Patient-centred outcomes in severe asthma: fatigue, sleep, physical activity and work

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Severe asthma's burden extends beyond physical symptoms. This review highlights four key patient needs: fatigue, sleep, physical inactivity and work productivity. These needs impact asthma control and quality of life and call for targeted interventions. https://bit.ly/3PLCm9D

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Abstract

Severe asthma places a significant burden on patients, with recent research revealing overlooked patient needs extending beyond physical symptoms. To optimise the patient-centred approach to managing severe asthma, it is crucial to deepen our understanding of these needs. This review examines the prevalence and impact of four prioritised patient needs in severe asthma, namely fatigue, sleep disturbances, physical inactivity and reduced presence and productivity at work. It explores how these factors relate to classic asthma outcomes and quality of life, and the potential impact of interventions. Fatigue affects up to 90% of patients, while sleep difficulties impact 70–75% of severe cases, contributing to impaired daily function and quality of life. Although both are linked to asthma control, the cause-and-effect relationship remains unclear, making it clinically intriguing to investigate whether interventions targeting fatigue or sleep problems affect asthma control. In asthma patients, physical inactivity occurs both as consequence and contributing factor to uncontrolled disease. Interventions promoting physical activity improve asthma control and quality of life, suggesting a potential role in severe asthma management. Finally, work productivity loss, notably present in severe asthma cases, strongly correlates with asthma control and exacerbations. While biologic therapies show potential to reverse this loss, their effects on physical activity, fatigue and sleep disturbances warrant further investigation. Nonpharmacological interventions targeting these needs, such as pulmonary rehabilitation and behavioural therapies, may provide opportunities to enhance patients' well-being. Overall, this review highlights significant gaps in understanding patient-centred aspects of severe asthma, urging for research on comprehensive interventions to improve patients' lives.

Introduction

While most asthma patients manage well with inhalation therapy, approximately 3–8% suffer from severe asthma, as defined by European Respiratory Society/American Thoracic Society guidelines [1], where existing medications prove to be insufficient despite optimisation efforts [1–3]. Severe asthma is a complex and heterogeneous condition, characterised by persistent symptoms and an increased risk of severe attacks, which imposes a heavy daily burden and often necessitates high doses of corticosteroids, with associated side-effects [4–8]. Fortunately, for most patients, but not all, the situation has improved considerably with the availability of biologics; however, residual disease manifestations are still at play in many cases [9]. The impact of severe asthma extends beyond patients to family, caregivers and society, accounting for a disproportionate share of asthma-related social costs [10, 11].

While current research emphasises the effect of targeted therapies on exacerbations, maintenance oral corticosteroid (OCS) use and lung function, recent qualitative and quantitative studies reveal overlooked patient needs, spanning emotional, financial, functional and medication-related burdens, all of which impact patients' quality of life (QoL) [12–15]. Of note, while physicians and patients often describe the direct physical consequences of asthma or medication in a concordant way, other aspects of importance to patients seem to be less visible to physicians [16]. These aspects are therefore rarely used as outcomes to assess whether a new treatment is working, while they are key outcomes for patients [12]. For patients, in addition to the well-known direct physical consequences of asthma, their overall QoL is of main importance and needs to be improved [14, 16, 17]. Focusing on specific aspects, they especially mention the limitations in daily life activities and the sense of "missing out" (*e.g.* "I want to be able to do more physical activity, to be more social, to improve my presence in the workplace and productivity"). They also highlight the indirect physical consequences of having asthma and asthma treatments, with prevalent concerns including "I want to be less tired, to sleep better" (figure 1) [12, 14, 16].

To improve the patient-centredness of severe asthma management, we need more insight and recognition of the outcomes that matter most to patients living with the condition [15]. Therefore, this narrative review explores four patient-centred needs. Firstly, it examines the prevalence and impact of fatigue, sleep disturbances, physical activity (PA) and loss of work productivity in severe asthma. Secondly, it explores whether poorer outcomes in these factors are related to poorer classical asthma outcomes as well as poorer QoL. Finally, the review describes the potential impact of asthma-targeted interventions on the discussed patient-centred outcomes, as well as interventions designed to enhance these outcomes and improve overall asthma management. By focusing on these specific aims, the review seeks to highlight the significance of these areas in the context of severe asthma and inform future research directions.

