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Physical activity and exercise capacity in severe asthma: Key clinical associations.

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Abstract

Background: Physical inactivity and sedentary time are distinct behaviors that may be more prevalent in severe asthma, contributing to poor disease outcomes. Physical activity and sedentary time in severe asthma however have not been extensively examined.

Objective: We aimed to objectively measure physical activity and sedentary time in people with severe asthma compared to aged-matched control participants, describing the associations of these behaviors with clinical and biological outcomes. We hypothesized that people with severe asthma would be less active and more sedentary. Additionally, more activity and less sedentary time would be associated with better clinical outcomes and markers of systemic and airway inflammation in people with severe asthma**.**

Methods: Adults with severe asthma (n=61) and gender and aged-matched controls (n=61) underwent measurement of lung function, exercise capacity, asthma control, health status, and airway and systemic inflammation. Physical activity and sedentary time were measured using an accelerometer.

Results: The severe asthma and control groups were matched in terms of age and gender (32 (53%) females in each group). Individuals with severe asthma accumulated less minutes/day in moderate and higher intensity activity, median [IQR] 21.9 [12.9-36.0] versus 41.7 [29.5 – 65.2] (*p* <0.0001); and accumulated 2232 fewer steps/day (p=0.0002). However, they engaged in more light-intensity physical activity. No differences were found for sedentary time. In a multivariate regression model, steps/day were strongly and independently associated with better exercise capacity in severe asthma participants [Coeff (95%CI) 0.0169 (0.008, 0.025); *p*<0.001].

Conclusion: People with severe asthma perform less moderate and vigorous activity than controls. Higher levels of activity and lower levels of sedentary time are associated with better exercise capacity, asthma control, and lower levels of systemic inflammation.

Highlight box:

1. *What is already known about this topic? People with severe asthma seem to engage in lower levels of activity than controls. Low physical activity in severe asthma is associated with impulse oscillometric airway resistance and small airway dysfunction.*

2. *What does this article add to our knowledge? Physical activity measured as steps/day is strongly associated with exercise capacity and systemic inflammation in severe asthma. To a lesser extent, activity and sedentary time are associated with asthma control, health status and lung function.*

3. *How does this study impact current management guidelines? These results suggest that addressing inactivity and sedentary time may be a potential nonpharmacological approach in the management of severe asthma.*

Key words: severe asthma; physical activity; sedentary time; accelerometry; exercise capacity; associations; clinical outcomes.

List of abbreviations:

PA: physical activity

LPA: light-intensity physical activity

MVPA: moderate and higher intensity physical activity

ST: sedentary time

6MWT: 6-minute walk test

6MWD: 6-minute walk distance

FEV_1: forced expiratory volume in the first second

FVC: forced vital capacity

ACQ: asthma control questionnaire

AQLQ: asthma quality of life questionnaire

Hs-CRP: high sensitivity C- reactive protein

FeNO: fractional exhaled nitric oxide

HADs: hospital anxiety and depression scale

COPD: chronic obstructive pulmonary disease

Introduction

Severe asthma is a heterogeneous and complex disease, where diverse clinical and physiological presentations are common[1]. Severe asthma represents a high patient and healthcare burden[2]. It is, thus, necessary to explore novel strategies to improve health status in severe asthma and to minimize this burden. The importance of multidisciplinary management approaches in severe asthma has been recognized[3]. Within these, the identification and subsequent management of modifiable risk factors or behaviors, such as inactivity, can be seen as an adjunct strategy for the management of the disease[4].

In general populations, physical activity (PA) and exercise are regarded as highly beneficial, leading to positive health outcomes[5-7]. Engagement in excess sedentary time (ST) is an important risk factor for the development of several chronic diseases and premature mortality[8, 9]. Physical activity is defined as any bodily movement generated by the skeletal muscles and resulting in energy expenditure. Depending on intensity and metabolic equivalent of task (MET) units, it is classified in light, moderate or vigorous PA, where light corresponds to the lower METs or energy expenditure[5]. Mild stretching, low impact dancing, and running correspond to examples of light, moderate and vigorous PA, respectively[10]. Sedentary time refers to activities performed while awake, in a lying or sitting position and expending low levels of energy ($\leq$ 1.5 METs)[11]. The physical activity and sedentary guidelines recommend engaging in at least 150 minutes/week of moderate activity, or 75 minutes/week of vigorous activity (or equivalent combination), and to sit less and for shorter periods of time[12]. In other obstructive airway diseases such as Chronic Obstructive Pulmonary Disease (COPD), physical inactivity and sedentary time are increased compared to healthy controls[13, 14]. These behaviors have been independently associated with worse clinical and inflammatory outcomes[15], and increased mortality in this disease[16, 17]. In asthma, a potential link between inactivity and mortality has not been reported. However, higher adherence to PA in asthma has been associated with better asthma control[18], reduced exacerbations[19] and reduced health care use[20]. Data on inflammatory parameters is scarce[21].

In severe asthma, inactivity and sedentary time are likely to be particularly extreme due to the poor disease control and associated comorbidities, such as obesity, anxiety, and depression[1]. Despite this, very few studies have objectively measured PA in this population[22], and the prevalence of sedentary time has not been addressed in severe asthma. In addition, very few studies have assessed the impact of these behaviors on health outcomes in the disease[22].

The aims of this study therefore are to objectively measure physical activity and sedentary time in a severe asthma population compared to aged-matched controls, and to describe the associations of these behaviors with clinical measures such as asthma control, health status, exercise capacity, lung function, and markers of airway and systemic inflammation.

We hypothesized that people with severe asthma are less active and more sedentary than their age and gender-matched counterparts, and that higher levels of physical activity and lower levels of sedentary time in severe asthma are associated with better clinical outcomes, and lower levels of systemic and airway inflammation. Additionally, we sought to test the hypothesis that moderate intensity physical activity can counteract the detrimental health outcomes associated with high levels of sedentary time, as it has been previously suggested[23, 24].

Methods

Participant selection

A cross sectional characterization study was conducted. Adults with severe asthma and gender and age-matched controls were recruited and underwent a multidimensional assessment with objective measures of physical activity and sedentary time. Severe asthma participants were recruited consecutively from the respiratory ambulatory care clinics at John Hunter Hospital (Newcastle, Australia) and the clinical research databases of the Priority Research Centre for Healthy Lungs at the University of Newcastle (Newcastle, Australia). Participants with respiratory physician diagnosed severe asthma were eligible if they met the current guideline definition for severe asthma[1]: prescribed Global Initiative for Asthma (GINA) step 4 treatment or above, defined as 1000mcg inhaled corticosteroid (ICS) fluticasone equivalent and long-acting β2-agonists[25], had evidence of airflow limitation (Forced Expiratory Volume in the first second [FEV_1] <80% predicted), and ongoing poor asthma control [Asthma Control Questionnaire (ACQ)[26] ≥1.5 units or had experienced a severe exacerbation in the last 12-months requiring oral corticosteroid]. Participants were clinically stable during visits (no increase of asthma symptoms in the last four weeks). Otherwise, their enrolment was postponed until they were stable. Exclusion criteria included malignancy with poor prognosis (<3 month).

