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BRIEF REPORT

Physical Activity in Adults with Severe Asthma On-Treatment with Biological Therapies: A 1-Year Retrospective Analysis of Real-World Data

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ABSTRACT

Introduction: Asthma is a complex airways disease that affects over 350-million people worldwide. It is estimated that up to 10% of adults and 2.5% of children with asthma have severe disease, which is associated with reduced physical activity. The introduction of biological therapies has revolutionised the management of severe asthma; however, it remains to be determined whether this translates into improvements in physical activity status.
Method: This 1-year retrospective study evaluated step-based physical activity (via a smartphone pedometer) in adults with severe asthma (n = 20) and two matched sub-groups (n = 20 mild asthma and n = 20 healthy controls).
Results: The annual daily step count was significantly less in adults with severe asthma (4698 ± 1927) versus mild asthma (7239 ± 1815) (P = 0.009) and healthy controls (8252 ± 2115) (P = 0.001). No difference in physical activity was observed between those with mild asthma and healthy controls ($P > 0.05$).
Conclusion: Despite long-term treatment with biological therapies, physical activity remains significantly lower in adults with severe asthma. The development of personalised evidence-based interventions to promote physical activity in people with severe asthma remains a priority.

Keywords: Asthma; Biologics; Management; Physical activity; Treatment

Key Summary Points

Why carry out this study?

Severe asthma is a debilitating condition associated with life-threatening acute exacerbations, activity limitation and impaired health-related quality of life.

The recent introduction of biological therapies has revolutionised the management of severe asthma; however, it remains to be determined whether this translates into improvements in physical activity status.

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The purpose of this 1-year study was to characterise step-based physical activity in adults with severe asthma on-treatment with biological therapies.

What was learned from the study?

Despite long-term treatment with biological therapies, step-based physical activity is significantly lower in adults with severe asthma in comparison to individuals with mild asthma and healthy controls.

While biological therapies are highly effective at improving exacerbation frequency, lung function, symptom scores and quality of life, this does not appear to translate to improvements in physical activity status.

The development and implementation of personalised evidence-based interventions to promote daily physical activity in people with severe asthma remains an important priority for future research.

INTRODUCTION

Asthma is a complex heterogeneous airways disease that affects over 350-million people worldwide [1]. It is estimated that up to 10% of adults and 2.5% of children with asthma have severe disease [2], which results in debilitating disease burden with potential life-threatening acute exacerbations and impaired health-related quality of life [3]. Severe asthma requires treatment with high dose inhaled corticosteroids (ICS) plus a second controller medication and/or systemic corticosteroids to prevent the condition from becoming or remaining "uncontrolled" [3]. In recent years, the introduction of biological therapies (i.e., monoclonal antibodies targeting specific inflammatory cytokines involved in the pathogenesis of asthma) has revolutionised the management of severe disease, leading to reduced symptom burden and improved clinical stability [2, 4]. While previous short-term prospective studies indicate that people with severe asthma undertake less physical activity compared to healthy counterparts [5, 6], it remains to be determined whether this is the case for individuals on long-term treatment with biological therapies. This is an important consideration given that physical activity is associated with improved asthma-related outcomes and overall quality of life [7, 8]. The purpose of this study was therefore two-fold; first, to characterise step-based physical activity in adults with severe asthma on biological therapies, and, second, to explore the interaction between physical activity and exacerbation frequency in the same cohort.

METHODS

The study was conducted as a 1-year retrospective analysis. Ethical approval was granted by the Health Research Authority and Health and Care Research Wales Committee (reference: 21/PR/0160). All participants were recruited from the Leeds Difficult Asthma Service (Leeds, UK) following multidisciplinary team assessment. Inclusion criteria: adults ≥ 18 years with a severe asthma diagnosis [3] receiving a personalised asthma management plan including a form of biological therapy [Global Initiative for Asthma (GINA) step 5] and who had not previously completed pulmonary rehabilitation. Two matched sub-groups [according to age, biological sex and body mass index (BMI)] were also recruited: (1) mild asthma on either as-needed low-dose ICS + formoterol or maintenance treatment with low-dose ICS as preferred controller therapy (GINA step 1–2); and (2) healthy controls (i.e., entirely asymptomatic with no prior history of chronic disease) recruited from the general population. All participants provided written informed consent.