Methods

In preparing this narrative review, we conducted a search in Medline using separate search strings for fatigue, sleep, PA and work productivity combined with search terms for asthma in an adult population (supplementary table S1). Additionally, reference lists were reviewed for relevant articles, as well as authors' personal files. To include as many relevant studies as possible, we did not restrict our search terms to severe asthma. However, as the definition of severe asthma has evolved over time and can differ across studies, we present the specific definitions used in each study in supplementary table S2. We aimed to report the results of this narrative review in accordance with the Scale for the Assessment of Narrative Review Articles (SANRA) guidelines [18], noting that, in line with these guidelines, this review does not provide a comprehensive overview but highlights key studies. Large language models (including ChatGPT) were used exclusively to enhance the textual quality of this review.

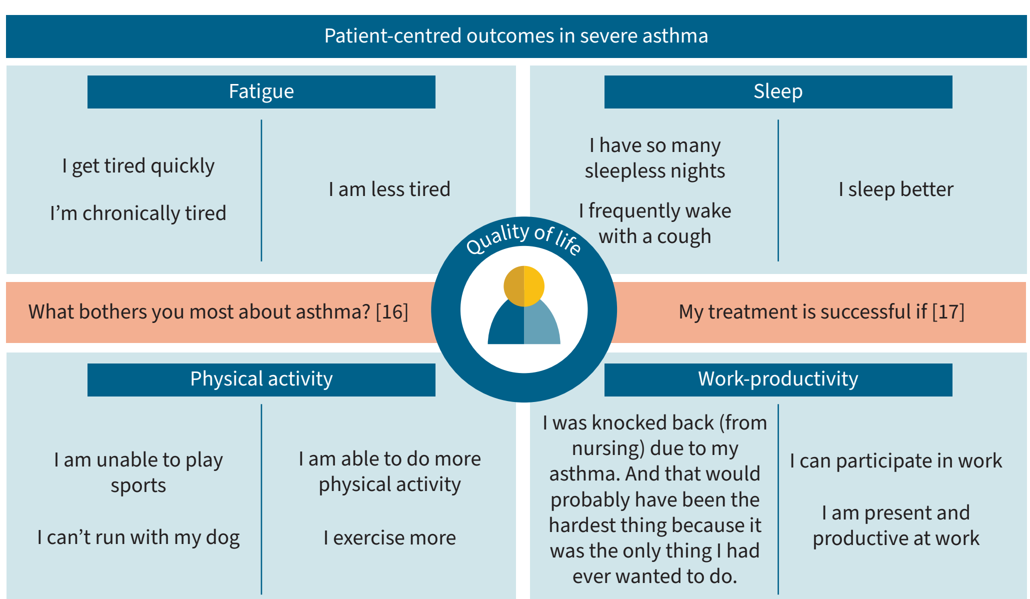

FIGURE 1 Important outcomes from a patient perspective. The left-hand panel within each outcome refers to the question "what bothers you most?'. The right-hand panel within each outcome highlights important outcomes for successful treatment. Phrases are adapted from [14, 16, 17].

Fatigue

Fatigue, defined as a "persistent, overwhelming sense of tiredness, weakness, or exhaustion resulting in decreased capacity for physical or mental work", is not uncommon in the general population [19–21]. However, in various clinical conditions, such as chronic inflammatory diseases, it can be a significant source of disability, often reported as one of the most bothersome symptoms [22–25]. Unfortunately, fatigue is frequently overlooked in symptom assessments and rarely serves as an end-point in interventional trials. This may stem from its subjective nature and the lack of a widely accepted measure of fatigue [20] or because of disagreements over its significance. Rheumatological diseases stand as an exception, where fatigue has been a core outcome measure in drug research for several years [26].

In recent years, there has been an increased interest in recognising fatigue as an extrapulmonary trait in asthma, emphasising its importance in clinical practice [27, 28]. Depending on the asthma population studied and measures used, studies indicate that fatigue prevalence in asthma ranges from 50% to 90% [27–32], comparable to rates experienced by oncology patients [33]. A recent Dutch study in asthma patients referred to a pulmonologist, identified fatigue as the most prevalent extrapulmonary treatable trait, with severe fatigue linked to more uncontrolled asthma (OR 3.0, 95% CI 1.9–4.7) and reduced QoL (OR 4.6, 95% CI 2.7–7.9) [30]. Cross-sectional studies in varying asthma severities confirm the association between higher fatigue scores and poorer asthma control, more frequent exacerbations, and lower QoL [27, 28, 32]. In addition, associations of higher fatigue scores have been reported with female gender, younger age and comorbidities such as obesity, reflux and depression and anxiety [27, 28, 32], but these findings are not yet conclusive.

