

Disease Control, Not Severity, Drives Job Absenteeism in Young Adults with Asthma – A Nationwide Cohort Study

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Introduction: The impact of asthma and disease control on job absenteeism in young adults is sparsely investigated and conflicting evidence exist. Based on a nationwide cohort, the present study aims to describe the overall job absenteeism across asthma severities and describe the possible influence of asthma control.

Methods: REASSESS is a nationwide cohort of Danish asthma patients aged 18–45 using controller medication between 2014 and 2018, followed retrospectively for up to 15 years using national databases. Impact of asthma was investigated using negative binomial regression adjusted for age, sex, Charlson score and level of education and presented as adjusted incidence rate ratios with 95% confidence intervals.

Results: A total of 60,534 patients with asthma (median age 33 (25, 39), 55% female, 19% uncontrolled disease and 5.7% possible severe asthma) were followed for 12.7 (6.5–14.8) years. The prevalence of any absenteeism was more common in both mild-to-moderate and possible severe asthma compared to the background population (67%, 80% and 62%, respectively; $p < 0.0001$). Compared to the background population, mild-to-moderate and possible severe asthma were more likely to have temporary sick leave (1.37 (1.33–1.42); 1.78 (1.62–1.96)), unemployment (1.11 (1.07–1.14); 1.26 (1.15–1.38)) and obtain disability benefits (1.67 (1.66–1.67); 2.64 (2.63–2.65)). Uncontrolled asthma had increased temporary sick leave (1.42 (1.34–1.50)), unemployment (1.40 (1.32–1.48)) and disability (1.26 (1.26–1.27)) when compared to controlled disease. Significant increases in absenteeism could be measured already at ≥ 100 annual doses of rescue medication (1.09 (1.04–1.14)), patients' first moderate or severe exacerbation (1.31 (1.15–1.49) and 1.31 (1.24–1.39), respectively). Further increases in absenteeism were observed with increasing rescue medication use and severe exacerbations.

Conclusion: Across severities, job absenteeism is increased among patients with asthma compared to the background population. Increases in absenteeism was seen already at ≥ 100 annual doses of rescue medication, representing a substantial, and probably preventable, reduction in productivity among young adults.

Keywords: airway diseases, burden of disease, cost of disease, observational cohort, societal cost

Introduction

Morbidity caused by airway inflammation and the variable respiratory symptoms associated with asthma poses a significant burden both for patients and societies worldwide.¹ Disease control is the utmost goal of asthma management, with well controlled patients experiencing few to none day-to-day symptoms, no restrictions in daily activities and no acute exacerbations.² Treatment with inhaled corticosteroids (ICS) makes disease control an achievable goal for many patients. However, despite the existence of an effective controller treatment, uncontrolled asthma still represents a significant factor with regard to morbidity and mortality across all ages.^{1,2}

The majority of patients with asthma have mild-to-moderate disease, with possible severe asthma comprising a minority (5–10%) of patients.^{3–5} However, poor asthma control is common,⁶ and 60–80% of patients with sub-optimal disease

control and/or possible severe asthma are managed in primary care.^{4,5,7} As such, a large unmet need for improving asthma control exists.⁶ Furthermore, significant socioeconomic and geographic barriers of entry exist in access to both specialist care and novel treatments such as biologics,^{5,8,9} despite their favourable effects on asthma control and not least exacerbation rates.^{7,10,11} Consequently, the question is not whether societal and individual burden can be reduced, but by how much – especially when it comes to uncontrolled mild-to-moderate asthma.

While the evidence associating asthma severity with job absenteeism is conflicting, the link between poor asthma control and increased absenteeism is clearer.^{12–14} Indeed, lack of asthma control has dire consequences for both individual patients and the society at large. At an individual level, lack of control has been linked to poor quality of life (QoL), an increase in perceived symptoms, and even (preventable) death.^{6,14–16} On a societal level, uncontrolled asthma is a driver of productivity loss, decreased job retention and increases in both healthcare and welfare expenditure.^{1,12,14,17} As asthma is a chronic disease affecting patients in the working age, closing the gap between achievable and current control is vital to reducing both individual and societal burden of asthma.⁶

Based on a nationwide cohort of all individuals with actively treated asthma and universal linkage between Danish welfare and health-care databases, the present study aims to quantify job absenteeism of young adult asthma patients across the asthma severity spectrum in comparison to a matched background population. Furthermore, we aim to describe the impact of uncontrolled asthma on absenteeism to elucidate excess absenteeism preventable by improving asthma control across the population.

