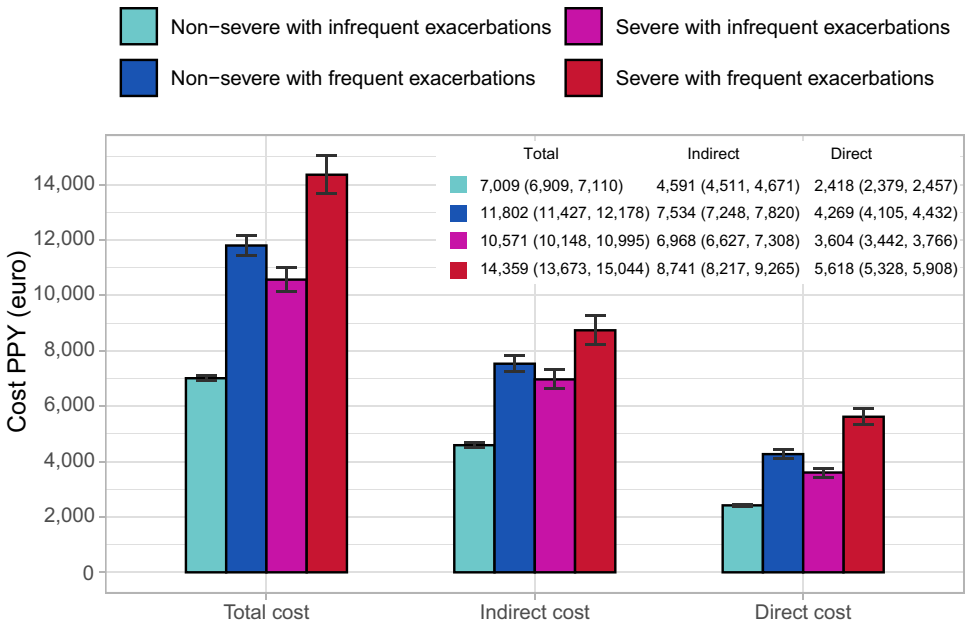

Figure 2 Overall costs per patient year (PPY) in patients <65 years stratified by asthma severity and exacerbation frequency, as well as indirect costs based on sick leaves and disability pensions, and direct costs based on healthcare contacts and medication purchases. Mean total overall cost and 95% CI are shown in the bars, and in table.

patients with non-severe asthma and infrequent exacerbations, the annual overall cost was 2.0-fold higher in those with severe asthma and frequent exacerbations, and 1.7-fold higher in non-severe asthma with frequent exacerbators.

Next, we assessed the contribution of respiratory and other causes to the overall costs. The proportion of respiratory related overall costs were the highest among those with severe asthma and frequent exacerbations (26% of overall costs), followed by severe asthma and infrequent exacerbations (17%) (Figure 3). The most common reason for utilization of public healthcare, other than respiratory reasons, was depression in 1.9–2.8% of the patients. Depression was also the most common reason for long term sick leaves (13.5–18.9%), and disability pensions (20.2–21.3%). Cardiovascular causes were observed in less than 2.5% of the patients. The top 10 diagnoses per respiratory, cardiovascular and other diagnoses for healthcare contacts, sick leaves and disability pensions are presented in Supplementary Tables 3–5.

Most of the annual overall costs were attributable to indirect costs of disability pensions (45–50%) and direct costs of specialty care (20–25%) in all four subgroups, even if sick leaves were more common (Figure 3). The distribution of events per patient-year related to primary healthcare, secondary healthcare, medication purchases, home care, sick leaves, disability pensions, and premature mortality are described in Supplementary Table 6.