The impact of fatigue in patients with severe disease is underexplored, with one study indicating no difference in fatigue scores between severe and mild asthma [27]. However, the noteworthy observation that 74% of severe asthma patients report "waking up and still feeling tired" weekly, with about half experiencing it daily [29] highlights fatigue as a significant concern in this population, warranting further in-depth research on this disabling symptom.

Interestingly, only 22.5–28.9% of the variance in fatigue scores is explained by asthma control and dyspnoea score [27, 28]. Fatigue is also only moderately significantly associated with Asthma Quality of Life Questionnaire (AQLQ) score [31, 32]. This suggests that fatigue is conceptually different from asthma control and QoL, prompting the question of the cause-and-effect relationship between uncontrolled asthma and fatigue. Longitudinal studies are essential to understand whether fatigue is particularly problematic during active disease, improves with asthma therapy or persists during periods of good asthma control.

Limited data exists on interventions targeting fatigue in (severe) asthma. While biologics for severe asthma have shown beneficial effects on some extrapulmonary manifestations, their impact on fatigue remains uncertain in terms of improvement, magnitude or potential predictive patterns for treatment response. Fortunately, recent data collection on fatigue severity in severe asthma registries and cohorts holds promise for offering more insights into the effects of biological and other treatments on this troublesome symptom in the near future. Pulmonary rehabilitation, whether through home-based programmes or in clinical settings [34, 35], may also have a beneficial effect on fatigue severity, but this needs confirmation through robustly designed randomised and controlled studies. The observed similarity in extrapulmonary symptom patterns between severe asthma and fibromyalgia suggests a common complex aetiology [29]. Exploring whether evidence-based behavioural interventions for fibromyalgia could be beneficial for severe asthma patients reporting extrapulmonary symptoms, including fatigue, is a promising avenue for further research.

Overall, despite the high prevalence of fatigue in (severe) asthma, this complaint is largely ignored in the asthma literature. To address this oversight, future research should focus on determining the most appropriate fatigue measure and exploring multifactorial mechanisms and treatment strategies for fatigue in asthma. As fatigue is of great importance to both patients and society, it should be a key consideration in future studies assessing drug effects in asthma.

Sleep disturbances

Sleep quality is important for general health and well-being and the recommendation for the general population is at least 7 h of regular sleep per night [36]. Short sleep duration is linked to various health issues, including type 2 diabetes, hypertension, depression, obstructive sleep apnoea, cancer and cardiovascular disease [37, 38]. Additionally, individuals who sleep for shorter durations experience a higher prevalence of respiratory symptoms compared to those with normal sleep patterns [39].

Asthma patients frequently report sleep disturbances, with prevalence rates exceeding 70–75% in severe cases [40–42]. These disturbances encompass challenges in falling asleep, night-time awakening, early morning awakening, altered sleep duration and compromised sleep quality. In a recent qualitative study, individuals with moderate-to-severe asthma identified shorter sleep duration, poor sleep quality and, particularly, night-time awakening as the most bothersome aspects of disturbed sleep [43]. These disturbances contribute to daytime sleepiness, affecting 40% of a severe asthma cohort, thereby negatively impacting daily functioning and QoL [43–45].

Several studies indicate a link between poor sleep quality, inadequate sleep duration and asthma control [45, 46]. Specifically, insomnia, characterised by sleep-specific complaints accompanied by daytime symptoms, was highly prevalent (37%) in the SARP (Severe Asthma Research Program) asthma cohort [40]. Moreover, it was associated with 2.4-fold increased odds of having poorly controlled asthma, as well as a higher likelihood of asthma-related emergency room visits and admission in the preceding year [40].

However, the relationship between sleep disturbances and asthma control is complex and suggests bidirectional causality [47]. Sleep disturbances may stem from poorly controlled asthma, linked to nocturnal asthma symptoms, potentially due to circadian activation of inflammatory cells [48] and reduction in lung volume [49]. In addition, the side-effects of asthma medications, especially corticosteroids, may impact sleep quality [50]. Importantly, common comorbidities in severe asthma, such as rhinosinusitis, obstructive sleep apnoea, gastro-oesophageal reflux disease, obesity, depression and anxiety, all affect sleep and can complicate the picture, but also provide treatment options with potential beneficial effects for sleep [45, 51, 52]. Of note, while treatment improving asthma control and optimising comorbid factors may alleviate sleep disturbances in some patients, it does not universally resolve them. This suggests a bidirectional relationship where asthma may impact sleep, but poor sleep itself may also cause or worsen the disease.