Age and gender-matched controls were recruited via the research database of the Hunter Medical Research Institute and community advertisement, and were eligible if they were over 18 years, non-smokers, and had no objective evidence of chronic respiratory disease.

Ethics approval was granted from the Human Research Ethics Committees of the Hunter New England Local Health District (08/08/20/3.10) and the University of Newcastle, Australia. The study was conducted according to Good Clinical Practice Guidelines and each participant provided written informed consent.

Procedures

Clinical measurements

Participants underwent a multidimensional assessment[27] involving measurement of height, weight, allergy skin prick tests, serum IgE, comorbidities[28], anxiety and depression[29], and smoking status. Further assessments are described below.

Exercise capacity.

The 6-minute walk test (6MWT) was performed according to current guidelines[30] to measure exercise capacity. The 6-minute walk distance (6MWD) was calculated.

Asthma control and health status

Asthma control was assessed using the ACQ[26]. Higher scores represent poorer asthma control. Health status was measured using the Asthma Quality of Life Questionnaire (AQLQ)[31]. Higher scores represent better asthma related quality of life. A change of ≥0.5 unit is considered clinically significant for both questionnaires[32, 33].

Airflow limitation

Airflow limitation was assessed by measuring spirometry: FEV_1, forced vital capacity (FVC) and FEV_1/FVC ratio (Medgraphics, CPFS/D™ USB Spirometer, BreezeSuite v7.1, MGC Diagnostics, Saint Paul, MN, USA[34]. FEV_1 and FVC percent predicted were calculated using NHANES III predicted equations[35].

Airway inflammation

Eosinophilic airway inflammation was assessed in two ways: using FeNO (ANALYZER CLD 88 Series with DENOX 88, Eco Physics AG, Duernten, Switzerland)[36]; and from sputum eosinophil counts obtained from induced sputum. The samples were induced[37] using nebulized 4.5% or 0.9% saline if the pre-bronchodilator FEV_1 was ≤1L. Lower respiratory sputum portions were selected and dispersed using dithiothreitol. Total cell counts and cell viability (Trypan blue exclusion) were performed, followed by preparation of cytospins for differential cell counts using May-Grunwald–Giemsa. Airway eosinophilia was defined as sputum differential eosinophil count ≥3%[38].

Systemic inflammation

Systemic inflammation was measured by peripheral blood high sensitivity C-reactive protein (hs-CRP) and analyzed through the Hunter Area Pathology Service.

Physical activity and sedentary time

Physical activity and sedentary time were assessed using the ActiGraph wGT3X-BT (ActiGraph, Pensacola, Florida), a device widely used in research[39-41], and validated for COPD population[42]. This is a small device (4.6cm x 3.3cm x 1.5cm) that participants were fitted with to wear on a belt around their waist, positioned over the dominant hip, for 14 consecutive days. They were instructed to remove the monitor during water-based activities and to record sleeping time and non-wear periods in a diary. The ActiGraph measure time-varying changes in force and activity levels typically are recorded as counts, which are then summed over a user-specified time frame, or epoch[43]. The device was initialized using the ActiLife 6.11.6 Data Analysis Software, to collect raw data (accelerations or counts) in the vertical axis at 30 Hz rate in an epoch length of time of 10-seconds. Sleep and any non-wear time were estimated from the diaries and visual examination of the ActiGraph data and removed prior to classification. ActiLife software was used to summarize the data. We classified time according to the widely used Freedson 1998 cut-points: Sedentary (0-99 counts per minute [CPM]); Light PA (100-1951 CPM); and Moderate and above PA (≥1952 CPM)[44]. The ActiGraph also captures steps per day. Our measures of physical activity and sedentary time are: daily time in sedentary time (minutes/day), daily time in light physical activity (minutes/day), daily time moderate- to vigorous-intensity physical activity (minutes/day) and daily number of steps (steps/day). We reported both, MVPA and Steps, because while MVPA informs the volume of moderate to high intensity activity and can be compared with the physical activity recommendations[12], the steps per day is an output easy to interpret and could be used as a motivational and informative tool both for patients and clinicians. Sedentary time and light physical activity were standardised for wear time by the residuals method[45]. The data were considered valid if there were ≥4 days of recordings, with ≥10 hours of recording each day.

Statistical Analysis

Data were analyzed using STATA 13 (Stata Corp., College Station, TX, USA). Values are expressed as means with confidence intervals (CI) for parametric data and medians with interquartile range [IQR] for non-parametric data. Differences between the severe asthma and the aged and gender-matched control group were assessed using the Student's t-test or the Wilcoxon Rank Sum test based on normality.

The associations between the different clinical and biological outcomes, the behavioral variables (sedentary time, moderate and vigorous PA, and Steps), and potential confounders (current smoking status, and BMI) were estimated using simple linear regression analysis. Each behavioral variable was used as a predictor of a given clinical or biological outcome (dependent variable: FEV_1% predicted, 6MWD, ACQ score, AQLQ score, FeNO and hs-CRP). Age and gender were regarded as biological confounders and included in all the models. Behavioral variables and confounders with a P value <0.2 were also included into a stepwise multiple linear regression analyses to identify the associations between each behavioral variable (ST, MVPA, and Steps) with each biological/clinical outcome (Model 1). To test whether moderate physical activity (Steps or moderate and vigorous PA) can counteract the detrimental health outcomes associated with sedentary time, further models (Model 2) adjusted for confounders and sedentary time assessed the associations of Steps or MPVA with each dependent variable. Assumptions for linear regressions were met. Co-linearity between the activity (MVPA or STEPS) and sedentary variables was rejected. Hs-CRP and FeNO were transformed to the natural logarithm for the linear regression. This means that the dependent variable changes by 100 x [exp(coefficient)-1] percent for each one-unit increase in the independent continuous variable. Logistic regressions were used to test the associations of sedentary and active time with airway eosinophilia, and the association between better performance in the 6MWT (defined as ≥median [≥499 m]) and higher engagement

(≥30 minutes) in MVPA. Spearman's rank correlation tested relationship between activity variables and 6MWD. Results were reported as significant when $P<0.05$.

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Results

Characteristics of the study population

A total of 143 participants (SA=74, Controls=69) completed the study and 122 (SA=61, Controls=61) were included in the analysis; 21 participants were excluded due to not having valid accelerometer data (SA=8, Controls=5) or, because they did not fulfil the disease inclusion criteria after assessment (SA=5, Controls=3). Participants with severe asthma had long-standing disease (median 27 years), and poor asthma control. They also had a higher BMI and increased prevalence of atopy, lower lung function, and higher scores of anxiety and depression compared to age and gender-matched controls. Demographic and clinical characteristics are provided in Table I.