Methods

The REASSESS Cohort

The REASSESS Danish Asthma cohort is built on nationwide registers provided by the Danish Clinical Quality Program – Asthma (DrAsthma),¹⁸ Statistics Denmark and the DREAM database of public welfare use.

The cohort includes all Danish individuals aged 18–45 redeeming at least two ICS inhalers in a calendar year during the study period 2014–2018, based on age at first ICS redemption. Statistics Denmark provided an age- and sex-matched background population.

Ethics and Data Sharing

All data access complies with relevant data- and privacy protection regulations. Study approvals were granted by the Capital Region of Copenhagen's Data Safety Board (ref. P-2019-142) and the Capital Region of Copenhagen's Scientific Ethics Committee (ref. H-19042597). Data are available upon reasonable request. Approval from data sources and data safety boards may be required as per Danish law.

Medication Dosage, Asthma Severity and Control Definitions

Global Initiative for Asthma (GINA) GINA 2020 guidelines were used to define treatment steps,² and level of ICS treatment was calculated as average daily ICS dose exposure during the study period. Doses reported as standard-particle beclomethasone dipropionate equivalents as described in the [Supplementary Materials Appendix 1](#).

A moderate exacerbation was defined as a prescription of at least 37.5 mg prednisolone for 5 days or more. A severe exacerbation was defined as an exacerbation requiring hospitalization. Excessive short-acting beta₂-agonist (SABA) use was defined as redemption of at least 600 annual doses of SABA.¹⁹ Uncontrolled asthma was defined as either excessive SABA use, two moderate exacerbations and/or one severe exacerbation. Possible severe asthma was defined using International Severe Asthma Registry (ISAR) and GINA 2020 guidelines as Step 4 treatment with two moderate exacerbations or one severe exacerbation or Step 5 treatment irrespective of exacerbation burden.^{2,20}

Comorbidities

Non-respiratory (eg, the group Chronic Respiratory Disease was removed) Charlson Comorbidity Index (“Charlson score”) with updated weights by Quan et al^{21,22} was used to quantify the comorbidity burden in the cohort.

Job Absenteeism

Absenteeism was assessed during an observational period defined as:

- Inclusion: Date of first ICS container redemption after 1/1/2004 unless below the age 18 as of 1/1/2004, where cohort entry was defined as first redemption after the day of the 18th birthday.
- Censor date: 31/12/2018 unless censored by 1) death or 2) emigration.

Absenteeism was defined as either: Disability (Any permanent or temporary disability pension due to severe and chronic illness), Temporary Sick Leave (Any temporary sick leave paid for by public sector funds) or Unemployment (Unemployment benefits) as described in the online [Supplementary Materials Appendix 1](#).

Statistics

Descriptive data is presented as median (interquartile range, IQR). For groupwise comparisons, Wilcoxon rank-sum test or Chi-squared test of independence were used depending on continuous or categorical data.

For comparison of absenteeism between patient groups (background population, mild-to-moderate and possible severe asthma; uncontrolled versus controlled asthma; by GINA 2020 Treatment Step), negative binomial regression analyses were used due to overdispersion, with total observational time used as the exposure/offset variable. Covariates chosen for adjusted analyses were selected based on iterative selection with Vuong's closeness tests of candidate variables (age, sex, modified Charlson score, taxable income, residence area, education level, civil status and white/blue collar occupation) with the final model including age, sex, non-respiratory Charlson score and education level (Basic education, Vocational education or Higher education, as previously defined).⁵ Results are presented as incidence rate ratio (IRR) with corresponding 95% confidence intervals (CI).

R 4.0.2 (The R Foundation, AU) was used for statistical analyses. P-values ≤ 0.05 were considered to be statistically significant.

Results

The present study comprises 60,534 patients with actively treated asthma and a median follow-up time of 12.7 (IQR 6.5–14.8) years. The median age was 33 (25, 39) and 54.6% of participants were female. A total of 5.7% of participants were classified as having possible severe asthma, whereas 19.0% were deemed uncontrolled during the cohort inclusion period of 2014–2018. Further patient characteristics can be found in [Table 1](#).