Indeed, in an 11-year follow-up in the HUNT study, involving the entire adult Norwegian population, individuals experiencing chronic insomnia symptoms had a threefold higher risk of developing asthma than those without such symptoms [53]. A recent meta-analysis further substantiated the positive association between sleep disorders and the increased prevalence and incidence of asthma in adults, although cautioning about confounding factors [54]. The role of sleep disturbances in the onset or development of severe disease remains unknown. A very interesting recent prospective Chinese cohort study identified reduced sleep duration in asthma as an independent risk factor for poorly controlled asthma and future exacerbations, potentially mediated by nontype 2 airway inflammation [52]. While valuable as the first study prospectively evaluating the association between sleep duration and asthma exacerbations, this study also highlights the challenges for research in this area, including outcomes influenced by self-reported *versus* objective sleep measures such as actigraphy or polysomnography and the choice of potential confounders [47]. Above all, it emphasises the need for intervention studies exploring the impact of improved sleep quality on asthma control.

Currently, only a few studies have investigated asthma-targeted interventions in terms of sleep disturbances in patients with moderate-to-severe asthma. In two *post hoc* analyses of OCS-dependent severe asthma patients, dupilumab appeared to reduce the impact of asthma on sleep disturbance compared with placebo, although the outcome measures used were not very specific [55, 56]. Results from a prospective study designed to evaluate the effect of dupilumab on various aspects of sleep in patients with severe asthma are awaited. From another perspective, data suggest that sleep duration can be increased by behavioural interventions [57], although there are limited data within asthma populations. A small randomised controlled trial (RCT) involving moderate-to-severe asthma patients, which focused on a behaviour change intervention, reported significant improvements in sleep efficiency and latency with increased PA levels; however, its relation to asthma control is unknown [58]. A pilot study of internet-based cognitive-behavioural therapy for insomnia in adults with asthma and comorbid insomnia found it to be feasible and potentially efficacious, showing significant improvements in both sleep measures and asthma outcomes [59]. This supports further research aimed at optimising this programme for individuals with asthma.

In conclusion, despite limitations in current evidence, there is a substantial impact of sleep disturbances on the disease burden and well-being of patients with asthma. The identified associations suggest potential opportunities to investigate sleep as a target for enhancing QoL, possibly through a multicomponent intervention. Therefore, longitudinal and intervention studies are essential to deepen our understanding of the interplay between asthma control and sleep disturbances. With insights into possible underlying mechanisms, implementing appropriate interventions becomes crucial to ultimately enhance outcomes for asthma patients.

Physical activity

PA is regularly defined as any bodily movement produced by skeletal muscles that requires energy expenditure (>1.5 metabolic equivalent of task (MET)) [60] and can be performed at a variety of intensities [61]. For optimal health benefits and improved QoL, adults, including those with chronic conditions, are strongly advised to engage in either 150 min of moderate-intensity or 75 min of vigorous-intensity aerobic PA per week, or a combination of both [61, 62]. Additionally, recent evidence advocates for reducing sedentary behaviour, defined as low-energy expenditure (⩽1.5 MET) activities such as sitting or lying down while awake, and replacing it with any intensity of PA [61].

In asthma, physical inactivity has been identified as a nonpharmacological treatable trait [63] and is highly prevalent as shown among Dutch patients with a first time ever referral to a pulmonologist (53%) [30]. Indeed, a large body of evidence, including systematic reviews with meta-analyses, indicates lower levels of PA in patients with asthma *versus* healthy controls [64–67]. Moreover, lower PA levels are associated with poorer asthma control [64, 67–71], more exacerbations [72], lower lung function [70, 72] and poorer QoL [64, 67, 73]. Lower PA may also be associated with increasing disease severity [74], although those findings are conflicting. A German study reported fewer daily steps in severe asthma compared to mild-to-moderate cases [74]. Additionally, Australian patients with severe asthma exhibited reduced levels of moderate PA compared to healthy controls [72]. However, two smaller studies did not observe this trend [75, 76]. Discrepancies could be due to variations in sample size or covariate adjustments and the use of different accelerometers, therefore complicating result comparisons [77].