Physical activity and sedentary time in severe asthma and aged-and gender matched control

Compared to controls, people with severe asthma performed less activity of at least moderate-intensity. The severe asthma group had a median difference of 19.8 fewer minutes of moderate and vigorous physical activity per day (p<0.0001), and 2,455 fewer steps per day (p=0.0002). Conversely, the severe asthma population engaged in more light physical activity, with a mean (95%CI) difference of 21.7 (2.2, 41.1) more minutes/day (p=0.029). No statistically significant differences were found in sedentary time between the two populations (Figure 1).

Associations of physical activity and sedentary time with clinical outcomes and biological markers in severe asthma participants

Exercise capacity

Physical activity (Steps and MVPA) and sedentary time were significantly associated with exercise capacity, explaining 35.25%, 29.69% and 27.3% of the adjusted variance in the 6MWD, respectively (Table II/Model 1). For every additional 1000-steps there was a 16.9-meter increase in the 6MWD. For every minute increase in sedentary time there was a decrease in the 6MWD of 0.47 meters. Accordingly, every additional hour spent sedentary is associated with a 28.2-meter reduction in the 6MWD.

There was a linear relationship between Steps and the 6MWD (Figure 2a). For moderate and vigorous physical activity (Figure 2b) there was also an apparent threshold effect where those participants with a 6MWD performance ≥the median (499 meters) were also the participants engaging in ≥30 minutes daily of MVPA, a volume of activity that fits within the physical activity recommendations[12] (Odds Ratio 6.09; p = 0.005). This suggests that a value around 500 meters in the 6MWD could identify individuals engaging in recommended levels of MVPA.

Simultaneously including sedentary time with moderate and vigorous physical activity or Steps in the model attenuated the associations of MVPA and ST to the null. However, the association of Steps with exercise capacity remained similar and still statistically significant (Table II/Model 2). A 1000-step increase was associated with better performance in the 6MWD by 21-meters. This suggests that, regardless of the time spent sedentary, higher levels of walking were still strongly associated with a significant improvement in exercise capacity.

Lung function, asthma control, and health status.

The activity and sedentary variables were also significantly associated with lung function, asthma control and health status, except for Steps and FEV_1% predicted, and sedentary time and the AQLQ. In contrast to the impact of activity on exercise capacity, the effect on these clinical outcomes were weaker but nonetheless statistically significant and biologically plausible. For every 10-minute increase in moderate and vigorous physical activity, the ACQ score decreased (improved) by 0.21 units, while the AQLQ increased (improved) by 0.16 units (Table III/Model 1). These results suggest that a 25-minute increase in MVPA is associated with a clinically significant improvement in ACQ (0.52 units). Regarding sedentary time, every 100-minute increase in this behavior is associated with a clinically significant decline in the ACQ (0.51 units).

The only activity variable that remained statistically significant after adjustment for sedentary time, was ACQ and MVPA. Every 15-minute increase in MVPA was associated with a decrease (improved) ACQ score of 0.29 units (Table III/Model 2). The coefficient of sedentary time was also attenuated to the null in this model.

In the remaining models, the activity (MVPA or Steps) and sedentary variables together were mutually excluded. Nevertheless, in most of the models the direction of the coefficients indicated that the decrease in sedentary time and the increase in activity, leads to modest improvements in clinical markers.

Biological markers

No relationship was found between the behavioral variables and eosinophilic airway inflammation measured by sputum cell counts (Table IV). In the simple linear regression analyses, the significance level for FeNO was >0.2 and thus not included into the stepwise model.

Steps were significantly associated with hs-CRP. For every increase of 1000-steps, the hs-CRP was reduced by 13%. No relationship was found between hs-CRP and moderate and vigorous physical activity or sedentary time (Table V/Model 1)

Only Steps remained significantly associated with hs-CRP after adjustment for sedentary time. For every increase of 1000-steps, the hs-CRP was reduced by 17% (Table V/Model 2). The coefficients for the associations of sedentary time were attenuated to the null. The model explained the 48.6% of the variance in systemic inflammation.

Discussion

This study has described the extent to which individuals with severe asthma engage in physical activity and sedentary time compared to a gender and age-matched control population. We have demonstrated that people with severe asthma are considerably less active. Additionally, we found that the levels of activity and sedentary time are strongly and independently associated with exercise capacity, and to a lesser extent to other important clinical and biological outcomes. Our results also demonstrate that the detrimental effects of sedentary time are attenuated when participants engage in some physical activity, especially of moderate or higher intensity.

In terms of the levels of activity and sedentary time, our results are consistent with several studies conducted in mild and moderate asthma using both objective and subjective activity measurement[18, 22, 46-48]. However, very few studies have objectively examined physical activity in severe asthma[22], and to our knowledge this is the first study to report levels of sedentary time in this population. Our finding that people with severe asthma move 31.4% fewer steps/day compared to a control group is consistent with a recent study that reported 31% lower steps[22]. However, in comparison to Bahmer et al.[22] our study reported a larger difference in MVPA between people with severe asthma and controls (47.5% vs 23%), and the participants in our study were less active than that reported by Bahmer et al.[22] (22 vs 125 minutes/day of MVPA). It should be noted though that the authors[22] used a different device to measure MVPA (SenseWear, BodyMedia). Studies using the ActiGraph in bronchiectasis population[49], have reported similar activity results as our study.

We observed that the difference in physical activity between severe asthma and controls is larger for higher intensities of activity than for steps. This finding has also been reported in mild to moderate COPD patients[50], and suggests that activity limitation is first manifested at higher intensities of activity rather than lighter. In fact, our severe asthma population accumulated more minutes in light physical activity than the healthy controls.

In the general adult population, a widely promoted target for a desirable level of activity is 10,000 steps[51]. Our severe asthma population only achieved 5362 daily steps, thus a little more than half of the recommended level, and similar to the level reported in moderate to severe COPD[50, 52] and bronchiectasis[49]. This suggests that people with obstructive airway disease regardless of diagnosis are engaging in levels of activity that are far below those recommended for adult populations. Direct comparisons between these populations have not yet been reported.

The beneficial role of physical activity and exercise on outcomes such as exacerbations, asthma control, cardiopulmonary fitness, and health status has been previously described in general asthma populations[19, 20, 53-55]. However, to our knowledge, this is the first time that the association between exercise capacity and objectively measured physical activity and sedentary time has been reported in severe asthma. Sedentary time attenuated the associations of MVPA with exercise capacity but not the associations of Steps with exercise capacity. This suggests that the greatest benefit on exercise capacity is achieved by performing activity of light to moderate intensity distributed throughout the day, rather than more vigorous but sporadic activity.

The 6MWD has been identified as a predictor of survival in COPD[56] and associated with hospitalization and increased mortality[57-59]. In COPD, a 6MWD of ≤350 meters is regarded as poor performance [58]. We found that individuals with a 6MWD of ≥499 meters were six times more likely to engage in recommended levels of MVPA (≥30 minutes daily)[12], suggesting this distance may be a suitable cut-off for people with severe asthma. However, this requires further investigation. A difference of ≥30 meters has been proposed as the minimal clinically important difference (MCID), and furthermore a decrease of this magnitude is associated with increased risk of death in COPD[60]. To date the 6MWD MCID for severe asthma is not known. However, the fact that an increase of 1000-steps was associated with an increase of 22 metres (after adjusting for sedentary time), indicates the potential benefits of targeting physical activity as a modifiable behavior in severe asthma.

