

Physical Activity and Exercise Capacity in Severe Asthma: Key Clinical Associations



Laura Cordova-Rivera, BPhy(Hons)^{a,b,c}, Peter G. Gibson, MBBS^{a,b,c,d}, Paul A. Gardiner, PhD^{e,f}, Heather Powell, MMedSc^{b,c,d}, and Vanessa M. McDonald, PhD^{a,b,c,d} *New Lambton Heights and Newcastle, New South Wales, Australia; and Woolloongabba and South Brisbane, Queensland, Australia*

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.

What does this article add to our knowledge? Physical activity measured as steps per 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.

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.

^aNational Health and Medical Research Council Centre of Excellence in Severe Asthma, New Lambton Heights, New South Wales, Australia

^bPriority Research Centre for Healthy Lungs, The University of Newcastle, Newcastle, New South Wales, Australia

^cHunter Medical Research Institute, New Lambton Heights, New South Wales, Australia

^dDepartment of Respiratory and Sleep Medicine, John Hunter Hospital, Newcastle, New South Wales, Australia

^eCentre for Health Services Research, The University of Queensland, Woolloongabba, Queensland, Australia

^fMater Research Institute, The University of Queensland, South Brisbane, Queensland, Australia

This research was supported by a University of Newcastle and Priority Research Centre for Healthy Lungs postgraduate scholarship and the Hunter Medical Research Institute, Australia.

Conflicts of interest: L. Cordova-Rivera has received research support from John Hunter Hospital Charitable Trust and Hunter Medical Research Institute. P. G. Gibson has participated in educational symposia funded by AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, and Novartis; has participated in studies funded by GlaxoSmithKline and AstraZeneca; and holds a National Health and Medical Research Council (NHMRC) Practitioner Fellowship. P. A. Gardiner is supported by an NHMRC-Australian Research Council Dementia Research Development Fellowship and has participated in an educational symposium funded by Boehringer Ingelheim. V. M. McDonald has received research support from John Hunter Hospital Charitable Trust and Hunter Medical Research Institute, NHMRC Translating Research Into Practice (TRIP) fellowship, University of Newcastle, Cyclopharm, AstraZeneca, GlaxoSmithKline, and Lung Foundation Australia; has received lecture fees for participation in educational symposia funded by AstraZeneca, GlaxoSmithKline, Novartis, and Menarini; has participated in advisory boards for GlaxoSmithKline, AstraZeneca and Menarini; and has received travel support from Menarini. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication June 19, 2017; revised September 9, 2017; accepted for publication September 28, 2017.

Available online November 10, 2017.

Corresponding author: Vanessa M. McDonald, PhD, Level 2 West Wing, 1 Kookaburra Circuit, New Lambton Heights, NSW 2305, Australia. E-mail: vanessa.mcdonald@newcastle.edu.au.

2213-2198

© 2017 American Academy of Allergy, Asthma & Immunology

<https://doi.org/10.1016/j.jaip.2017.09.022>

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 with age-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. In addition, 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 sex- and age-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 sex (32 [53%] females in each group).

Individuals with severe asthma accumulated less minutes per day in moderate and higher intensity activity, median (IQR) 21.9 (12.9-36.0) versus 41.7 (29.5-65.2) ($P < .0001$) and accumulated 2,232 fewer steps per day ($P = .0002$). However, they engaged in more light-intensity physical activity. No differences were found for sedentary time. In a multivariate regression model, steps per day were strongly and independently associated with better exercise capacity in participants with severe asthma (coefficient, 0.0169; 95% CI, 0.008-0.025; $P < .001$).