Interestingly, there is some evidence suggesting that patients with severe asthma, despite performing less moderate PA, might exhibit slightly lower sedentary behaviour and perform more light PA compared to controls [64, 78]. This suggests a potential substitution of moderate PA with light PA, possibly due to disease-specific barriers to moderate and vigorous PA. Replacing sedentary behaviour with larger amounts of light PA may be a more achievable goal for these patients, with greater health benefits, than replacing it with smaller amounts of moderate PA [78]. However, while PA has received much attention in asthma research, sedentary behaviour has not yet been studied as extensively [70, 78, 79]. As reducing sedentary behaviour correlates with health benefits independently of PA [61], it should be explored both as a potential outcome measure and as a target for intervention in future asthma studies [80].

The challenges encountered in addressing PA behaviour in people with asthma are diverse and have been thoroughly examined [70, 81]. One of the reasons why patients with asthma are less active than healthy controls is that PA, particularly when vigorous, is a potent stimulus for asthma symptoms. Additionally, asthma-specific barriers such as fear of symptoms, exacerbation concerns, motivational issues and lack of support, hinder exercise [70, 81–83]. Supportive networks, including healthcare professionals or family and friends, can encourage exercise [70]. However, discussing exercise in clinical practice often takes a low priority due to the competing demands faced by both patients and healthcare providers [81]. Providers may also lack the knowledge and guidelines to effectively promote lifestyle changes. Overcoming these barriers may require supervised programmes led by professionals [81]. Interestingly, distinct asthma clusters based on clinical characteristics reveal different patterns of PA, calling for personalised approaches [69, 80, 84]. Moreover, changing PA involves understanding its complexity, as it may concurrently affect or be affected by factors such as fatigue or sleep, underscoring the need for a multidimensional approach.

As physical inactivity may not only be a consequence of asthma, but poor levels of PA may also worsen asthma outcomes [85], increasing PA may provide opportunities to optimise asthma management, particularly in severe cases [81, 85, 86]. Many PA interventions and pulmonary rehabilitation programmes of different types, durations, frequencies and intensities exist for patients with asthma. Reviews highlight their effectiveness in boosting PA, enhancing asthma outcomes and improving QoL [79, 87, 88]. Moreover, a recent study revealed that 6 months of exercise for untrained asthma patients yielded a sustainable and clinically relevant reduction in daily inhaled corticosteroid dose without compromising asthma control [89]. For severe asthma specifically, a systematic review and meta-analysis showed a promising effect of PA interventions on steps per day, asthma control and QoL [86]. Of interest, more recent RCTs showed that behavioural change programmes were not only successful in increasing moderate to vigorous PA, reducing sedentary time and enhancing asthma control, but also resulted in less anxiety and depression and improved sleep quality [58, 90]. While specific intervention recommendations lack ample evidence, recent studies hint at potential differential effects [91, 92]. For example, in patients with moderate-to-severe asthma, constant-load exercise and high-intensity interval training (HIIT) both enhanced aerobic fitness, yet HITT notably reduced dyspnoea [92]. In another study, moderate exercise significantly reduced sputum eosinophils, as compared to controls, whereas vigorous exercise had no effect [91]. Moreover, these effects were greatest in patients with the eosinophilic phenotype. Other important questions for future research involve the sustainability of pulmonary rehabilitation effects post-intervention and their impact on long-term asthma outcomes [80]. Encouragingly, recent findings from a 10-week pulmonary rehabilitation programme show increased daily steps and enhanced asthma control, sustained even at a 1-year follow-up [93].

Interventions not primarily targeting increased PA may still yield benefits by addressing underlying causes or barriers. On one hand, behaviour change techniques, particularly those focusing on self-regulation, sustained motivation and behaviour modification, are suggested to be effective in asthma interventions [79]. Regarding pharmacological interventions, two small studies explored the impact of biological treatments on PA in severe asthma patients [94, 95]. An Italian study of 30 patients receiving omalizumab or mepolizumab reported a sustained and significant increase in PA levels over 6 months compared to standard care [94]. It noted a positive correlation between steps per day and QoL but not with forced expiratory volume in 1 s % predicted or asthma control. In a Greek study with 21 severe asthma patients, mepolizumab led to a significant rise in daily step count and increased activity intensity without altering duration [95]. Future (real-world) studies should consider PA as an outcome measure in evaluating biological therapy as it has the potential to help patients meet PA recommendations.