Our study also found that physical activity and sedentary time are associated with asthma control, health status, and lung function. The strength of the associations was rather modest and a very large change in activity (>4000 Steps or >25 minutes of MVPA) was necessary to reach the 0.5 unit MCID defined for the ACQ[33] and AQLQ[32]. However, since the promotion of activity in severe asthma should be considered as an adjunct treatment, it may contribute to improved disease control when combined with pharmacological and other risk factor management.

We did not find any association between the activity or sedentary variables and measures of eosinophilic airway inflammation. However, it should be also noted that our population were on maximum intensity ICS therapy, and this may have modified any potential relationship between airway eosinophilia or FeNO, and the behavioural variables. This is further supported by the finding that FeNO levels, a marker of corticosteroid responsiveness[36], were not different between the severe asthma and control populations, suggesting that FeNO was suppressed by ICS treatment. These findings suggest that the pathway of inactivity in severe asthma may be more related to breathlessness and/or exercise capacity, than airway inflammation. e the positive impact of exercise on markers of airway inflammation (FeNO and sputum eosinophilia). This may relate to the baseline characteristics of the participants rather than exercise itself as studies have reported decrease in FeNO after a bout of exercise in physically inactive people with asthma and not in those who were active[61], and participants with increased inflammatory parameters (FeNO ≥26 ppb and ≥3% sputum eosinophils) had the greatest improvement after exercise training[54]. Whether the positive effects of exercise on airway inflammation can be reproduced by shifting to higher and extended levels of daily physical activity needs further investigation.

In terms of systemic inflammation, we found that more steps/day were associated with lower hs-CRP levels, after adjustment for BMI, sedentary time, and other confounders. This suggests a potential benefit of physical activity as a complementary therapy to target systemic inflammation in severe asthma. The role of hs-CRP in the clinical management of severe asthma is still unclear. However, there are data linking systemic inflammation to increased risk of exacerbation[62], and to increased asthma severity[63]. Exercise also appears to have anti-inflammatory effects[64]. In COPD, it has been demonstrated that higher levels of physical activity are independently associated with lower levels of hs-CRP[65, 66]. However, very little data exist on systemic inflammation and exercise in asthma. One study reported a reduction in serum pro-inflammatory cytokines

(IL6 and Monocyte chemotactic protein 1 (MCP-1)) after aerobic training[54]. Interestingly, Scott et al.[67] reported decreases in serum IL6 with exercise and diet, but with not with exercise alone, and no change in hs-CRP with either intervention. Our findings may support the idea that activity carried out at a moderate level has a more beneficial effect on systemic inflammation than more strenuous, but acute, activity.

Our study has some limitations. Due to its cross-sectional design, it is not possible to infer causality of our findings. We choose to use the ActiGraph, because despite being developed as a research tool, it is becoming increasingly used in population studies[24, 40] as well as in clinical setting studies[49]. This device has been validated in COPD population, being one of the most accurate in detecting different walking speeds[68], and estimating activity energy expenditure[42, 69]. However, sedentary time has been shown to be more accurately measured with postural-based accelerometers, such as activPAL[70]. Also, there are conflicting data regarding the most suitable cut-point for ActiGraph to measure sedentary time in adult populations, with cut-points ranging from 25 to 500 CPM[70-73]. It has been suggested that both activity and sedentary parameter can vary greatly depending on cut-point used[73]. The <100 CPM cut-point that we used has been shown to be detrimentally associated with cardiometabolic measures in adults[41], and previously reported in large population studies[39]. Thus, our prevalence results could be compared with previous estimates in the literature[41, 49, 74]. Additionally, considering the scarce information available on sedentary time in severe asthma, these data provide useful insight into how this behavior is associated both, with different spectrums of activity, and with different disease outcomes. Lastly, we acknowledge that we have not addressed several comorbidities, such as cardiovascular diseases, and musculoskeletal conditions that may negatively impact on the level of activity and sedentary time, or interact with some of the dependent outcomes, this is an area for future research. These conditions however, are not more prevalent in severe asthma than in a control group[1], and so our study design would account for these issues.

Conclusions

This study reports novel data on physical activity and sedentary time in severe asthma. We found that severe asthma is associated with lower levels of moderate and vigorous intensity physical activity. Higher levels of activity and lower levels of sedentary time were linked to better exercise capacity, asthma control and decreased systemic inflammation. Our results highlight a need to develop and test interventions in severe asthma that aim to improve exercise capacity and systemic inflammation by increasing walking and decreasing sedentary time, and improve asthma control by increasing the volume of moderate or higher intensity physical activity.

References

1. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J 2014; 43:343-73.
2. O'Neill S, Sweeney J, Patterson CC, Menzies-Gow A, Niven R, Mansur AH, et al. The cost of treating severe refractory asthma in the UK: an economic analysis from the British Thoracic Society Difficult Asthma Registry. Thorax 2015; 70:376-8.
3. McDonald VM, Vertigan AE, Gibson PG. How to set up a severe asthma service. Respirology 2011; 16:900-11.
4. Gibson P, McDonald VM. Phenotyping Asthma and COPD. BRN Rev. 2016; 2:239-52.
5. WHO. Global Recommendations on Physical Activity for Health. Geneva: World Health Organization, 2010.
6. WHO. Global health risks: mortality and burden of disease attributable to selected major risks. Geneva: World Health Organization, 2009.
7. Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT, et al. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. Lancet 2012; 380:219-29.
8. Owen N, Bauman A, Brown W. Too much sitting: a novel and important predictor of chronic disease risk? Br J Sports Med 2009; 43:81-3.
9. Katzmarky PT, Church TS, Craig CL, Bouchard C. Sitting time and mortality from all causes, cardiovascular disease, and cancer. . Med Sci Sports Exerc 2009; 41:998-1005.
10. Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, et al. Compendium of physical activities: an update of activity codes and MET intensities. Med Sci Sports Exerc 2000; 32:S498-504.
11. Pate RR, O'Neill JR, Lobelo F. The evolving definition of "sedentary". Exerc Sport Sci Rev 2008; 36:173-8.
12. Brown WJ, Bauman A, Bull FC, Burton NW. Development of Evidence-based Physical Activity Recommendations for Adults (18-64 years). Australian Government Department of Health.: Australian Government Department of Health., 2012.
13. Watz H, Waschki B, Meyer T, Magnussen H. Physical activity in patients with COPD. Eur Respir J 2009; 33:262-72.
14. Pitta F, Troosters T, Spruit MA, Probst VS, Decramer M, Gosselink R. Characteristics of physical activities in daily life in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2005; 171:972-7.
15. Watz H, Pitta F, Rochester CL, Garcia-Aymerich J, ZuWallack R, Troosters T, et al. An official European Respiratory Society statement on physical activity in COPD. Eur Respir J 2014; 44:1521-37.
16. Garcia-Aymerich J, Lange P, Benet M, Schnohr P, Anto JM. Regular physical activity reduces hospital admission and mortality in chronic obstructive pulmonary disease: a population based cohort study. Thorax 2006; 61:772-8.
17. Furlanetto KC, Donaria L, Schneider LP, Lopes JR, Ribeiro M, Fernandes KB, et al. Sedentary Behavior Is an Independent Predictor of Mortality in Subjects With COPD. Respir Care 2017.
18. Van't Hul AJ, Frouws S, Van Den Akker E, Van Lummel R, Starrenburg-Razenberg A, Van Bruggen A, et al. Decreased physical activity in adults with bronchial asthma. Respiratory Medicine 2016; 114:72-7.
19. Garcia-Aymerich J, Varraso R, Anto JM, Camargo CA, Jr. Prospective study of physical activity and risk of asthma exacerbations in older women. American Journal of Respiratory & Critical Care Medicine 2009; 179:999-1003.
20. Strine TW, Balluz LS, Ford ES. The associations between smoking, physical inactivity, obesity, and asthma severity in the general US population. Journal of Asthma 2007; 44:651-8.