CONCLUSIONS: People with severe asthma perform less moderate and vigorous activity than do controls. Higher levels of activity and lower levels of sedentary time are associated with

Abbreviations used

6MWD- 6-minute walk distance

ACQ- Asthma Control Questionnaire

AQLQ- Asthma Quality of Life Questionnaire

COPD- Chronic obstructive pulmonary disease

FENO- Fractional exhaled nitric oxide

hs-CRP- High-sensitivity C-reactive protein

MVPA- Moderate- to vigorous-intensity physical activity

better exercise capacity, asthma control, and lower levels of systemic inflammation. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2018;6:814-22)

Key words: Severe asthma; Physical activity; Sedentary time; Accelerometry; Exercise capacity; Associations; Clinical outcomes

Severe asthma is a heterogeneous and complex disease in which diverse clinical and physiological presentations are common.¹ Severe asthma represents a high patient and health care 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 and exercise are regarded as highly beneficial, leading to positive health outcomes.⁵⁻⁷ Engagement in excess sedentary time 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 units, it is classified as light, moderate, or vigorous physical activity, where light corresponds to the lower metabolic equivalent of tasks or energy expenditure.⁵ Mild stretching, low impact dancing, and running correspond to examples of light, moderate, and vigorous physical activity, respectively.¹⁰ *Sedentary time* refers to activities performed while awake in a lying or sitting position and expending low levels of energy (≤ 1.5 metabolic equivalent of tasks).¹¹ The physical activity and sedentary guidelines recommend engaging in at least 150 min/wk of moderate activity, or 75 min/wk 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 with 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 physical activity in asthma has been associated with better asthma control,¹⁸ reduced exacerbations,¹⁹ and reduced health care use.²⁰ Data on inflammatory parameters are 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 physical activity 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 were to objectively measure physical activity and sedentary time in a severe asthma population compared with age-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 are their age- and sex-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. In addition, 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 sex- and age-matched controls were recruited and underwent a multidimensional assessment with objective measures of physical activity and sedentary time. Participants with severe asthma 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 asthma¹: prescribed Global Initiative for Asthma step 4 treatment or above, defined as 1,000 μ g inhaled corticosteroid fluticasone equivalent and long-acting β 2-agonists,²⁵ had evidence of airflow limitation ($FEV_1 < 80\%$ predicted), and ongoing poor asthma control (Asthma Control Questionnaire [ACQ]²⁶ score ≥ 1.5 units or had experienced a severe exacerbation in the last 12 months requiring oral corticosteroids). Participants were clinically stable during visits (no increase in asthma symptoms in the last 4 weeks). Otherwise, their enrolment was postponed until they were stable. Exclusion criteria included malignancy with poor prognosis (< 3 months).

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

Ethics approval was granted by 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 assessment²⁷ involving measurement of height and 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 was performed according to current guidelines³⁰ 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 or more units is considered clinically significant for both questionnaires.^{32,33}

Airflow limitation. Airflow limitation was assessed by measuring spirometry: FEV₁, forced vital capacity, and FEV₁/forced vital capacity ratio (Medgraphics, CPFS/D USB Spirometer; BreezeSuite v7.1, MGC Diagnostics, Saint Paul, Minn).³⁴ FEV₁ and forced vital capacity percent predicted were calculated using the Third National Health and Nutrition Examination Survey predicted equations.³⁵

Airway inflammation. Eosinophilic airway inflammation was assessed in 2 ways: using fraction of exhaled nitric oxide (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 induced³⁷ using nebulized 4.5% or 0.9% saline if the prebronchodilator FEV₁ was less than or equal to 1 L. 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 cytopins for differential cell counts using May-Grunwald Giemsa. Airway eosinophilia was defined as sputum differential eosinophil count of greater than or equal to 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, Fla), a device widely used in research,³⁹⁻⁴¹ and validated for populations with COPD.⁴² This is a small device (4.6 cm × 3.3 cm × 1.5 cm) 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 nonwear periods in a diary. The ActiGraph measures time-varying changes in force and activity levels 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 (ActiGraph, Pensacola, Fla), 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 nonwear time were estimated from the diaries and visual examination of the ActiGraph data and removed before classification. ActiLife software was used to summarize the data. We classified time according to the widely used Freedson 1998 cutoff points: Sedentary (0-99 counts per minute [CPM]), light physical activity (100-1951 CPM), and moderate and above physical activity (≥1,952 CPM).⁴⁴ The ActiGraph also captures steps per day. Our measures of physical activity and sedentary time were daily time in sedentary time (min/d), daily time in light physical activity (min/d), daily time in moderate- to vigorous-intensity physical activity (MVPA) (min/d), and daily number of steps (Steps [steps/d]). We reported both MVPA and Steps because

although the MVPA describes the volume of moderate- to high-intensity activity and can be compared with the physical activity recommendations,¹² Steps is an output easy to interpret and could be used as a motivational and informative tool both for patients and for clinicians. Sedentary time and light physical activity were standardized for wear time by the residuals method.⁴⁵ The data were considered valid if there were recordings of 4 or more days, with 10 or more hours of recording each day.