To conclude, physical inactivity is a treatable trait, which is prevalent in patients with severe asthma. Patients experience both general and disease-specific barriers, but at the same time will benefit from increasing PA levels and decreasing sedentary time and should be assisted in achieving this goal. However, at present, this is a low priority due to conflicting priorities, a lack of guidelines, insufficient financial reimbursements for physiotherapy and other interventions, and the fact that many healthcare providers are not adequately trained to provide this type of care. Pharmacological and nonpharmacological therapies, including multidimensional or behavioural interventions, have been shown successful in increasing PA levels and improving asthma control and QoL. It may be hypothesised that starting a supervised intervention may remove the initial barrier to exercise experienced by some patients. Patients with severe asthma may benefit most from PA behaviour that can be sustained in order to improve asthma control and eventually their QoL. Initially, focusing on replacing sedentary behaviour with light PA seems suitable. However, a personalised approach considering various clinical characteristics and PA clusters is essential. Future research should prioritise examining the long-term effects of PA interventions and increasingly use sedentary behaviour as an outcome measure [64, 70].

Work productivity

Work productivity loss encompasses work at suboptimal capacity (presenteeism), absenteeism and changes in employment status [96]. Chronic conditions, such as asthma, exert a significant impact on work productivity [97]. This has led to an increased focus on assessing work productivity as a patient-reported outcome measure, not only in the context of disease burden and QoL, but also considering the associated economic costs [96–98]. While there is no universally accepted gold standard for measuring work productivity, the Work Productivity and Activity Impairment questionnaire, addressing general health and asthma-specific aspects, serves as a widely utilised tool. It assesses presenteeism (impaired productivity while working) and absenteeism (percentage of work time missed due to asthma) and provides an overall measure of work productivity loss based on both presenteeism and absenteeism [99].

Compared to the general population, individuals with asthma commonly experience reduced productivity at work, increased rates of absenteeism and longer periods of absence [100–102]. These factors may even be evident in individuals with undiagnosed asthma [103]. Severe asthma, notably, has been associated with influencing career choices [104]. Among patients with asthma, reported absenteeism and presenteeism vary widely, ranging up to 20 and 52%, respectively, with patients with severe asthma being at the higher end of this range. Studies reveal disparities in presenteeism between severe and nonsevere asthma, although distinctions in absenteeism are not consistently evident [101, 105–107]. One study in urban China [101] reported significantly higher rates of presenteeism in the self-reported moderate-to-severe asthma group compared to the mild asthma group. However, this finding was not replicated when the analysis was conducted based on asthma severity subgroups classified according to Global Initiative for Asthma (GINA) guidelines. Similarly, a multinational study [105] found that patients with severe refractory asthma were 3.2 times more likely to report presenteeism than those with nonsevere controlled asthma. However, neither study identified differences in absenteeism between the groups. In contrast, in a large US cohort [108, 109], a significant difference was reported, not only in presenteeism but also in absenteeism, between mild-to-moderate and severe asthma according to the GINA classification. Instead of asthma severity alone, other factors, such as asthma control and the presence of comorbidities, may play a crucial role in influencing productivity outcomes.

Indeed, asthma control has consistently been identified as a key factor associated with work productivity loss in various studies [105, 110–114]. Four recent studies [110–113], including two in severe asthma, consistently found about three times higher levels of presenteeism and absenteeism in patients with uncontrolled *versus* those with controlled asthma, resulting in large differences in costs associated with work impairment [109, 115]. Additionally, in a longitudinal study, deteriorating asthma control increased presenteeism over time [105]. The same study revealed that individuals with severe asthma were more prone to presenteeism when experiencing poor asthma control, lower QoL and symptoms of depression and anxiety. When comparing patients by medication use, those receiving maintenance OCS had higher rates of absenteeism and presenteeism than patients using high-dose inhaled corticosteroids and biologics [116], which may be attributed to differences in asthma control. In addition to asthma control, asthma comorbidities, such as comorbid anxiety, allergic rhinitis and sleep apnoea, may contribute to greater productivity loss [100, 117, 118]. Of note, in some countries, employment is associated with access to healthcare and asthma management, with unemployment potentially contributing to poorer asthma control.