Prevalence of Job Absenteeism in Young Adults

In the background population, the prevalence of job absenteeism was common with 62% of controls in the background population having at least one week of absenteeism during the follow-up period. In mild-to-moderate and possible severe asthma, the prevalence increased to 67% and 80%, respectively. Furthermore, increasing prevalence of any absenteeism was seen with mild-to-moderate and possible severe asthma in comparison to the background population across unemployment, temporary sick leave and disability benefits ([Figure 1A](#)).

In absolute terms, the number of weeks of absenteeism during the study period in the background population was 7.73 (7.59–7.86), whereas mild-to-moderate and possible severe asthma had 10.12 (9.94–10.30) and 15.90 (14.78–17.10) weeks, respectively. Temporary sick leave represented 1.99 (1.95–2.04) and 2.84 (2.58–3.12) of weeks of job absenteeism for mild-to-moderate and possible severe asthma ([Table 2](#)).

With asthma presence and increasing disease severity, a shift from temporary workforce detachment representing a large majority of absenteeism in the background population to permanent workforce detachment (eg, disability, early retirement) representing close to half (45%) of absenteeism in possible severe asthma was seen ([Figure 1B](#)).

Table I Demographics, Comorbidities, and Treatment of 60,534 Patients with Actively Treated Asthma and an Age- and Sex Matched Control Group

	Background Population (N = 60,534) ^a	Any Asthma (N = 60,534) ^a	Mild-to-Moderate Asthma (N = 57,059) ^a	Possible Severe Asthma (N = 3475) ^a
Age	33 (25, 39)	33 (25, 39)	33 (25, 39)	36 (29, 40)
Female	33,056 (54.6%)	33,056 (54.6%)	31,144 (54.6%)	1,912 (55.0%)
GINA 2020 Treatment Step				
Step 1	N/A	25,497 (42.1%)	25,497 (44.7%)	0 (0%)
Step 2	N/A	13,092 (21.6%)	13,092 (22.9%)	0 (0%)
Step 3	N/A	13,411 (22.2%)	13,411 (23.5%)	0 (0%)
Step 4	N/A	6,005 (9.9%)	5,059 (8.9%)	946 (27.2%)
Step 5	N/A	2,529 (4.2%)	0 (0%)	2,529 (72.8%)
Bronchodilator Use				
Long-acting Beta ₂ -agonists	N/A	23,302 (38.5%)	19,997 (35.0%)	3,305 (95.1%)
Long-acting antimuscarinics	N/A	1,574 (2.6%)	1,061 (1.9%)	513 (14.8%)
Dual long-acting bronchodilators	N/A	1,574 (1.7%)	545 (1.0%)	486 (14%)
Annual SABA Use	N/A	195 (60, 280)	180 (60, 267)	220 (100, 565)
>600 annual SABA doses	N/A	5,762 (9.5%)	4,908 (8.6%)	854 (24.6%)
Uncontrolled Disease^b		11,531 (19.0%)	9,627 (16.9%)	1,904 (54.8%)
Charlson Index ≥2	250 (0.4%)	468 (0.8%)	411 (0.7%)	57 (1.6%)

Notes: ^aStatistics presented: n (%); median (IQR). ^bBased on >600 annual SABA doses, 2+ moderate or 1+ severe exacerbation(s).

Abbreviations: GINA, Global Initiative for Asthma; SABA, short-acting bronchodilator.

The Burden of Asthma-Related Absenteeism

Overall, an increase in job absenteeism compared to the background population was seen across all types of absenteeism in both mild-to-moderate (incidence rate ratio (IRR) 1.24 (1.21–1.27)) and possible severe asthma (IRR 1.64 (1.52–1.76)). Significant increases were seen in temporary sick leave, unemployment, and disability for both mild-to-moderate and possible severe asthma (Figure 2A).

In analyses of asthma patients adjusted for GINA 2020 Treatment Step, consistent increases in absenteeism (IRR range 1.42 (1.34–1.50) to 1.26 (1.26–1.27) for sick leave and unemployment, respectively), were seen in patients with uncontrolled asthma compared to those deemed as having controlled asthma (Figure 2B).

When stratifying absenteeism by GINA 2020 Treatment Step, no significant differences or even reductions in overall absenteeism, sick leave and unemployment were seen in Step 2 to 4 compared to Step 1. Step 5 was associated with increased overall absenteeism and sick leave. Disability increased significantly with each increasing treatment step (Figure 2C).