Table 2 The Number and Proportion of Working-Aged Patients with Any Productivity Losses per Asthma Severity and Exacerbation Frequency Based Subgroup, and the Proportions with Disability Pension, Long Sick Leaves and Premature Mortality

Subgroup	Non-Severe with Infrequent Exacerbations	Non-Severe with Frequent Exacerbations	Severe with Infrequent Exacerbations	Severe with Frequent Exacerbations
N, total	71,493	8967	6118	3028
Any productivity loss N, (%)	30,082 (42%)	5135 (57%)	3122 (51%)	1867 (62%)
Disability pension N, (%)	8667 (12%)	1767 (20%)	1136 (19%)	684 (23%)
Sick leaves N, (%)	23,227 (32%)	3763 (42%)	2172 (36%)	1305 (43%)
Premature mortality N, (%)	565 (0.8%)	194 (2.2%)	86 (1.4%)	63 (2.1%)

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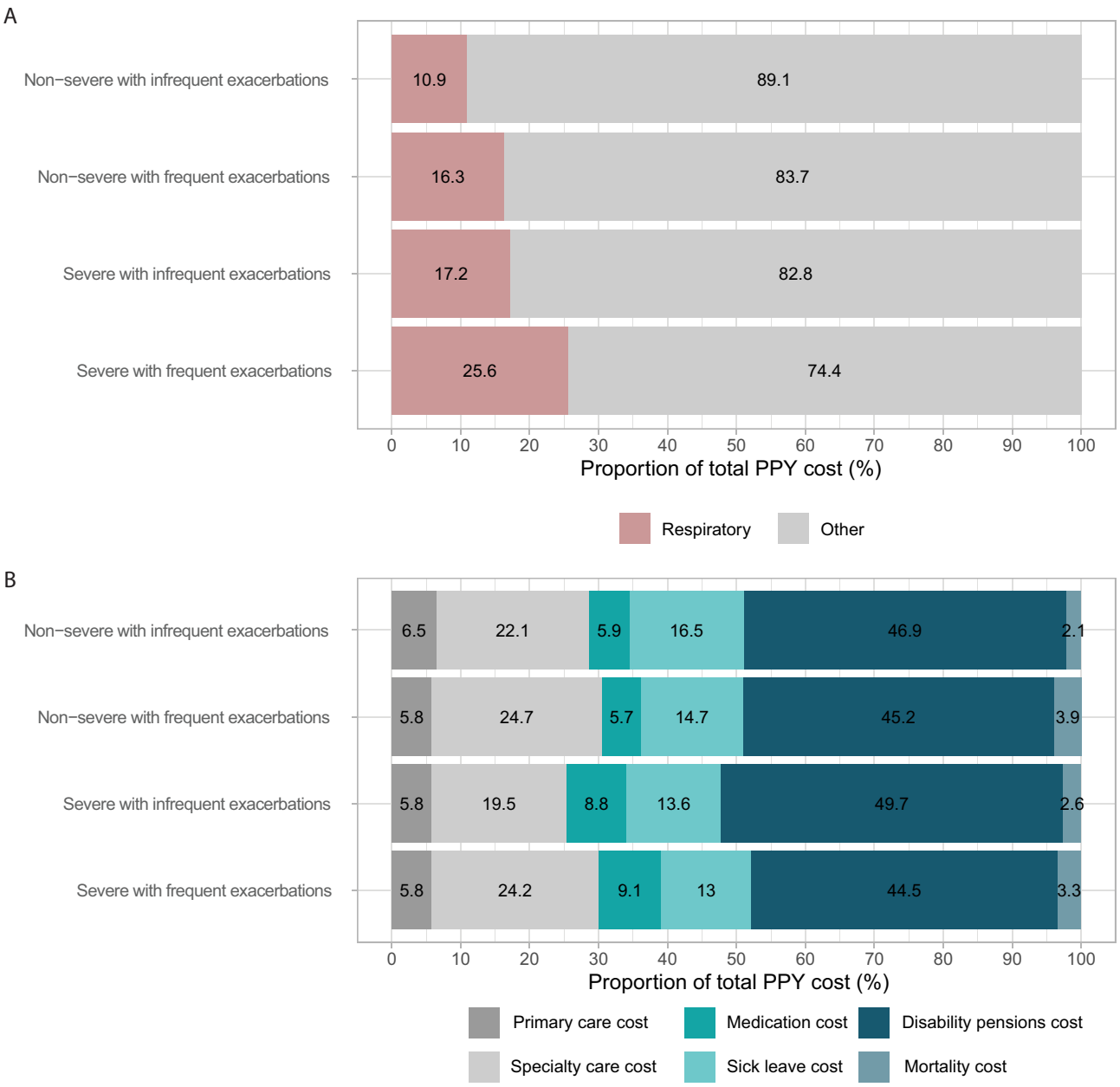