21. Lovstrom L, Emtner M, Alving K, Nordvall L, Borres MP, Janson C, et al. High levels of physical activity are associated with poorer asthma control in young females but not in males. Respirology 2016; 21:79-87.
22. Bahmer T, Waschki B, Schatz F, Herzmann C, Zabel P, Kirsten AM, et al. Physical activity, airway resistance and small airway dysfunction in severe asthma. Eur Respir J 2017; 49.
23. Ekelund U, Steene-Johannessen J, Brown WJ, Fagerland MW, Owen N, Powell KE, et al. Does physical activity attenuate, or even eliminate, the detrimental association of sitting time with mortality? A harmonised meta-analysis of data from more than 1 million men and women. Lancet 2016; 388:1302-13010.
24. Chau JY, Grunseit AC, Chey T, Stamatakis E, Brown WJ, Matthews CE, et al. Daily sitting time and all-cause mortality: a meta-analysis. PLoS One 2013; 8:e80000.
25. GINA. Global Strategy for Asthma Management and Prevention.: Available from www.ginasthma.org, 2017.
26. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. Eur Respir J 1999; 14:902-7.
27. Gibson PG, McDonald VM, Marks GB. Asthma in older adults. Lancet 2010; 376:803-13.
28. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987; 40:373-83.
29. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983; 67:361-70.
30. Holland AE, Spruit MA, Troosters T, Puhan MA, Pepin V, Saey D, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. Eur Respir J 2014; 44:1428-46.
31. Juniper EF. Evaluation of impairment of health-related quality of life in asthma: development of a questionnaire for use in clinical trials. Thorax 1992; 47:76-83.
32. Juniper EF, Guyatt G, Willan A, Griffith LE. Determining a minimal important change in a disease-specific quality of life instrument. J Clin Epidemiol. 1994; 47:81-7.
33. Juniper EF, Svensson K, Mork AC, Stahl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. Respir Med 2005; 99:553-8.
34. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J 2005; 26:319-38.
35. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med 1999; 159:179-87.
36. Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. Am J Respir Crit Care Med 2011; 184:602-15.
37. Gibson PG, Wlodarczyk JW, Hensley MJ, Gleeson M, Henry RL, Cripps AW, et al. Epidemiological association of airway inflammation with asthma symptoms and airway hyperresponsiveness in childhood. Am J Respir Crit Care Med 1998; 158:36-41.
38. Pavord ID, Brightling CE, Woltmann G, Wardlaw AJ. Non-eosinophilic corticosteroid unresponsive asthma. Lancet 1999; 353:2213-4.
39. Matthews CE, Chen KY, Freedson PS, Buchowski MS, Beech BM, Pate RR, et al. Amount of time spent in sedentary behaviors in the United States, 2003-2004. Am J Epidemiol 2008; 167:875-81.
40. Troiano RP, Berrigan D, Dodd KW, Masse LC, Tilert T, McDowell M. Physical activity in the United States measured by accelerometer. Med Sci Sports Exerc 2008; 40:181-8.
41. Healy GN, Matthews CE, Dunstan DW, Winkler EA, Owen N. Sedentary time and cardio-metabolic biomarkers in US adults: NHANES 2003-06. Eur Heart J 2011; 32:590-7.
42. Rabinovich RA, Louvaris Z, Raste Y, Langer D, Van Remoortel H, Giavedoni S, et al. Validity of physical activity monitors during daily life in patients with COPD. Eur Respir J 2013; 42:1205-15.
43. Department AS. ActiLife 6 User's Manual. In: Wyatt J, ed. Pensacola, FL 32502: Actigraph, 2012.