The Impact of Disease Control on Job Absenteeism

Exploratory analyses to estimate at what level of loss of disease control significant increases in absenteeism begins were performed. Annual SABA use and the number of moderate or severe exacerbations were used as primary covariates and the models were adjusted for GINA 2020 Step, age, sex, education level and Charlson score.

Already in patients redeeming ≥100 doses of SABA annually, absenteeism was significantly increased compared to patients not redeeming SABA (IRR for 100–199 annual doses 1.09 (1.04–1.14)). Further significant increases were seen at 400–599 and ≥600 annual doses (IRR 1.31 (1.23–1.40) and 1.51 (1.42–1.62), respectively) (Figure 3A).

In terms of exacerbations, a consistent increase in job absenteeism was seen in patients experiencing moderate exacerbations, irrespective of the number of exacerbations, with an IRR of approx. 1.36 (Figure 3B). In contrast to moderate exacerbations, a dose-response increase in absenteeism per exacerbation was seen in severe, hospitalization-requiring

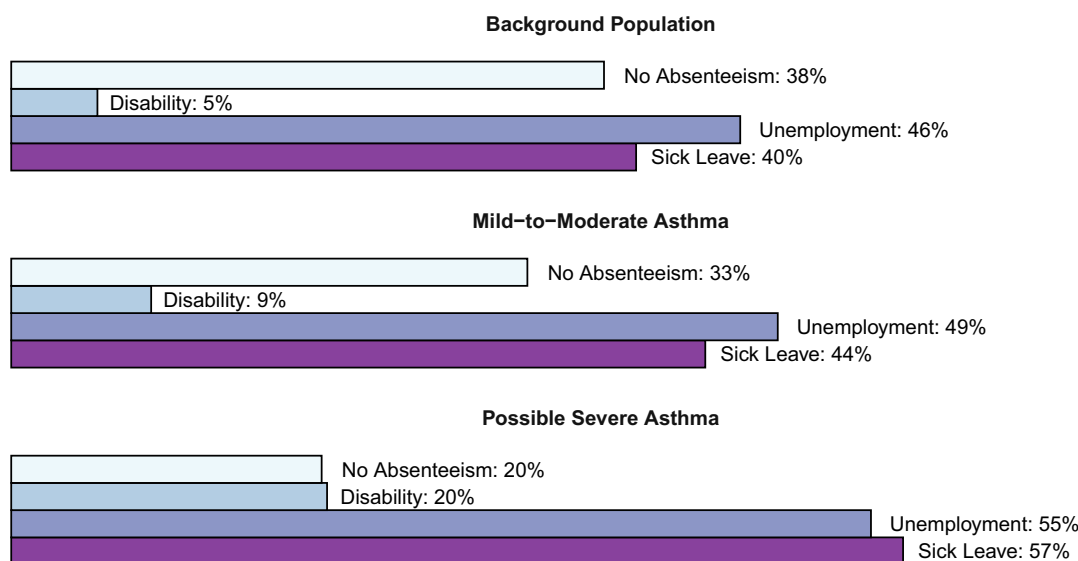
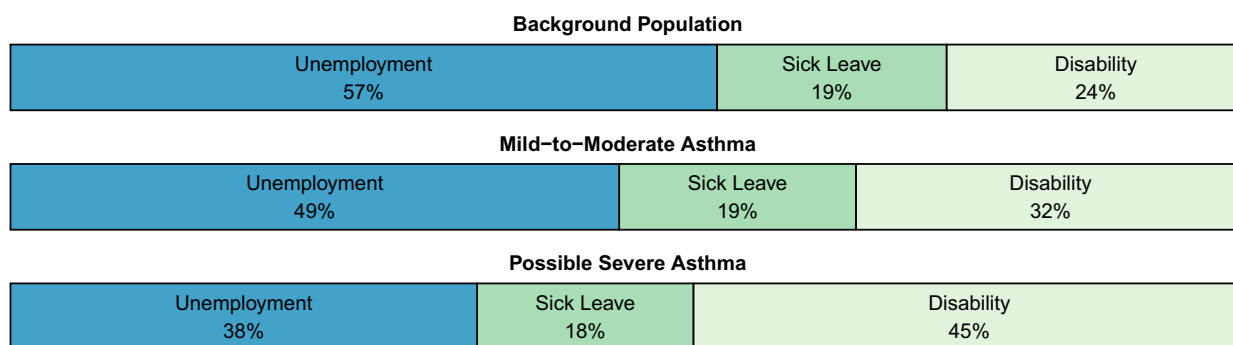
A**B**

Figure 1 Prevalence of job absenteeism in 60,534 patients with actively treated asthma stratified by asthma severity and presented as **(A)** absolute prevalences and **(B)** relative absenteeism. N.B.: Individual patients can claim more than one kind of absenteeism benefits during the observation period.

exacerbations with IRRs ranging from 1.31 (1.24–1.39) to 2.06 (1.83–2.33) for 1 and ≥ 4 exacerbations, respectively (Figure 3C).