Figure 3 Overall costs per patient year (PPY) in patients <65 years stratified by asthma severity and exacerbation frequency. The proportion of overall costs related to respiratory causes and other causes (**A**), and the proportion of total costs by type (**B**) including primary care, specialty care, medication, sick leaves, disability pensions and premature mortality-related costs.

Finally, we evaluated the impact of asthma severity and exacerbation frequency on overall costs. Severe asthma was associated with a 30% increase in costs compared to non-severe asthma and frequent exacerbations with a 25% increase in the overall costs versus infrequent exacerbations. Both independently predicted the overall costs irrespective of age, sex and Charlson comorbidity index (Table 3).

Similarly, direct healthcare costs increased with severe asthma by 38% compared to non-severe asthma, and with frequent exacerbations by 40% versus infrequent exacerbations, both independent of sex, age and Charlson comorbidity index (Supplementary Table 7). Furthermore, the risk of incurring any productivity loss related costs was elevated in both groups. Based on the Cox regression model, individuals with severe asthma had a 14% higher risk (hazard ratio [HR] 1.14), and those with frequent exacerbations had a 23% higher risk (HR 1.23) of any productivity loss, compared to

Table 3 Gamma Regression Model (with Log Link) of Impact of Asthma Severity and Exacerbation Frequency on Overall Costs in Working-Aged Patients (<65 years of Age)

Overall Costs					
Variable	**Level**	**β**	**exp (β)**	**95% CI (exp (β))**	**P-value**
Asthma severity Reference: non-severe	Severe	0.26	1.30	1.25–1.36	<0.001
Exacerbation frequency Reference: infrequent	Frequent	0.22	1.25	1.20–1.30	<0.001
Age at index (years)		0.02	1.02	1.02–1.03	<0.001
Sex Reference: female	Male	−0.43	0.65	0.59–0.71	<0.001
Charlson comorbidity index Reference: 0	1	0.48	1.62	1.57–1.65	<0.001
	2	1.06	2.89	2.64–3.42	<0.001
	3	1.15	3.16	2.94–3.42	<0.001
	4	1.39	4.01	3.13–5.31	<0.001
	5+	1.65	5.21	4.31–6.42	<0.001
Interaction term of age at index and sex		0.01	1.01	1 – 1.01	<0.001
Intercept		7.45	1719.86	1619.71–1826.21	<0.001

Abbreviation: CI, confidence interval.

individuals with non-severe asthma or infrequent exacerbations, respectively. These associations were also independent of age, sex, and Charlson comorbidity index (Supplementary Table 8).

Discussion

The study focused on direct healthcare and indirect productivity loss-related costs of working-aged patients with asthma. A novel aspect of the study is the comparison of direct and indirect costs in relation to asthma severity and exacerbation frequency, providing a holistic updated overview of the whole asthma population. The overall costs of healthcare contacts, drug purchases and lost productivity varied between €7009 and €14,359 per patient-year, being 2-fold higher in those with severe asthma and frequent exacerbations compared to non-severe asthma with infrequent exacerbations. Productivity loss costs varied between €4591 and €8741 per patient-year and accounted for 57–66% of the overall costs. These costs are somewhat higher than data reported from Sweden with an expenditure of €6500 annually per patient with severe asthma, including direct healthcare costs and lost productivity. Yet, productivity loss related costs accounted for a similar proportion (63%) of total costs.[18] A Danish study showed that the excess cost of healthcare expenditure, productivity loss and welfare expenditure of asthma, compared to matched controls from the general population was €4095, and in patients with severe asthma up to €15,749 annually per patient.[9] Even if methodological differences exist between studies, cost for the patients with severe asthma repeatedly have been shown to be higher than for non-severe asthma.[9,18,19] Our study uniquely highlights that not only asthma severity but also exacerbation frequency have a major impact on the overall costs related to asthma.