Statistical analysis

Data were analyzed using STATA 13 (Stata Corporation, College Station, Texas). Values are expressed as means with CIs for parametric data and medians with interquartile range for nonparametric data. Differences between the group with severe asthma and the age- and sex-matched control group were assessed using the Student *t* test or the Wilcoxon rank sum test based on normality.

The associations between the different clinical and biological outcomes and the behavioral variables (sedentary time, MVPA, and Steps) adjusting for potential confounders (body mass index and current smoking status) were estimated using simple linear regression analysis. Each behavioral variable was used as a predictor of a given clinical or biological outcome (dependent variable: FEV₁% predicted, 6MWD, ACQ score, AQLQ score, FENO, and hs-CRP). Age and sex were regarded as biological confounders and included in all the models. Behavioral variables and confounders with a *P* value of less than .2 were also included in a stepwise multiple linear regression analysis to identify the associations between each behavioral variable (sedentary time, MVPA, and Steps) and each biological/clinical outcome (model 1). To test whether moderate physical activity (Steps or MVPA) can counteract the detrimental health outcomes associated with sedentary time, further models were used, adjusting for sedentary time as well as other confounders (model 2). Assumptions for linear regressions were met. Colinearity 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 × [exp(coefficient) − 1] percent for each 1-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 6-minute walk test (defined as ≥median [≥499 m]) and higher engagement (≥30 minutes) in MVPA. Spearman rank correlation tested the relationship between activity variables and 6MWD. Results were reported as significant when *P* was less than .05.

RESULTS

Characteristics of the study population

A total of 143 participants (those with severe asthma = 74, controls = 69) completed the study and 122 (those with severe asthma = 61, controls = 61) were included in the analysis; 21 participants were excluded because of not having valid accelerometer data (those with severe asthma = 8, controls = 5) or because they did not fulfill the disease inclusion criteria after assessment (those with severe asthma = 5, controls = 3). Participants with severe asthma had long-standing disease (median, 27 years) and poor asthma control. They also had a higher body mass index and increased prevalence of atopy, lower lung function, and higher scores of anxiety and depression compared with age- and sex-matched controls. Demographic and clinical characteristics are presented in [Table 1](#).

TABLE I. Demographic and clinical characteristics

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

BMI, Body mass index; CCI, Charlson comorbidity index; FVC, forced vital capacity; HADS, Hospital Anxiety and Depression Scale; ICS, inhaled corticosteroid; ICS*, fluticasone equivalent; IQR, interquartile range; NA, not applicable or not assessed; OCS, oral corticosteroid. Bold indicates statistical significance ($P < .05$).

Physical activity and sedentary time in the group with severe asthma and the age- and sex-matched control group

Compared with controls, people with severe asthma performed less activity of at least moderate intensity. The group with severe asthma had a median difference of 19.8 fewer minutes of MVPA per day ($P < .0001$) and 2455 fewer steps per day ($P = .0002$). Conversely, the population with severe asthma engaged in more light physical activity, with a mean (95% CI) difference of 21.7 (2.2–41.1) more minutes per day ($P = .029$). No statistically significant differences were found in sedentary time between the 2 populations (Figure 1).

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

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 1,000 steps, there was a 16.9-m increase in the 6MWD. For every minute increase in sedentary time, there was a decrease of 0.47 m in the 6MWD. Accordingly, every additional hour spent sedentary is associated with a 28.2-m reduction in the 6MWD.

There was a linear relationship between Steps and the 6MWD (Figure 2, A). For MVPA (Figure 2, B) there was also an apparent threshold effect where those participants with a 6MWD performance of greater than or equal to the median (499 m) were also the participants engaging daily in 30 minutes or more of MVPA, a volume of activity that fits within the physical activity recommendations¹² (odds ratio, 6.09; $P = .005$). This suggests that a value of around 500 m in the 6MWD could identify individuals engaging in recommended levels of MVPA.