Covariates and their associations for all regression analyses are provided in the [Supplementary Tables S1–S4](#).

Discussion

The present study demonstrates increased absenteeism from job and/or education in a large nationwide cohort of young adult asthma patients, when compared to an age- and sex-matched background population. Mild-to-moderate asthma was

Table 2 Job Absenteeism During 15 Years of 60,534 Patients with Actively Treated Asthma and an Age- and Sex Matched Control Group

Job Absenteeism	Any Job Absenteeism		Temporary Sick Leave		Unemployment		Disability	
	Total weeks	95% CI	Total weeks	95% CI	Total weeks	95% CI	Total weeks	95% CI
Background Population	7.73	7.49–7.86	1.45	1.42–1.49	4.39	4.29–4.49	1.93	1.93–1.94
Mild-to-Moderate Asthma	10.12	9.94–10.30	1.99	1.95–2.04	5.02	4.91–5.14	3.26	3.25–3.26
Possible Severe Asthma	15.90	14.78–17.10	2.84	2.58–3.12	6.04	5.51–6.63	7.22	7.19–7.25

Abbreviation: CI, confidence interval.

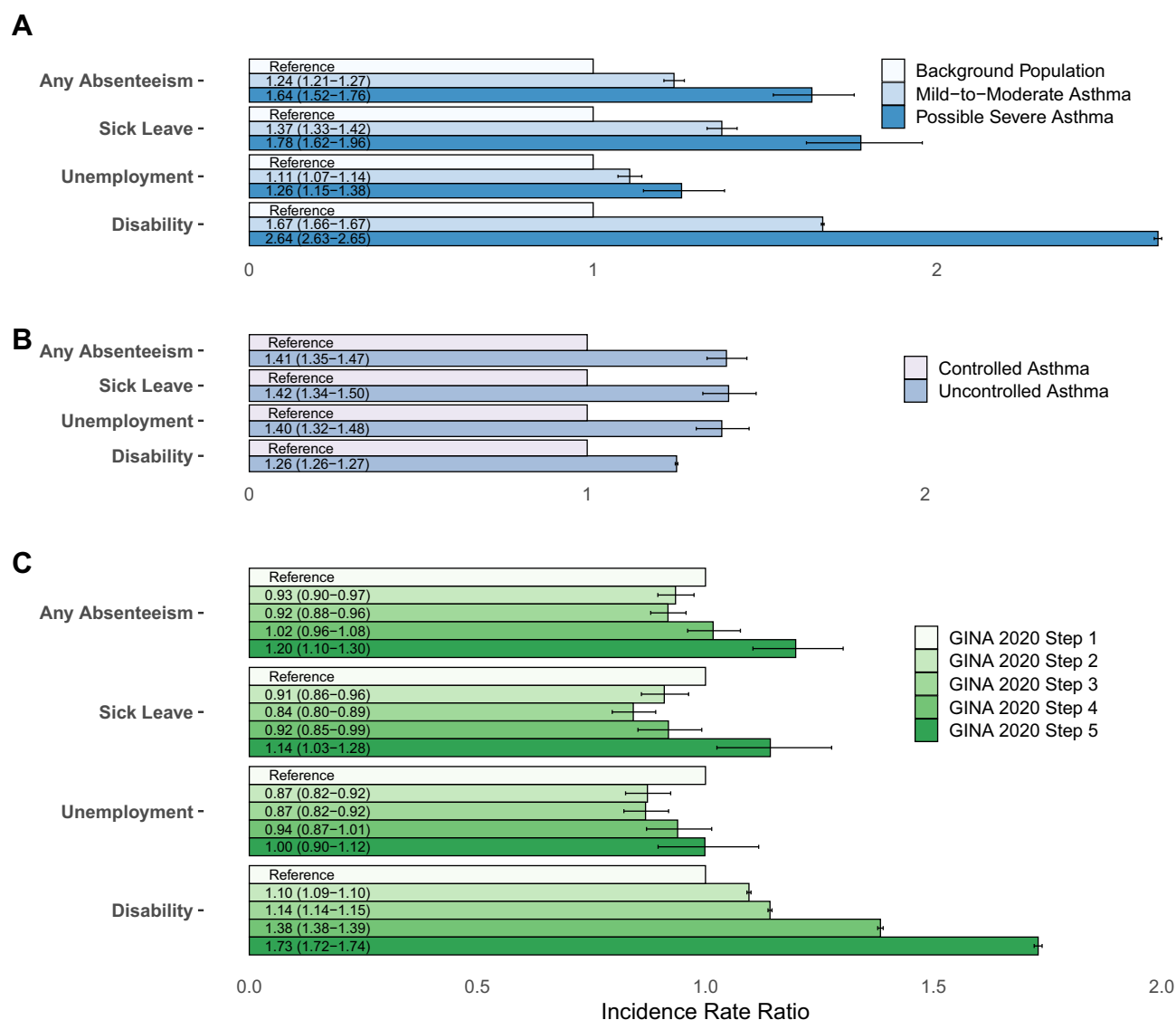


Figure 2 Relative incidence of job absenteeism in 60,534 patients with actively treated asthma stratified by (A) disease severity in comparison to a 1:1 age- and sex-matched background population, (B) asthma control (uncontrolled defined as either ≥ 600 annual doses of rescue medication, ≥ 2 prescriptions of oral corticosteroids or ≥ 1 asthma-related hospitalization) or (C) GINA 2020 Treatment Step during the study inclusion period. All models adjusted for age, sex, Charlson score and education level.

shown to significantly increase job absenteeism, whereas a shift towards permanent workforce detachment was seen with increasing asthma severity. Furthermore, even in patients not typically considered to have uncontrolled asthma due to low SABA use, significant increases in absenteeism were seen.

Prevalence of Job Absenteeism and Productivity Loss

Asthma has a well-known impact on patients' productivity, career progression and job security.¹² In a previous Danish study utilizing the same Ministry of Employment DREAM database by Hansen et al, patients with self-reported asthma were shown to have increased job absenteeism with blue-collar workers being particularly at risk.¹⁷ The present study confirms Hansen et al's¹⁷ findings of increased absenteeism yet, interestingly, fail to find a dose-response relationship between GINA 2020 Treatment Step and absenteeism, supporting the assumption that disease control, not asthma severity itself is the main driver of increased absenteeism. Whether the major determinant of absenteeism is control or severity has been previously investigated with conflicting results probably attributable to differences in settings and mode of absenteeism reporting,^{12,13,23,24} yet the present study adds valuable evidence from a large nationwide cohort without selection bias and