44. Freedson PS, Melanson E, Sirard J. Calibration of the Computer Science and Applications, Inc. accelerometer. Med Sci Sports Exerc 1998; 30:777-81.
45. Willett WC, Howe GR, Kushi LH. Adjustment for total energy intake in epidemiologic studies. Am J Clin Nutr 1997; 65:1220S-8S; discussion 9S-31S.
46. Chen Y, Dales R, Krewski D. Leisure-time energy expenditure in asthmatics and non-asthmatics. Respiratory Medicine 2001; 95:13-8.
47. Ford ES, Heath GW, Mannino DM, Redd SC. Leisure-time physical activity patterns among US adults with asthma. Chest 2003; 124:432-7.
48. Doggett N, Dogra S. Physical inactivity and television-viewing time among Aboriginal adults with asthma: a cross-sectional analysis of the Aboriginal Peoples Survey. Health Promotion and Chronic Disease Prevention in Canada 2015; 35:54-61.
49. Bradley JM, Wilson JJ, Hayes K, Kent L, McDonough S, Tully MA, et al. Sedentary behaviour and physical activity in bronchiectasis: a cross-sectional study. BMC Pulm Med 2015; 15:61.
50. Troosters T, Sciurba F, Battaglia S, Langer D, Valluri SR, Martino L, et al. Physical inactivity in patients with COPD, a controlled multi-center pilot-study. Respir Med 2010; 104:1005-11.
51. Tudor-Locke C, Bassett Jr DR. How many steps/day are enough? Preliminary pedometer indices for public health. Sports Med 2004; 34:1-8.
52. Watz H, Waschki B, Boehme C, Claussen M, Meyer T, Magnussen H. Extrapulmonary effects of chronic obstructive pulmonary disease on physical activity: a cross-sectional study. Am J Respir Crit Care Med 2008; 177:743-51.
53. Carson KV, Chandratilleke MG, Picot J, Brinn MP, Esterman AJ, Smith BJ. Physical training for asthma. The Cochrane database of systematic reviews 2013; 9:CD001116.
54. Franca-Pinto A, Mendes FAR, de Carvalho-Pinto RM, Agondi RC, Cukier A, Stelmach R, et al. Aerobic training decreases bronchial hyperresponsiveness and systemic inflammation in patients with moderate or severe asthma: A randomised controlled trial. Thorax. 2015; 10.
55. Bacon SL, Lemiere C, Moullec G, Ninot G, Pepin V, Lavoie KL. Association between patterns of leisure time physical activity and asthma control in adult patients. BMJ Open Respiratory Research 2015; 2:1-7.
56. Pinto-Plata VM. The 6-min walk distance: change over time and value as a predictor of survival in severe COPD. Eur Respir J 2004; 23:28–33.
57. Spruit MA, Polkey MI, Celli B, Edwards LD, Watkins ML, Pinto-Plata V, et al. Predicting outcomes from 6-minute walk distance in chronic obstructive pulmonary disease. J Am Med Dir Assoc 2012; 13:291-7.
58. Cote CG, Casanova C, Marin JM, Lopez MV, Pinto-Plata V, de Oca MM, et al. Validation and comparison of reference equations for the 6-min walk distance test. Eur Respir J 2008; 31:571-8.
59. Celli B, Tetzlaff K, Criner G, Polkey MI, Sciurba F, Casaburi R, et al. The 6-Minute-Walk Distance Test as a Chronic Obstructive Pulmonary Disease Stratification Tool. Insights from the COPD Biomarker Qualification Consortium. Am J Respir Crit Care Med 2016; 194:1483-93.
60. Polkey MI, Spruit MA, Edwards LD, Watkins ML, Pinto-Plata V, Vestbo J, et al. Six-minute-walk test in chronic obstructive pulmonary disease: minimal clinically important difference for death or hospitalization. Am J Respir Crit Care Med 2013; 187:382-6.
61. Scott HA, Latham JR, Callister R, Pretto JJ, Baines K, Saltos N, et al. Acute exercise is associated with reduced exhaled nitric oxide in physically inactive adults with asthma. Annals of Allergy, Asthma, & Immunology 2015; 114:470-9.
62. Fu JJ, McDonald VM, Baines KJ, Gibson PG. Airway IL-1beta and Systemic Inflammation as Predictors of Future Exacerbation Risk in Asthma and COPD. Chest 2015; 148:618-29.
63. Qian FH, Zhang Q, Zhou LF, Liu H, Huang M, Zhang XL, et al. High-sensitivity C-reactive protein: a predicative marker in severe asthma. Respirology 2008; 13:664-9.
64. Gleeson M, Bishop NC, Stensel DJ, Lindley MR, Mastana SS, Nimmo MA. The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. Nat Rev Immunol 2011; 11:607-15.

65. Watz H, Waschki B, Kirsten A, Muller KC, Kretschmar G, Meyer T, et al. The metabolic syndrome in patients with chronic bronchitis and COPD: frequency and associated consequences for systemic inflammation and physical inactivity. Chest 2009; 136:1039-46.
66. Garcia-Aymerich J, Serra I, Gomez FP, Farrero E, Balcells E, Rodriguez DA, et al. Physical activity and clinical and functional status in COPD. Chest 2009; 136:62-70.
67. Scott HA, Gibson PG, Garg ML, Pretto JJ, Morgan PJ, Callister R, et al. Dietary restriction and exercise improve airway inflammation and clinical outcomes in overweight and obese asthma: a randomized trial. Clinical & Experimental Allergy 2013; 43:36-49.
68. Van Remoortel H, Raste Y, Louvaris Z, Giavedoni S, Burtin C, Langer D, et al. Validity of six activity monitors in chronic obstructive pulmonary disease: a comparison with indirect calorimetry. PLoS One 2012; 7:e39198.
69. Santos-Lozano A, Santin-Medeiros F, Cardon G, Torres-Luque G, Bailon R, Bergmeir C, et al. Actigraph GT3X: validation and determination of physical activity intensity cut points. Int J Sports Med 2013; 34:975-82.
70. Kozey-Keadle S, Libertine A, Lyden K, Staudenmayer J, Freedson PS. Validation of wearable monitors for assessing sedentary behavior. Med Sci Sports Exerc 2011; 43:1561-7.
71. Hart TL, McClain JJ, Tudor-Locke C. Controlled and free-living evaluation of objective measures of sedentary and active behaviors. J Phys Act Health 2011; 8:848-57.
72. Aguilar-Farias N, Brown WJ, Peeters GM. ActiGraph GT3X+ cut-points for identifying sedentary behaviour in older adults in free-living environments. J Sci Med Sport 2014; 17:293-9.
73. Gorman E, Hanson HM, Yang PH, Khan KM, Liu-Ambrose T, Ashe MC. Accelerometry analysis of physical activity and sedentary behavior in older adults: a systematic review and data analysis. Eur Rev Aging Phys Act 2014; 11:35-49.
74. Healy GN, Clark BK, Winkler EA, Gardiner PA, Brown WJ, Matthews CE. Measurement of adults' sedentary time in population-based studies. Am J Prev Med 2011; 41:216-27.

Table I: Demographic and clinical characteristics

	Severe asthma	***Controls***	***P -value***
N	61	61	
Gender, F|M (% females)	32|29 (52.46)	32|29 (52.46)	1
Age (years), median [IQR]	59 [43 - 68]	54 [34 - 63]	0.0633
BMI (kg/m^2), mean (95%CI)	30.00 (28.06, 31.89)	25.40 (24.42, 26.38)	**0.0001**
Smoking status, (%) current | ex	6.6|47.5	0 |29.5	
Pack year, mean (95%CI)	5.0 (2.71, 7.28)	3.0 (-0.43, 6.35)	0.322
Years since diagnosis, median [IQR]	27.11 [15.03 - 50.76]	n/a	
OCS, % participants medicated	39.34	n/a	
ICS dose (mcg), mean(95%CI)*	1091.10 (961.25, 1220.96)	n/a	
Pre-bronchodilator FEV$_1$ (liters), mean (95%CI)	2.27 (2.05, 2.49)	3.20 (2.98, 3.42)	**< 0.0001**
Pre-bronchodilator FEV$_1$%predicted, mean (95%CI)	75.12 (69.41, 80.82)	96.94 (93.44, 100.45)	**< 0.0001**
Pre-bronchodilator FVC (liters), mean (95%CI)	3.39 (3.13, 3.66)	4.01 (3.75, 4.27)	**0.0012**
Pre-bronchodilator FVC% predicted, mean (95%CI)	87.01 (82.32, 91.71)	96.51 (93.16, 99.85)	**0.0013**
FEV$_1$/FVC ratio, mean (95%CI)	0.67 (0.63, 0.69)	0.80 (0.78, 0.81)	**< 0.0001**
Hs-CRP (mg/L), median [IQR]	1.8 [1 - 6]	1.1 [0.6 - 2.5]	**0.0024**
FeNO (ppb), median [IQR]	11.5 [5.42 - 31.45]	9.84 [4.6 - 18.3]	0.1024
Sputum Eosinophilia (≥3%), n (%)	29 (59.2)	5 (11.36)	**< 0.0001**
IgE (IU/mL), median [IQR]	225.500 [70 - 498]	n/a	
Atopy, n (%)	48 (82.76)	35 (58.33)	**0.0037**
HADS (anxiety score), mean (95%CI)	6.67 (5.70, 7.64)	3.80 (3.02, 4.58)	**< 0.0001**
HADS (depression score), mean (95%CI)	4.57 (3.81, 5.34)	1.37 (0.92, 1.82)	**< 0.0001**
CCI score ≥ 1, n (%)	16 (26.70)	2 (3.28)	**0.0003**
ACQ (units), mean (95%CI)	2.23 (1.95 - 2.50)	n/a	
AQLQ (unit), mean (95%CI)	5.15 (4.85 - 5.46)	n/a	
Severe exacerbation past 12 months, median [IQR]	2 [1 - 5]	n/a	
6MWD (meters), median [IQR]	499 [417.7 - 542.2]	616.2 [568.4 - 659.30]	**< 0.0001**
6MWD % predicted, mean (95%CI)	71.78 (68.13, 75.44)	85.71 (82.51, 88.92)	**< 0.0001**