Simultaneously including sedentary time with MVPA or Steps in the model attenuated the associations of MVPA and sedentary time to the null. However, the association of Steps with exercise capacity remained similar and still statistically significant (Table II/model 2). A 1,000-step increase was associated with better performance in the 6MWD by 21 m. 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 FEV₁% predicted, and sedentary time and the AQLQ score. In contrast to the impact of activity on exercise capacity, the effect on these clinical outcomes was weaker but

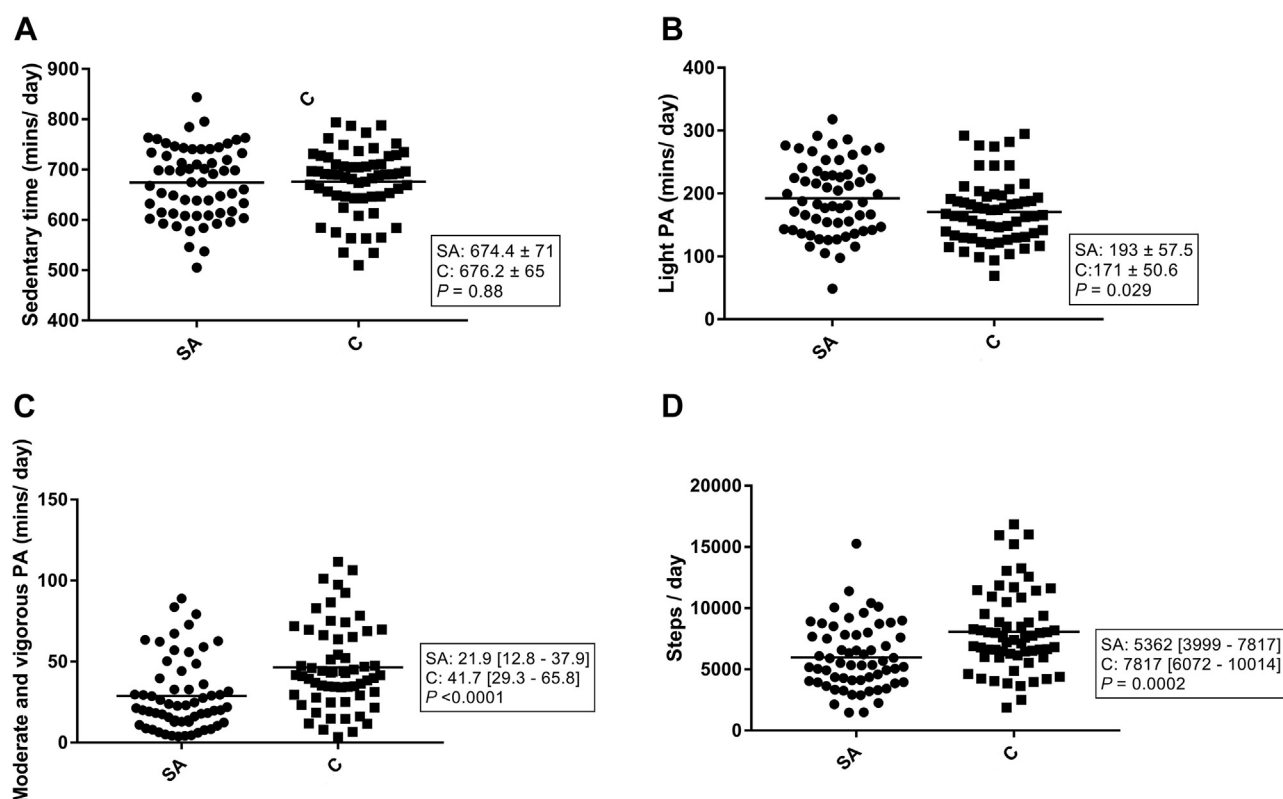


FIGURE 1. Sedentary time (A), Light PA (B), Moderate and vigorous PA (C), and Steps (D) in severe asthma and aged-matched control. Values reported as mean ± SD or median [interquartile range]. Number of participants in each group (n = 61). C, controls; PA, physical activity; SA, severe asthma.

