



# Association between physical activity and risk of hospitalisation in bronchiectasis

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**Adult patients with bronchiectasis and reduced physical activity (<6290 steps-day<sup>-1</sup>) or high sedentary behaviour (≥7.8 h-day<sup>-1</sup>) have a higher than average risk of hospital admission due to exacerbation after 1-year follow-up** <http://bit.ly/2wX2Y2D>

**Cite this article as:** Alcaraz-Serrano V, Gimeno-Santos E, Scioscia G, *et al.* Association between physical activity and risk of hospitalisation in bronchiectasis. *Eur Respir J* 2020; 55: 1902138 [<https://doi.org/10.1183/13993003.02138-2019>].

## ABSTRACT

**Background:** Patients with bronchiectasis have a less active lifestyle than healthy peers, but the association with hospital admission has not been explored. The aim of this study was to investigate the association between 1) any physical activity variable; and 2) sedentary time, with hospitalisation due to exacerbation in adults with bronchiectasis.

**Methods:** In this prospective observational study, baseline lung function, quality of life, exercise tolerance, severity of bronchiectasis and physical activity were recorded. Physical activity was objectively assessed over a week using a SenseWear armband and the results were expressed in steps-day<sup>-1</sup> and sedentary time. Number of hospitalisations due to a bronchiectasis exacerbation and time to first event were recorded after 1-year follow-up.

**Results:** Sixty-four patients with bronchiectasis were analysed, of whom 15 (23%) were hospitalised during the follow-up. Hospitalised patients showed poor baseline clinical and severity outcomes, fewer steps walked per day and more sedentary behaviour than the non-hospitalised group. Patients who walked ≤6290 steps-day<sup>-1</sup> or spent ≥7.8 h-day<sup>-1</sup> in sedentary behaviour had an increased risk of hospital admission due to bronchiectasis exacerbation at 1-year follow-up. Specifically, ≥7.8 h-day<sup>-1</sup> of sedentary behaviour was associated with a 5.9-fold higher risk of hospital admission in the following year.

**Conclusions:** Low levels of physical activity and high sedentary time at baseline were associated with a higher risk of hospitalisation due to bronchiectasis exacerbation. If these findings are validated in future studies, it might be appropriate to include physical activity and sedentary behaviour as an item in severity scores.

This article has supplementary material available from [erj.ersjournals.com](http://erj.ersjournals.com)

Received: 4 Nov 2019 | Accepted after revision: 3 March 2020

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## Introduction

In adults with non-cystic fibrosis bronchiectasis, the pathogenic vicious circle of persistent infection, neutrophilic inflammation and impaired mucociliary clearance leads to an increase in bacterial load and recurrent exacerbations, which in turn raises healthcare costs [1, 2]. Moreover, the presence of comorbidities and a history of hospitalisations increase the risk of further hospital admission due to bronchiectasis exacerbation [3, 4]. In Spain [5], the annual incidence of hospitalisations due to bronchiectasis exacerbations is reported to be around 15.5 per 100 000 population, while in Germany [4] and the United States [6] it is 9.4 and 16.5, respectively. These hospitalisations are associated with higher mortality, as well as a decline in respiratory function and poor quality of life (QoL) [7, 8]. The current disease burden and hospitalisation trends due to bronchiectasis exacerbation are steadily increasing and appear to be related to age and disease severity [3].

Longitudinal studies in patients with chronic obstructive pulmonary disease (COPD) have consistently demonstrated the association between low levels of physical activity and a higher risk of both mortality and hospitalisation due to exacerbation [9–12]. Similarly, patients with cystic fibrosis (CF) who regularly participate in physical activity programmes have shown better prognostic outcomes, increased respiratory function, elevated QoL and enhanced clearance of sputum [13, 14].

Physical activity can be defined as “any bodily movement produced by the contraction of a skeletal muscle that increases energy expenditure above a basal level”, which includes exercise and activity as part of work, leisure or movement [15]. Physical activity is often classified as being of light, moderate or vigorous, according to the level of energy expenditure required [16]. For its part, sedentary behaviour is defined by low energy expenditure (less than 1.5 metabolic equivalent tasks (METs)) in a sitting or reclining posture during waking hours [17].

Although it has been demonstrated that only 11% of the bronchiectasis population met the recommended physical activity guidelines of  $\geq 150$  min of at least moderate activity per week [18], the current evidence on physical activity and sedentary behaviour, and their association with bronchiectasis hospitalisations, is scarce. We hypothesised that steps-day<sup>-1</sup> and sedentary time would be strongly associated with the presence of hospital admission due to a bronchiectasis exacerbation at 1-year follow-up.

Therefore, the principal aim of this longitudinal study was to investigate the association between 1) any physical activity variable (steps-day<sup>-1</sup>, moderate physical activity and moderate-to-vigorous physical activity (MVPA)); and 2) sedentary time, with hospital admission due to exacerbation in adults with bronchiectasis. The secondary aim was to estimate cut-off points for steps-day<sup>-1</sup> and sedentary time that might indicate the risk of hospital admission.