IQR: interquartile range; CI: confidence interval; BMI: body mass index; n/a: not applicable or not assessed; OCS: oral corticosteroids; ICS: inhaled corticosteroids, ICS: Fluticasone equivalent; FEV1: forced expiratory volume in the first second; FVC: forced vital capacity; hs-CRP: high sensitivity c-reactive protein; FeNO: fractional exhaled nitric oxide; IgE: immunoglobulin E; HADs: hospital anxiety and depression scale; CCI: Charlson comorbidity index, ACQ: asthma control questionnaire; AQLQ: asthma quality of life questionnaire; 6MWD: 6-minute walk distance. Statistically significant results in* ***bold.***

Table II: Association of physical activity and sedentary time with exercise capacity as 6-minute walk distance (6MWD)

Model 1.	**Models for 6MWD**		
	Coefficient (95%CI)	**Significance**	**Adj. R2**
ST	-0.47 (-0.79, -0.14)	**0.006**	0.27
MVPA	1.70 (0.64, 2.75)	**0.002**	0.30
Steps	0.01 (0.00, 0.02)	**0.000**	0.35
Model 2			
Steps	0.02 (0.00, 0.04)	**0.010**	0.35
ST	0.18 (-0.39, 0.75)	0.531	
MVPA	1.24 (-0.32, 2.80)	0.117	0.29
ST	-0.19 (-0.66, 0.28)	0.429	

Model 1= each behavioral variable (ST, MVPA, or Steps) as a predictor of exercise capacity. Model 2= PA (Steps or MVPA) as a predictor of exercise capacity, after adjustment for ST and confounders.
Models adjusted for age, sex, and BMI. BMI: body mass index; ST: sedentary time; MVPA: moderate and higher physical activity; Steps: steps/day; 6MWD: 6-minute walk distance; CI: confidence interval; Adj: adjusted.

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Table III: Association of physical activity and sedentary time with clinical outcomes

Model 1	**Models for FEV_1 (%)**			**Models for AQLQ (units)**			**Models for ACQ (units)**		
	Coefficient (95%CI) *	**Sig**	**Adj. R^2**	**Coefficient (95%CI) ***	**Sig**	**Adj. R^2**	**Coefficient (95%CI) ***	**Sig**	**Adj. R^2**
ST	-7.90 (-15.63, -0.17)	**0.045**	0.10	-0.35 (-0.76, 0.04)	0.081	0.15	0.51 (0.14, 0.89)	**0.007**	0.12
MVPA	28.69 (3.31, 54.07)	**0.027**	0.11	1.59 (0.29, 2.89)	**0.018**	0.19	-2.15(-3.33, -0.97)	**0.001**	0.19
Steps	0.17 (-0.03, 0.38)	0.096	0.08	0.01 (0.00,0.02)	**0.015**	0.20	-0.01(-0.02, -0.00)	**0.005**	0.13
Model 2									
Steps	-0.00(-0.38, 0.37)	0.994	0.08	0.01(-0.00, 0.03)	0.078	0.19	-0.00(-0.02, 00.0)	0.304	0.12
ST	-7.95(-22.25, 6.35)	0.27		0.19 (-0.53, 0.23)	0.597		0.21 (-0.47, 0.90)	0.537	
MVPA	20.65 (-17.43, 58.73)	0.282	0.10	1.59 (-0.37, 3.55)	0.111	0.18	-1.94(-3.69, -0.18)	**0.032**	0.18
ST	-3.27 (-14.78, 8.23)	0.571		-0.00 (-0.59, 0.59)	0.998		0.08(-0.44, 0.62)	0.740	

For rationale of Model 1 and 2 refer to captions in Table II.
*All models adjusted for age and sex. AQLQ adjusted for smoking status. ACQ adjusted for smoking status and BMI. *Coefficients and CI expressed as x10^{-2}.*
ST: sedentary time, MVPA: moderate and above physical activity, Steps: steps/day, BMI: body mass index, FEV_1: Forced expiratory volume in 1-second, AQLQ: asthma quality of life questionnaire, ACQ: asthma control questionnaire, CI: confidence interval, Sig: significance.

Table IV: Association of physical activity and sedentary time with airway inflammation.

Predictors	**Simple logistic regression airway eosinophilia**		
	Odds ratio (95%CI)	**Sig**	**Adj. R^2**
ST	1.00 (0.99, 1.01)	0.315	0.02
MVPA	1.01(0.98, 1.035)	0.470	0.01
Steps	1.00(0.99, 1.00)	0.246	0.02

Airway eosinophilia defined as eosinophil count in sputum cell ≥3%. ST: sedentary time, MVPA: moderate and above physical activity, Steps: steps/day. CI: confidence interval. Adj: adjusted.

Table V: Association of physical activity and sedentary time with inflammatory biomarkers.