TABLE II. Association of physical activity and sedentary time with exercise capacity as 6MWD

Model	Models for 6MWD		
	Coefficient (95% CI)	Significance	Adjusted R ²
Model 1			
ST	−0.47 (−0.79 to −0.14)	.006	0.27
MVPA	1.70 (0.64 to 2.75)	.002	0.30
Steps	0.01 (0.00 to 0.02)	.000	0.35
Model 2			
Steps	0.02 (0.00 to 0.04)	.010	
ST	0.18 (−0.39 to 0.75)	.531	0.35
MVPA	1.24 (−0.32 to 2.80)	.117	
ST	−0.19 (−0.66 to 0.28)	.429	0.29

BMI, Body mass index; PA, physical activity; ST, sedentary time.

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.

Bold indicates statistical significance ($P < .05$).

nonetheless statistically significant and biologically plausible. For every 10-minute increase in MVPA, the ACQ score decreased (improved) by 0.21 units, whereas the AQLQ score 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 score (0.52 units). Regarding sedentary time, every 100-minute increase in

this behavior is associated with a clinically significant decline in the ACQ score (0.51 units).

The only activity variable that remained statistically significant after adjustment for sedentary time was ACQ score and MVPA. Every 15-minute increase in MVPA was associated with a decrease (improved) of 0.29 units in ACQ score (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 led 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 simple linear regression analyses, the significance level for FENO was more than .2 and thus not included in the stepwise model.

Steps were significantly associated with hs-CRP. For every increase of 1,000 steps, the hs-CRP was reduced by 13%. No relationship was found between hs-CRP and MVPA or sedentary time (Table V/model 1).

Only Steps remained significantly associated with hs-CRP after adjustment for sedentary time. For every increase of 1,000 steps, the hs-CRP was reduced by 17% (Table V/model 2). The coefficients for the associations of sedentary time were

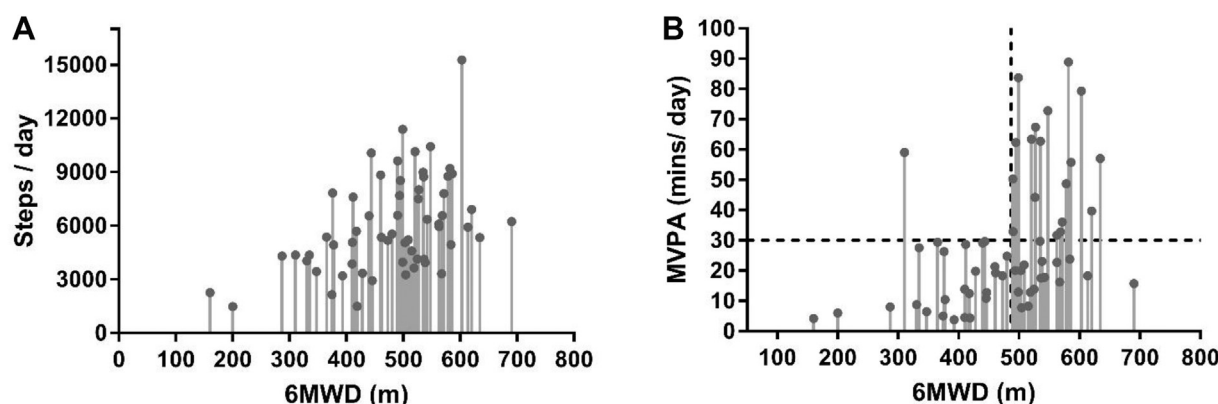


FIGURE 2. Relationship between physical activity and 6MWD in meters. A, $\rho = 0.453$. B, $\rho = 0.502$ ($P < .001$ both).