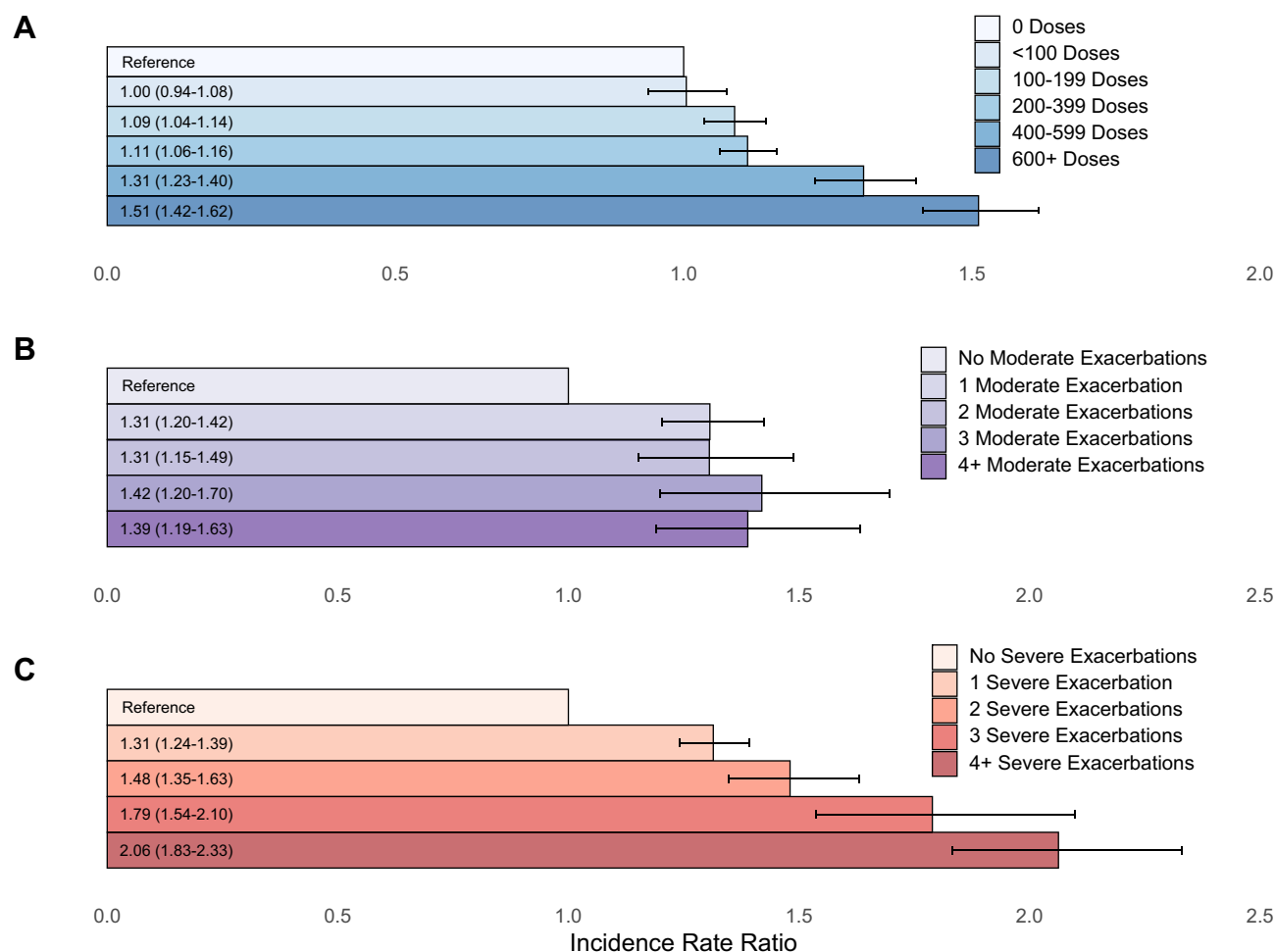


Figure 3 Relative incidence of overall job absenteeism in 60,534 patients aged 18–45 with actively treated asthma stratified by (A) annual rescue medication use, (B) number of oral corticosteroid prescriptions and (C) number of asthma-related hospitalizations during the study inclusion period. All models adjusted for age, sex, Charlson score and education level.

objective reporting of absenteeism. Asthma phenotypes have also been shown to affect job absenteeism with adult-onset asthma being a risk factor for increased disability use, in contrast to early onset asthma.^{17,25} As adult-onset asthma has a tendency to be relatively more comorbidity-driven and difficult to control,²⁶ the present study might underestimate the impact of asthma on absenteeism across the entire age spectrum due to its age restriction to 18–45-year-olds.

Presenteeism (defined as showing up for work despite being ill) has garnered attention when describing health and disease impacts within the recent decade.²⁷ In asthma, absenteeism has been described as the tip of the iceberg, with presenteeism being far more prevalent than actual absenteeism.²⁸ While social security for short- and long-term illness differs across the world and as presenteeism could be argued to depend on income security, Denmark is generally in a high position on the Organisation for Economic Co-operation and Development Social and Job-Security index,²⁹ indicating a relatively low risk of income security loss when ill and thus, hypothetically, relatively lower presenteeism. Indeed, Gruffydd-Jones et al³⁰ demonstrated that work productivity losses range between 3.5% in the UK to 17.4% in Brazil in a multi-national study on productivity loss in asthma, signalling that beyond welfare security, health disparities and even differences in climate could affect asthma productivity loss. Furthermore, Gruffydd-Jones et al³⁰ found that approximately 3.4 hours of work were lost per week due to asthma, whereas another study found that patients with asthma missed an average of 5.3 days of work annually (corresponding to 0.7 to 0.9 hours of work per week).³¹ As such, while the DREAM database tracks publicly funded welfare transfers, and thus accurately describes the burden of

absenteeism from a perspective of societal burden, the present study might still underestimate a major part of asthma's impact on the workforce seen from the perspective of the individual or the employer.