Model 1	**SLR models for Ln-FeNO**			**Models for Ln_hs-CRP**		
	Coefficient (95%CI) *	**Sig**	**Adj. R^2**	**Coefficient (95%CI) ***	**Sig**	**Adj. R^2**
ST	1.92 (-2.23, 6.07)	0.358	-0.00	3.36(-0.08, 6.80)	0.56	0.45
MVPA	-1.02(-14.74, 12.70)	0.882	-0.02	-10.47 (-21.79, 0.84)	0.069	0.45
Steps	-0.02(-0.13, 0.08)	0.617	-0.01	-0.13(-0.22, -0.03)	**0.006**	0.49
Model 2						
Steps	N/D			-0.17(-0.34, -0.00)	**0.038**	0.49
ST				-2.09(-8.24, 4.04)	0.497	
MVPA	N/D			-5.15(-21.95, 11.63)	0.54	0.45
ST				2.20 (-2.92, 7.32)	0.393	

For rationale of Model 1 and 2 refer to captions in Table II.
*Ln_hs-CRP: adjusted for age, sex, and BMI. * Coefficients and CI expressed as x10 $^{-3}$. BMI: body mass index, SLR: simple linear regression analysis, FeNO: fractional exhaled nitric oxide, Ln_hs-CRP: natural logarithm C-reactive protein. ST: sedentary time, MVPA: moderate and above physical activity, Steps:*

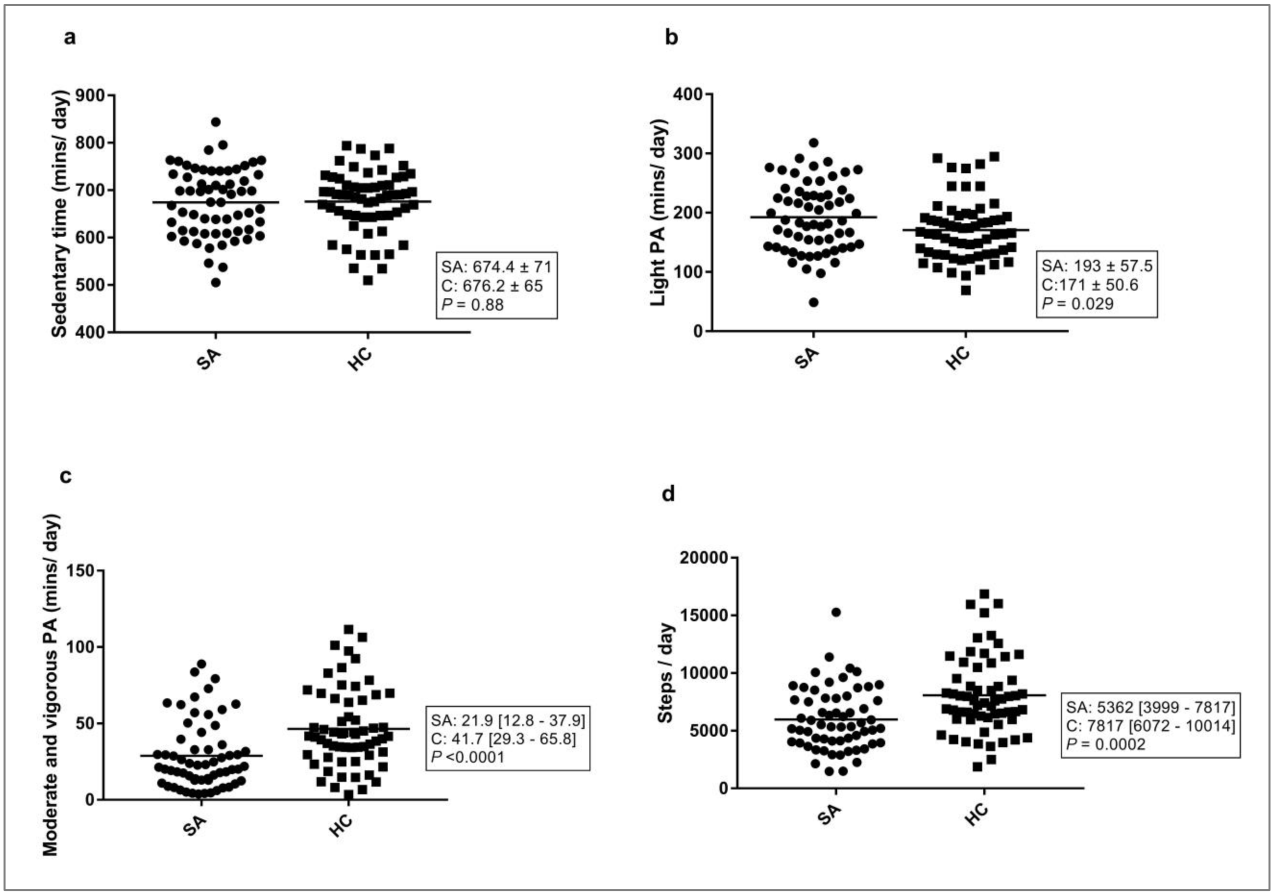

Figure 1: Sedentary time (a), Light PA (b), Moderate and vigorous PA (c), and Steps (d) in severe asthma and aged-matched control. Values reported as mean ± SD or median [IQR]. SA: severe asthma, C: controls. Number of participants in each group=61.

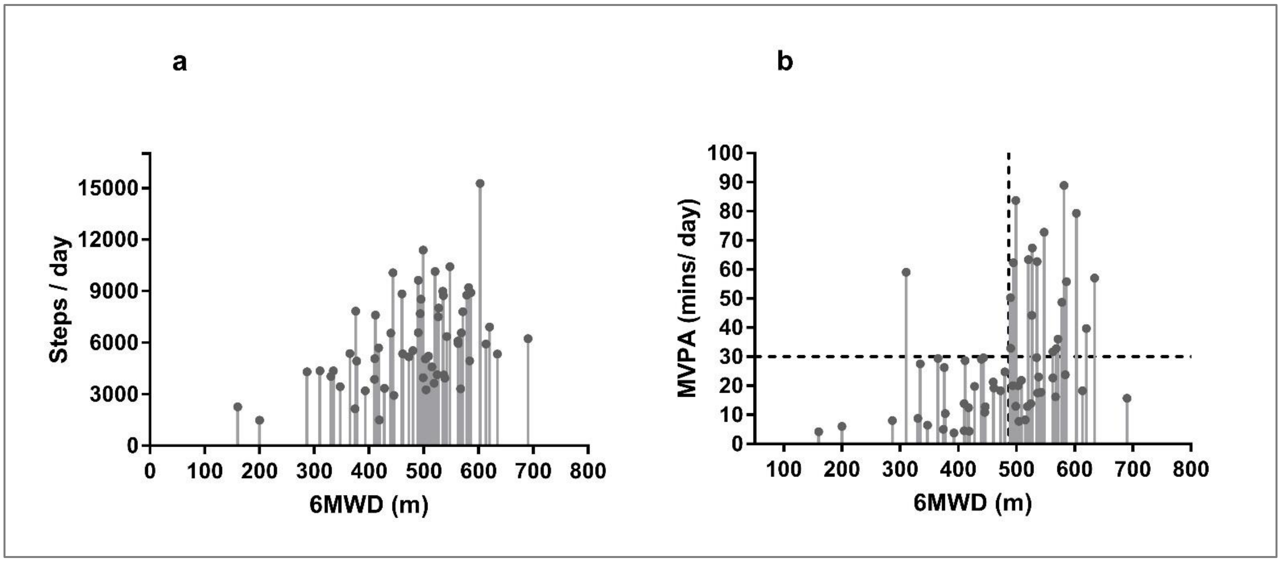

Figure 2: Relationship between physical activity and 6MWD in meters.

MVPA: moderate and above physical activity; 6MWD: 6-minute walk distance. Rho a= 0.453; rho b= 0.502 P < 0.001 both.