TABLE III. Association of physical activity and ST with clinical outcomes

Model	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
Model 1									
ST	−7.90 (−15.63 to −0.17)	.045	0.10	−0.35 (−0.76 to 0.04)	.081	0.15	0.51 (0.14 to 0.89)	.007	0.12
MVPA	28.69 (3.31 to 54.07)	.027	0.11	1.59 (0.29 to 2.89)	.018	0.19	−2.15 (−3.33 to −0.97)	.001	0.19
Steps	0.17 (−0.03 to 0.38)	.096	0.08	0.01 (0.00 to 0.02)	.015	0.20	−0.01 (−0.02 to −0.00)	.005	0.13
Model 2									
Steps	−0.00 (−0.38 to 0.37)	.994		0.01 (−0.00 to 0.03)	.078		−0.00 (−0.02 to 0.00)	.304	
ST	−7.95 (−22.25 to 6.35)	.27	0.08	0.19 (−0.53 to 0.23)	.597	0.19	0.21 (−0.47 to 0.90)	.537	0.12
MVPA	20.65 (−17.43 to 58.73)	.282		1.59 (−0.37 to 3.55)	.111		−1.94 (−3.69 to −0.18)	.032	
ST	−3.27 (−14.78 to 8.23)	.571	0.10	−0.00 (−0.59 to 0.59)	.998	0.18	0.08 (−0.44 to 0.62)	.740	0.18

Adj., Adjusted; BMI, body mass index; Sig., significance; ST, sedentary time.

For rationale of models 1 and 2, refer to captions in Table II. All models adjusted for age and sex. AQLQ score adjusted for smoking status. ACQ score adjusted for smoking status and BMI.

Bold indicates statistical significance ($P < .05$).

*Coefficients and CI expressed as $\times 10^{-2}$.

TABLE IV. Association of physical activity and ST with airway inflammation

Simple logistic regression airway eosinophilia			
Predictors	Odds ratio (95% CI)	Significance	Adjusted R ²
ST	1.00 (0.99-1.01)	.315	0.02
MVPA	1.01 (0.98-1.035)	.470	0.01
Steps	1.00 (0.99-1.00)	.246	0.02

ST, Sedentary time.

Airway eosinophilia defined as eosinophil count of $\geq 3\%$ in sputum cell.

attenuated to the null. The model explained 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 with a sex- and age-matched control population. We have demonstrated that people with severe asthma are considerably less active. In addition, we found that levels of activity and sedentary time are strongly and independently associated with exercise capacity, and to a lesser extent with 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 those of several studies conducted in patients with 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 patients with 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 per day compared with a control group is consistent with the finding of 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 the participants in the Bahmer et al²² study (22 min/d vs 125 min/d of MVPA). It should be noted though that the authors²² used a different device to measure MVPA (SenseWear Pro Armband; BodyMedia, Pittsburgh, Pa). Studies using the Acti-Graph in a bronchiectasis population⁴⁹ have reported similar activity results as our study.

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

Model	SLR models for Ln_FENO			Models for Ln_hs-CRP		
	Coefficient (95% CI)*	Sig.	Adj. R ²	Coefficient (95%CI)*	Sig.	Adj. R ²
Model 1						
ST	1.92 (−2.23 to 6.07)	.358	−0.00	3.36 (−0.08 to 6.80)	.56	0.45
MVPA	−1.02 (−14.74 to 12.70)	.882	−0.02	−10.47 (−21.79 to 0.84)	.069	0.45
Steps	−0.02 (−0.13 to 0.08)	.617	−0.01	−0.13 (−0.22 to −0.03)	.006	0.49
Model 2						
Steps				−0.17 (−0.34 to −0.00)	.038	
ST	ND			−2.09 (−8.24 to 4.04)	.497	0.49
MVPA				−5.15 (−21.95 to 11.63)	.54	
ST	ND			2.20 (−2.92 to 7.32)	.393	0.45

Adj., Adjusted; BMI, body mass index; Ln_FENO, natural logarithm FENO; Ln_hs-CRP, natural logarithm hs-CRP; ND, not done; Sig., significance; SLR, simple linear regression analysis; ST, sedentary time.

For rationale of models 1 and 2, refer to captions in Table II. Ln_hs-CRP was adjusted for age, sex, and BMI.

Bold indicates statistical significance ($P < .05$).

*Coefficients and CI expressed as $\times 10^{-3}$.