If asthma control, exacerbations and the use of maintenance OCS affect work productivity, interventions to improve these outcomes may be beneficial. In patients with severe asthma, biologics leads to major improvements in each of those asthma outcomes [119]. Indeed, in patients treated with omalizumab, the first approved biologic for the treatment of moderate-to-severe allergic asthma, changes in overall work productivity were observed within 6 months after starting treatment in one study [120], but not in another [121]. The latter trial being negative for the primary end-point as well due to improvements in the placebo group. In addition, positive effects on work productivity have been shown for anti-interleukin (IL)-5/5Rα biologics. In an RCT, 8 months after starting mepolizumab there was a reduction in presenteeism as compared to placebo (−8.6%), but not in absenteeism [122]. Two real-world studies showed a reduction not only in presenteeism, but also in absenteeism 12 months after initiating anti-IL-5/5Rα biologics [123, 124]. This improvement was associated with enhanced Asthma Control Questionnaire scores, but not with AQLQ scores [123]. In this study, patient employment rates remained consistent over the 12-month treatment period [123]. Consequently, it is unclear whether if and when alterations in employment rates might occur following the start of biologics. Finally, dupilumab has been shown to improve work productivity in patients with moderate-to-severe atopic dermatitis [125, 126], but results in asthma are awaited [127].

In summary, work productivity loss is prevalent in severe asthma, posing significant consequences for patients' physical, financial, social and emotional well-being [105, 107]. Work productivity loss, encompassing both absence from work and impaired productivity while working, is notably associated with poor asthma control. Hence, improving asthma control is pivotal for enhancing work productivity. Future interventional research, preferably with longer follow-up, will need to ascertain whether potential shifts in employment rates are feasible and contribute to the desired social participation and QoL by patients.

Discussion

Understanding patient perspectives is crucial in optimising personalised care for severe asthma. This review focuses on outcomes that patients with severe asthma reported as most bothersome, rather than the conventional clinical outcomes. We found that fatigue, sleep disturbances, physical inactivity and work productivity loss are notably underexplored in the asthma literature, especially in severe asthma, despite their high prevalence and substantial impact on QoL and daily functioning.

Fatigue is a major concern in severe asthma, correlating with poorer asthma control and reduced QoL. Similarly, sleep difficulties worsen with disease severity and negatively impact daily functioning, QoL and asthma control. Physical inactivity poses a substantial hurdle for individuals with severe asthma, impacting their ability to engage in regular activities and manage their condition effectively, and is associated with poor asthma control and increased exacerbation rate. Work productivity loss is common in severe asthma, seen in both absenteeism and presenteeism. Its impact on QoL is substantial, with asthma control emerging as a critical factor influencing work-related outcomes.

Despite their importance, we found that fatigue, sleep, PA and work productivity are rarely used as outcome measures in asthma trials, and it remains unclear whether directly addressing them can improve classical asthma outcomes. Interventions promoting PA show promise in improving asthma control and overall QoL, while biological therapies may reduce productivity loss, although their long-term impact on employment rates remains to be determined.

The interplay between QoL, the four patient-centred outcomes discussed and classical asthma outcomes is complex and likely involves bidirectional causalities as illustrated in figure 2. Interestingly, some evidence