At study entry, spirometric assessment of lung function was undertaken in accordance with American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines [9]. Step-based physical activity was quantified via a smartphone in-built pedometer and exported retrospectively [10]. For the severe asthma cohort, additional data were collected via review of clinical records. This included the frequency of exacerbations requiring systemic oral steroids (40–50 mg prednisolone per day

for 5-days) and frequency of administration documented. Statistical analysis was conducted using GraphPad Prism Version 10.0 (GraphPad Software, San Diego, CA, USA). Data are presented as mean ± SD or median [interquartile range (IQR)] for continuous variables dependent on normality, and percentages for categorical variables. A one-way repeated measures ANOVA and Kruskal–Wallis tests were used to compare between group differences for parametric and non-parametric data, respectively.

RESULTS

A total of 60 participants (n = 20 severe asthma, n = 20 mild asthma, n = 20 healthy controls) (62% female) completed the study. Clinical characteristics and baseline pulmonary function are presented in Table 1. In the severe asthma cohort, the forced expiratory volume in 1 s (FEV_1) was 2.27 ± 0.88 (74.3 ± 22.7%pred), FEV_1/forced vital capacity (FVC) ratio 66.0 ± 13.1%, with personalised asthma management plans including high dose ICS and long-acting beta-2 agonists (100%); long-acting muscarinic antagonists (55%); leukotriene receptor antagonists (35%); and theophylline (10%). One-quarter of the cohort were ex-smokers (7 ± 5 pack-year history). All participants with severe asthma were on active treatment with a biologic for a minimum of 2 years [mepolizumab (65%); omalizumab (20%); benralizumab (10%); dupilumab (5%)] and treated for the following asthma-related comorbidities: atopic disease (55%); allergic rhinitis (40%); nasal polyps (25%); gastrointestinal disease (20%). None of the participants had cardiac or musculoskeletal disease (i.e., conditions recognised to contribute to exercise limitation and physical activity avoidance). The median Asthma Control Questionnaire (ACQ) and Asthma Quality of Life Questionnaire (AQLQ) score were [IQR] 1.16 [1.31] and 4.75 [1.91] units, respectively.

The annual daily step count was significantly less in adults with severe asthma (4698 ± 1927) compared to those with mild asthma (7239 ± 1815) (P = 0.009) and healthy controls (8252 ± 2115) (P = 0.001). No difference in physical activity was observed between those with mild asthma and healthy controls (P > 0.05)