Prior studies have examined the impact of asthma on work disability compared to non-asthmatic controls, showing that asthma itself associates with an increased risk of long-term work disability, and that chronic comorbidities increase the risk further.[7] Asthma per se, as well as severe asthma, has also been shown to predict future reduced work ability in men with asthma.[8] Our study adds to the current evidence with more recent data investigating not only the contribution of asthma severity but also uniquely highlighting the contribution of exacerbation frequency on overall costs. We show that severe asthma was associated with a 30% increase in total healthcare and productivity costs, and frequent exacerbations

with a 25% increase, independently of each other. Although direct asthma-related costs accounted only for 11–26% of overall costs among the working aged patients, severe asthma and frequent exacerbations were independently associated also with higher overall costs, regardless of age, sex, or Charlson comorbidity index, underscoring the association with an increased overall morbidity burden. Similarly, severe asthma or frequent exacerbations also increased the risk of having any productivity loss by 14% to 23%. This indicates that the severity and exacerbation frequency themselves add to multimorbidity, evidenced as respiratory unrelated disease burden, and the accumulation of costs and lost productivity that possibly could be prevented.[7,10,20] Considering the patient numbers per subgroup and multiplying by the overall per patient-year costs in our study, the total overall costs for society were €715 million annually among those of working age. Controlling frequent exacerbations could potentially reduce costs annually by 25%, as shown by the regression model, resulting in €178 million yearly cost savings based on our analyses.

Previously we have shown that particularly frequent exacerbations, but also severe asthma, are associated with increased morbidity.[12] The increase in comorbid conditions such as depression, cardiovascular diseases, and metabolic diseases may be associated with the inflammatory state maintained by asthma and exacerbations.[21,22] High doses of corticosteroids, used by the severe frequently exacerbating asthma patients reaching OCS of 3600 mg prednisolone equivalent and 1170 mg of ICS FP equivalent over the four-year follow-up, can also be associated with adverse effects such as metabolic conditions, cardiovascular disease and hypertension.[19,23–25] Determining whether improving asthma control and reducing the inflammatory state and/or the corticosteroid load in patients could positively impact other morbidities and translate into reduced healthcare and lost productivity costs, remains a future area of study.

Timely diagnosis and effective management of mild to moderate asthma are essential for preventing exacerbations and may even help to halt progression to severe asthma.[26,27] Recently, asthma remission has emerged as a key therapeutic goal.[28] A central component of achieving remission is the reduction of exacerbations. Our findings suggest that minimizing exacerbations is not only beneficial for patients' health outcomes but may also contribute significantly to lowering both direct healthcare and indirect productivity loss-related costs associated with asthma.

We show a slight but significantly increasing overall asthma prevalence among working-aged people, per our eligibility criteria, during the years 2017 to 2020 from 2.7% to 3.0%, but also an increase in those fulfilling the criteria for severe asthma with frequent exacerbations from 0.09% to 0.1%. Notably, the criteria for asthma in our study are very stringent, having at least one obstructive airway drug purchase and granted reimbursement for asthma. Some asthma patients never receive a reimbursement number if their physician does not apply for it or the diagnosis has not been confirmed with the criteria despite responding to treatment, affecting prevalence estimates based on reimbursement right. Therefore, we are likely underestimating the prevalence of asthma as we miss many subjects with mild asthma.[4,6,29] However, using reimbursement criteria for cohort formation ensures high specificity for clinically validated asthma, and we likely cover most subjects with more severe asthma or with asthma exacerbations.