The Importance of Asthma Control

GINA was developed with the top priority of facilitating best-possible asthma control at a global level, as uncontrolled asthma is a significant driver for impaired quality of life, increased morbidity and even mortality.² In the present study, approximately one in five patients were deemed uncontrolled based on reliever use or exacerbations. Furthermore, and perhaps more alarming, our findings demonstrate that the impact of low disease control, measured as annual SABA use, on absenteeism begins much earlier (at ≥ 100 annual doses) than the cut-offs typically used for uncontrolled asthma or excessive SABA use,¹⁹ such as ≥ 450 –600 annual doses. Considering the global prevalence of SABA over-reliance ranging from 9% to 38%³² and the potential risks associated with high beta₂-agonist use,^{33,34} a considerable burden of not just uncontrolled, but also partially controlled asthma on absenteeism can be assumed.

Given the high degree of absenteeism shown in the present and earlier studies, as well as asthma's impact on presenteeism, improving disease control could be a compelling tool for reducing both present- and absenteeism. In a large study of five common chronic diseases, patients with asthma and/or COPD who were adherent to their controller medication had 10–23% lower absenteeism, resulting in 3–7 fewer annual days of absenteeism in a confounder adjusted model, suggesting that there are large gains that are achievable on both individual and societal levels.³⁵ Other studies have shown impressive reductions in productivity loss with increasing asthma control,²⁴ as well as a 13% increase in productivity losses in uncontrolled asthma when compared to controlled asthma.³⁶ However, a simulation study investigating the impact of increased adherence in asthma concludes that while improving adherence on a population level does reduce the prevalence of uncontrolled asthma and exacerbations, it casts doubts on the cost-effectiveness and, especially, the cost-saving capabilities of adherence interventions.³⁷

Mild-to-Moderate Asthma and Workforce Attachment

In terms of risk factors for workforce detachment for individuals with asthma, studies have focused on either severe asthma or persistent asthma.^{38,39} As most patients living with asthma are considered to have mild-to-moderate disease, the present study highlights that not just severe or persistent asthma, but asthma as a whole, negatively impacts workforce attachment. Indeed, even in terms of mild asthma, presenteeism has been shown to be increased by approx. 12%.⁴⁰ As mentioned above, symptomatic asthma is indeed a critical factor for job absenteeism, yet patients with asthma often underreport and accept their symptom burden and day-to-day limitations due to asthma.⁴¹ A change in physician, but also patient, attitude towards not accepting lack of symptom control may be supported considering the psychological ramifications of symptom burden and its associated workplace productivity impairment.³⁰ In terms of future perspectives, the recent change in GINA guidelines towards as-needed ICS/formoterol for mild-to-moderate disease has shown promise in reducing exacerbation and symptom burden,² showing promise for absenteeism and impaired productivity, yet its true impact remains unexplored.

Limitations

A major limitation in the current study is the lack of registration of temporary sick leave below 14 days, as the DREAM database is an administrative database of public transfer income rather than a research database; however, on the other hand, its content has been validated.⁴² While the first 14 days of absence are retroactively registered in DREAM on the 15th day of absence, short-term temporary sick leave below 14 days is paid by the employer and is thus unavailable for analysis. This limitation is accentuated by the fact that short-term sick leave may be hypothesized to be even further increased in patients with asthma compared to the background population due to an increased susceptibility to respiratory infection,⁴³ resulting in underestimation of the true asthma-related impact on absenteeism in the present study. Another major limitation is residual confounding from unmeasurable variables as job absenteeism is a multifaceted phenomenon with factors such as health literacy and self-efficacy having a large potential effect on absenteeism yet are unavailable in registry-based studies.

The REASSESS Young Adults cohort is based on public registries and has previously been described in detail.^{5,44} However, due to limitations of the Danish National Database of Reimbursed Prescriptions prescribed doses of ICS are not available for research purposes and ICS doses are thus calculated as average daily exposure based on prescription redemption during the study period. While this integrates real-world adherence into the calculated ICS dose, GINA Treatment Steps are based on prescribed dose, and this should be kept in mind when performing direct comparisons to other cohorts.

Conclusions

In a nationwide cohort of young adults with asthma, job absenteeism was significantly increased even in mild-to-moderate disease compared to the background population even after adjustment for known risk factors. Furthermore, considering the significant impact of even partially controlled disease, further attention to achieving asthma control in young adults to reduce the burden of asthma on both individual and societal levels is warranted.

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