Table 1 Clinical characteristics and baseline lung function

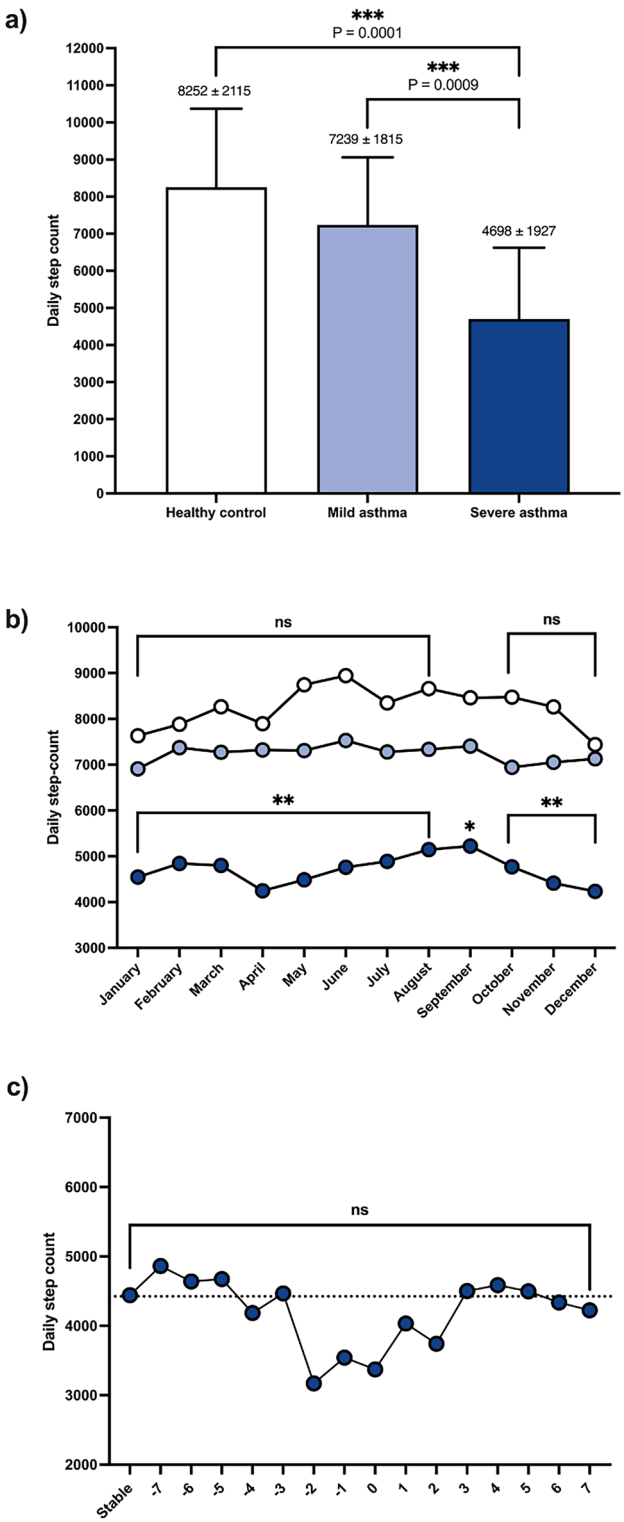
	Healthy control	Mild asthma	Severe asthma
Sex (M:F)	7:13	9:11	7:13
Age (year)	47 ± 15	48 ± 15	52 ± 16
Height (cm)	171 ± 8	171 ± 8	169 ± 9
Weight (kg)	78.6 ± 10	79.6 ± 6.5	84.9 ± 15.4
BMI (kg m^2)	27.0 ± 3.1	27.1 ± 2.9	29.0 ± 4.0
FEV_1 (L)	3.40 ± 0.57	3.07 ± 0.49**	2.27 ± 0.88$^{\#}$
FEV_1 (% predicted)	101.3 ± 10.0	90.9 ± 8.7**	74.3 ± 22.7$^{\#}$
FVC (L)	4.21 ± 0.75	4.05 ± 0.67	3.42 ± 1.07$^{\#}$
FVC (% predicted)	102 ± 12.1	98.8 ± 5.5	91.4 ± 17.4$^{\#}$
FEV_1/FVC (%)	94.0 ± 9.3*	80.1 ± 9.5**	66.0 ± 13.1$^{\#}$

Data presented as mean ± SD

BMI body mass index, *FEV_1* forced expiratory volume in 1 s, *FVC* forced vital capacity

*P < 0.05 (healthy control vs. mild asthma)

**P < 0.05 (mild asthma vs. severe asthma); $^{\#}P$ < 0.05 (healthy controls vs. severe asthma)



(Fig. 1a). This pattern was consistent when stratifying data according to average monthly steps over the course of 1 year ($P < 0.05$) (Fig. 1b). No sex-based differences in step-based physical activity were observed ($P > 0.05$). A significant reduction in daily steps was, however, observed

◂**Fig. 1** **a** Annual average daily steps in healthy controls (*open*); mild asthma (*light blue*); severe asthma (*dark blue*) ($n = 20$ per group) $^{***}P < 0.001$. **b** Daily steps stratified according to month in healthy controls (*open*); mild asthma (*light blue*); severe asthma (*dark blue*) ($n = 20$ per group) $^{**}P < 0.05$ (severe asthma vs. mild asthma and healthy controls); $^{*}P < 0.05$ (severe asthma vs. healthy controls only). **c** Interaction between physical activity and exacerbation frequency in severe asthma ($n = 20$) (*dashed horizontal line* denotes annual step count while clinically stable; timepoint zero denotes day of exacerbation); *ns* $P > 0.05$. SD error bars omitted to improve clarity

in healthy controls during the winter months ($P < 0.05$). In contrast, there were no seasonal changes in step count in either the severe or mild asthma cohorts ($P > 0.05$). Of individuals with severe asthma, 70% experienced at least one exacerbation requiring short-course prednisolone. Overall, step-based physical activity was significantly lower in those experiencing at least one annual exacerbation compared to those who remained clinically stable throughout the year: median [IQR] 4715 [6372] versus 3366 [3609] steps ($P < 0.0001$). No significant difference in step count was observed 7-days pre- and post-exacerbation compared to periods of clinical stability ($P > 0.05$) (Fig. 1c).