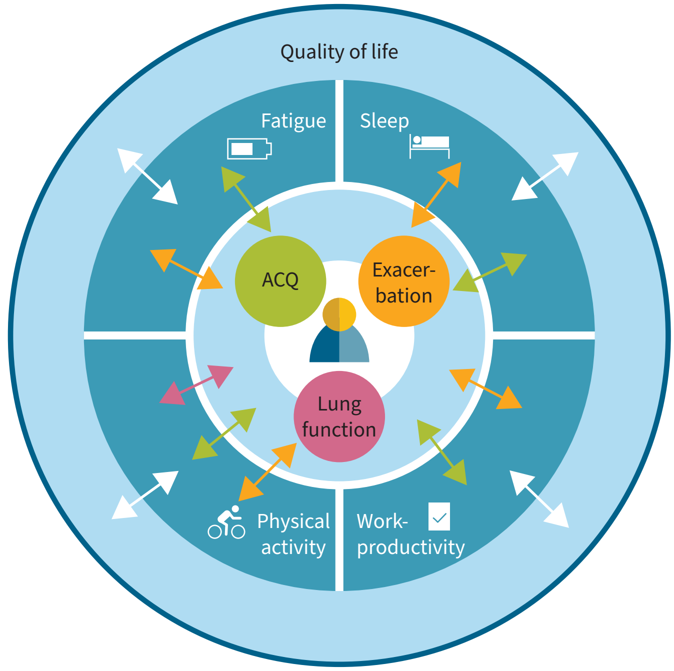

FIGURE 2 Conceptual framework based on findings from the current narrative review. This framework illustrates the potential bidirectional relationships between classical asthma outcomes (asthma control, exacerbations and lung function) and patient-centred outcomes (such as fatigue, sleep disturbances, physical activity and work productivity), as indicated by the arrows. Additionally, these outcomes may be interrelated or clustered and impacting overall quality of life. ACQ: Asthma Control Questionnaire.

suggests that fatigue, sleep disturbance and physical inactivity may not simply result from uncontrolled asthma. Rather, they could be independent treatable traits, with targeted interventions potentially improving asthma control in some patients. Presently, it is unclear whether these patient-centred traits persist during active disease, improve with asthma treatment or specific trait-targeted therapy, or persist even during periods of good asthma control.

We acknowledge several limitations in this narrative review. First, the definition of severe asthma has evolved over time and varied across studies. While most included studies used the 2014 GINA guidelines [16], supplementary table S2 shows heterogeneity in classifications, which may complicate comparisons. Additionally, variability in patient characteristics (*e.g.* age, gender and race/ethnicity) and disease subtypes (*e.g.* based on allergy status, age of onset and type-2 inflammation) was not explored in depth and should be addressed in future studies on these patient-centred outcomes. Side-effects of asthma medications and comorbidities, such as allergic rhinitis and obesity, also impact outcomes. Although briefly mentioned in the discussion of individual outcomes, these factors warrant further investigation for deeper understanding. Our focus on four outcomes identified as most bothersome by patients with severe asthma is not exhaustive. Other important patient-centred outcomes, including anxiety, depression, the effort required for self-management and medication burden, should also be considered [16]. Moreover, the most bothersome symptoms are not always the most prevalent in pulmonary diseases [128]. We highlighted existing knowledge on each individual outcome, yet it needs to be emphasised that symptom clusters are increasingly recognised as a better approach to understanding and studying symptoms [129]. Unfortunately, there is still a lack of data on clusters of patient-centred, extrapulmonary outcomes. Future studies on symptom clusters [130], particularly including extrapulmonary symptoms, could generate hypotheses on potential mechanisms and guide interventions.

In light of these considerations, further research involving both conventional therapies and a broader spectrum of (multicomponent) interventions is crucial to better understand the complex relationships between these patient-centred and classical asthma outcomes. While current treatments such as biologics exhibit promise in ameliorating some extrapulmonary symptoms, their specific effects on issues like fatigue and sleep disturbances warrant further investigation. In addition, research on tailored interventions, such as pulmonary rehabilitation and behavioural therapies adapted for severe asthma, offers potential pathways for improving patients' well-being. Longitudinal studies examining cause-and-effect relationships, intervention effectiveness and the impact of various therapies on factors such as fatigue, sleep quality, PA and work productivity would significantly contribute to a more holistic approach in severe asthma management.

In conclusion, there are significant knowledge gaps across various patient-centred aspects of severe asthma. The present review discusses four needs prioritised by patients with severe asthma, shedding light on these often-overlooked outcomes that greatly affect their QoL. Despite its limitations, current evidence underscores the substantial impact of sleep difficulties, fatigue, PA and work productivity on the disease burden and well-being of patients with severe asthma. It emphasises the significance of further research and calls for adopting a patient-centred approach in severe asthma management, urging for comprehensive interventions that address these multifaceted aspects to truly improve patients' lives.

Questions for future research

- Longitudinal studies are essential for understanding the cause–effect relationship between classical and patient-centred outcomes and its underlying mechanisms, taking into account subgroups based on age, sex and disease subtypes.
- Analysing symptom clusters can improve our understanding of the links between asthma symptoms, control, severity and patient-centred outcomes.
- It is important to explore if these patient-centred outcomes are problematic during active disease, improve with (pharmacological) therapy or persist during periods of good asthma control.
- Patient-centred outcomes should be included in interventional and real-world studies to determine if a treatment is successful from a patient's perspective.

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