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

In the general adult population, a widely promoted target for a desirable level of activity is 10,000 steps.⁵¹ Our population with severe asthma achieved only 5362 daily steps, thus a little more than half of the recommended level, and similar to the level reported in patients with moderate to severe COPD^{50,52} and patients with 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 populations with general asthma.^{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 patients with 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 COPD⁵⁶ and associated with hospitalization and increased mortality.⁵⁷⁻⁵⁹ In COPD, a 6MWD of 350 m or less is regarded as poor performance.⁵⁸ We found that individuals with a 6MWD of 499 m or more were 6 times more likely to engage in recommended levels of MVPA (≥ 30 minutes daily),¹² suggesting that this distance may be a suitable cutoff for people with severe asthma. However, this requires further investigation. A difference of 30 m or more has been proposed as the minimal clinically important difference, and furthermore a decrease of this magnitude is associated with increased risk of

death in COPD.⁶⁰ To date the 6MWD minimal clinically important difference for severe asthma is not known. However, the fact that an increase of 1,000 steps was associated with an increase of 22 m (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 ($>4,000$ Steps or >25 minutes of MVPA) was necessary to reach the 0.5 unit minimal clinically important difference defined for the ACQ³³ and the AQLQ.³² However, because 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 also be noted that our population was on maximum-intensity inhaled corticosteroid therapy, and this may have modified any potential relationship between the behavioral variables and airway eosinophilia or FENO. 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 inhaled corticosteroid treatment. These findings suggest that the pathway of inactivity in severe asthma may be more related to breathlessness and/or exercise capacity than to airway inflammation.

Others have reported 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 $\geq 3\%$ 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 per day were associated with lower hs-CRP levels, after adjustment for body mass index, 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 proinflammatory cytokines (IL-6 and monocyte chemoattractant protein 1) after aerobic training.⁵⁴ Interestingly, Scott et al⁶⁷ reported decreases in serum IL-6 levels with exercise and diet, but 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. Because of its cross-sectional design, it is not possible to infer causality of our findings. We chose 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 populations with COPD, being one of the most accurate in detecting different walking speeds⁶⁸ 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 cutoff point for ActiGraph to measure sedentary time in adult populations, with cutoff points ranging from 25 to 500 CPM.⁷⁰⁻⁷³ It has been suggested that both activity and sedentary parameters can vary greatly depending on the cutoff point used.⁷³ The less than 100 CPM cutoff 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} In addition, considering the scarce information available on sedentary time in patients with severe asthma, these data provide useful insight into how this behavior is associated with both different spectrums of activity and different disease outcomes. Last, 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 patients with 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 patients with severe asthma. We found that severe asthma is associated with lower levels of MVPA. 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 patients with 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 MVPA.

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. World Health Organization. Global recommendations on physical activity for health. Geneva: World Health Organization; 2010.
6. World Health Organization. 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. Katzmarzyk 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; 2012. Available from: [http://www.health.gov.au/internet/main/publishing.nsf/Content/health-pubhlth-strateg-phys-act-guidelines/\\$File/DEB-PAR-Adults-18-64years.pdf](http://www.health.gov.au/internet/main/publishing.nsf/Content/health-pubhlth-strateg-phys-act-guidelines/$File/DEB-PAR-Adults-18-64years.pdf). Accessed October 20, 2017.
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;62:579-87.
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. *Respir Med* 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. *Am J Respir Crit Care Med* 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. *J 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;49:1601827.
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;388:1302-10.

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. Global Initiative for Asthma. Global strategy for asthma management and prevention. Available from: www.ginasthma.org; 2017. Accessed October 20, 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. ActiGraph Software Department AS. ActiLife 6 User's Manual. Pensacola, FL: ActiGraph; 2012. Available from: <http://actigraphcorp.com/wp-content/uploads/2015/11/SFT12DOC13-ActiLife-6-Users-Manual-Rev-A-110315.pdf>. Accessed October 20, 2017.
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-31.
46. Chen Y, Dales R, Krewski D. Leisure-time energy expenditure in asthmatics and non-asthmatics. *Respir Med* 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 Promot Chron Dis Prev 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 DR Jr. 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. *Cochrane Database Syst Rev* 2013;9:CD001116.
54. Franca-Pinto A, Mendes FA, 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;70:732-9.
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 Respir Res* 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, Salto N, et al. Acute exercise is associated with reduced exhaled nitric oxide in physically inactive adults with asthma. *Ann Allergy Asthma Immunol* 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. *Clin Exp 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.

Reproduced with permission of copyright owner. Further reproduction prohibited without permission.