DISCUSSION

The results of this 1-year study suggest that adults with severe asthma on-treatment with biological therapies undertake significantly fewer daily steps in comparison to individuals with mild asthma and healthy controls. These findings are consistent with previous short-term prospective studies evaluating physical activity in people with severe asthma [5, 6], but, at the same time, offer novel insight in relation to those specifically escalated to GINA step-5. While biological therapies are widely recognised to be highly effective at improving exacerbation frequency, lung function, symptom scores and quality of life [2, 4], our data indicate that this does not appear to translate to improvements in physical activity status. Although further prospective studies comparing physical activity (i.e., total daily steps and time spent in moderate-to-vigorous activity) pre- and post-initiation of biological therapies are required, our preliminary findings support the concept that conventional strategies and current guideline-based treatments in isolation appear to be relatively ineffective with respect to reducing physical inactivity [11]. It is therefore essential that further studies are undertaken to determine barriers and facilitators to physical activity engagement in people with severe asthma [12, 13]. The evaluation of evidence-based lifestyle and behaviour change strategies (e.g., wearable devices in conjunction with established techniques such as goal setting and self-monitoring) [12], alongside pharmacological intervention to target non-clinical outcomes measures such as body composition and physical activity (i.e., factors which are considered highly important to patients), also remains a key research priority [11, 14].

A secondary aim of this study was to determine how physical activity interacts with exacerbation frequency. Interestingly, our data indicate that, while no significant differences in daily steps were identified when comparing clinical stability versus 7 days pre-- and post-exacerbation, a clinically meaningful reduction in step count (i.e., exceeding the minimal important difference applied to people with COPD [15, 16]) occurred 2 days prior to an impending exacerbation (902–1273 steps day^{-1}). While this observation should be viewed as preliminary and interpreted with caution until the results of larger prospective studies are made available, a reduction in daily steps may represent an early prognostic signal for an impending exacerbation which could offer value as a preventive measure in the context of asthma self-management.

We acknowledge important methodological considerations. The assessment of physical activity remains a significant challenge due to a lack of gold-standard and universally accepted methods [17]. While triaxial accelerometers are generally considered to be the optimal approach to objectively assess physical activity, potential limitations include participant reactivity (i.e., behaviour change in response to being observed) and challenges associated with long-term surveillance. Smartphone pedometers track daily steps automatically, and therefore offer

a pragmatic solution to the assessment of step-based physical activity in a real-world setting. Importantly, this approach has previously been shown to provide a valid and reliable estimate of daily steps in both standardised laboratory, self-paced walking challenges and free-living conditions in people with asthma (with comparable ACQ scores to those in the present study) [10] and healthy volunteers [18]. While failure to carry the device on-person throughout the day is a potential limitation when utilising smartphones to assess physical activity, this is less of a concern when analysing large datasets collected over extended time periods (i.e., outliers are less likely to distort trends or group averages). In addition, the average annual and monthly step count for severe asthma in the present study aligns closely with previous studies [5, 6], which provides reassurance regarding the validity of our findings.

In conclusion, despite long-term treatment with biological therapies, step-based physical activity is significantly lower in adults with severe asthma in comparison to individuals with mild asthma and healthy controls. The development and implementation of personalised evidence-based interventions to promote daily physical activity in people with severe asthma remains an important priority for future research.

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Declarations

Conflict of Interest. Oliver J Price has received grants from Merck and AstraZeneca outside the submitted work. Ian J. Clifton has received honoraria from AstraZeneca, GSK, Chiesi and Infex Theraputics. IJC has received grants from AstraZeneca outside the submitted work. Caroline Reilly, Daniel Peckham, Antonios Stavropoulos-Kalinoglou have no real or perceived conflict of interest in respect of this manuscript.

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