If the prevalence trend continues, the societal burden and healthcare costs will rise, despite the positive impact of national allergy and asthma programs in reducing direct healthcare and productivity loss costs in the past.[2,3,30,31] Thus, this study highlights the need for enhanced and holistic treatment focusing especially on patients with severe asthma but also on those with frequent exacerbations for potential overall cost savings. However, future studies with longer follow-up should verify the prevalence trends further.

Most costs observed in the study were due to productivity loss. This view may be limited as Finnish employers must provide at least preventive healthcare, often including primary and specialized services. These occupational healthcare costs, provided by private actors, are missing in this study. Additionally, short-term sickness absences (up to 5 days without a medical certificate) were not included. However, medication use, sick leaves with medical certificates, and pensions from private care are included. As asthma can cause several short-term absences due to pollen season and winter respiratory infections, and reduced presenteeism, we likely underestimate the impact of asthma on productivity costs. Future evaluations should include short-term sick leaves and private healthcare costs. Also, distinguishing between costs associated with asthma or asthma-related comorbidities is difficult and the overall costs should be considered the maximum, and disease related costs the minimum costs related to asthma.[32–35]

Information on asthma symptoms, their impact on daily life, and smoking history were not available for the study. While asthma symptoms are crucial for clinical decisions, the study only used medication use and healthcare contacts to

assess severity and exacerbations a potential source of confounding. This approach may miss exacerbations not linked to OCS purchases, and it cannot evaluate under- or overtreatment of asthma. Since our definition of severe asthma was based on the intensity of prescribed medications, individuals classified as having non-severe asthma but experiencing frequent exacerbations may, in fact, have undertreated severe asthma that does not meet the formal criteria for severity, and should be considered in future studies. Also, as the number of available treatments and the uptake of biological asthma drugs is increasing, whether these have a positive impact on the financial disease burden remains a direction for future research.

Conclusion

We demonstrate a substantial financial disease burden associated with frequent exacerbations in both patients with and without severe asthma, leading to increased productivity loss and direct healthcare costs. Even though most costs were not directly related to asthma, both severe asthma and frequent exacerbations independently increased overall costs, highlighting the potential to reduce these with adequate disease control.

Abbreviations

ATS, American Thoracic Society; ATC, anatomical therapeutic class; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ER, emergency room; ERS, European Respiratory Society; FP, fluticasone propionate; HR, hazard ratio; IBD, inflammatory bowel disease; ICD-10, International Classification of Diseases, Tenth Revision; ICS, inhaled corticosteroid; LAMA, long-acting muscarinic antagonist; LABA, long acting beta-agonist; LTRA, leukotriene receptor antagonist; MCF, mean cumulative function; OCS, oral corticosteroid; SABA, short-acting beta-2 agonist; SII, Social Insurance Institution.

Data Sharing Statement

The single-level data cannot be shared. Only the data holders or Finnish Social and Health Data Permit Authority Findata can grant rights to third parties to use the data in accordance with the Act on Secondary Use of Health and Social Data. This study benefited from data from the following data sources: National Institute for Health and Welfare, the Social Insurance Institution of Finland, Centre for Pensions, and Statistics Finland.

Ethics Approval and Informed Consent

This non-interventional, retrospective register study was conducted in accordance with the Declaration of Helsinki and the Act on Secondary Use of Health and Social Data 552/2019, Finland. The study permission was granted by the Finnish Social and Health Data Permit Authority Findata (permission number THL/2385/14.02.00/2021). Ethical approval and written informed consents were not needed as the present study was based on secondary use of register data, as authorized by Findata in accordance with the Act on Secondary Use of Health and Social Data.

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Author Contributions

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for the authorship of this article. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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