## Methods

### *Study design and subjects*

This was a prospective observational study conducted at the pulmonology service of a tertiary care hospital in Barcelona, Spain. Subjects who met the selection criteria were included in the study consecutively between March 2016 and August 2017. Inclusion criteria were as follows: 1) adults ( $\geq 18$  years of age) diagnosed with bronchiectasis, as confirmed by computed tomography (CT) and with symptoms of the disease; 2) clinical stability (no exacerbations and no significant change in symptoms and/or medication in the last 4 weeks); 3) the ability to perform all the clinical tests and understand the process and the purposes of the study; 4) willing to give informed consent. Exclusion criteria were: 1) any physical or psychological disorder that might interfere with protocol compliance; 2) diagnosis of CF, sarcoidosis, pulmonary fibrosis, active tuberculosis (TB) or non-TB mycobacterial infection in treatment; 3) participation in a pulmonary rehabilitation (PR) programme in the last year; 4) respiratory insufficiency and/or oxygen therapy.

The study was approved by the Clinical Research Ethics Committee of the Hospital Clínic de Barcelona (Ethics Approval Reference: HCB/2016/0012).

### *Measurements*

#### *Baseline clinical and physical activity measurements*

Socio-demographic and clinical data were collected at baseline, including the aetiological diagnosis of bronchiectasis, current treatment, comorbidities (using the Charlson Comorbidity Index (CCI) [19]), the presence and number of exacerbations that did not require hospitalisation and hospitalisations due to bronchiectasis in the 12 months prior to the study. Exacerbations were defined according to the international consensus statement [7]. Disease severity was calculated using the Bronchiectasis Severity Index (BSI) [20] score. Dyspnoea was measured using the Medical Research Council (MRC) scale [21]. Lung function was assessed with an EasyOne™ World Spirometer (ndd Medical Technologies, Zurich, Switzerland) and was classified according to the European Respiratory Society (ERS)/American Thoracic

Society (ATS) guidelines [22]. Exercise capacity was measured using the 6-min walk test (6MWT) [23]. QoL was assessed using the Quality of Life Bronchiectasis Questionnaire (QoL-B) [24] and the impact of coughing on QoL by the Leicester Cough Questionnaire (LCQ) [25].

Physical activity was the independent variable and was measured using the tri-axial accelerometer SenseWear Armband (BodyMedia Inc., Pittsburgh, PA, USA). Participants were asked to wear the armband for the maximum period of time over 7 days, except during water-based activities. It was worn in the triceps area, at the back of the dominant arm.

Intensity of physical activity was reported in relation to METs and classified as sedentary ( $\leq 1.5$  METs), light (1.6 to  $< 3.0$  METs), moderate (3.0 to  $< 6.0$  METs) and vigorous ( $\geq 6.0$  METs) [26]. The mean time (in min) spent at each level of intensity was recorded. MVPA was calculated with the mean of minutes spent in moderate and vigorous physical activity on the valid days. Sedentary time was analysed considering the number of minutes that the patient spent at an intensity of  $\leq 1.5$  METs.

#### *Follow-up data collection*

The follow-up period lasted 12 months. The number of patients hospitalised at least once during the follow-up period due to a bronchiectasis exacerbation and the time to first hospitalisation were recorded prospectively through the revision of the medical dataset. The dependent variable was the presence of hospitalisation due to an exacerbation of bronchiectasis during the 12 months of follow-up.

The need for hospitalisation and discharge were defined by an independent medical doctor who was not involved in the study. The authors checked that all exacerbations met the consensus definition [7]. Patients were classified into hospitalised *versus* non-hospitalised groups depending on the presence or absence of hospitalisation due to a bronchiectasis exacerbation during the follow-up period.

Patients who participated in a PR and/or physical activity programme during the follow-up period were excluded from the final analysis.

#### *Statistical analysis*

Prior to any analysis we calculated whether the number of patients included would allow the identification of significant differences in physical activity and sedentary time between hospitalised *versus* non-hospitalised groups. Calculations were performed using GRANMO 7.10 [27], with an accepted alpha risk of 0.05, in a two-sided test with 15 subjects in the hospitalised group and 49 in the non-hospitalised group. The statistical power needed to recognise a statistically significant difference was 94% in physical activity and 96% in sedentary time.

Data are presented as n (%) for categorical variables, as mean $\pm$ SD for normally distributed data and as median (P<sub>25</sub>–P<sub>75</sub>) (1st and 3rd percentiles) for non-normally distributed data. The assumption of normality was checked by means of Shapiro–Wilk tests.

In accordance with previous research for reducing the noise in physical activity analyses [28], the data were considered valid if patients presented  $\geq 8$  h of waking hours (08:00 to 22:00) per day for  $\geq 4$  weekdays during the assessment period. A sensitivity analysis was performed including weekend data.

A receiver operating characteristic (ROC) curve was constructed to determine the best cut-off point in steps-day<sup>-1</sup> for the presence of bronchiectasis hospitalisation (hospitalisation “yes” or “no”) and also for sedentary time, moderate physical activity and MVPA. Youden’s index [29] was defined for all points along these ROC curves and the maximum values of these indices were used as criteria in selecting the optimum cut-off points. Kaplan–Meier analysis was used to compare the association of steps-day<sup>-1</sup> and sedentary time with time to first hospitalisation due to an exacerbation of bronchiectasis. The probabilities of hospitalisation in the two groups were analysed using the log-rank test. Univariate and multivariable logistic regression analyses were performed to identify variables associated with bronchiectasis hospitalisation. Due to the limited number of patients in the hospitalised and non-hospitalised groups, and in order to exclude bias related to overestimation or underestimation of regression coefficient variance, the only variables analysed in the univariate analysis were age, gender, chronic colonisation by *Pseudomonas aeruginosa*, hospitalisations 12 months prior to the study, MRC dyspnoea scale, % predicted forced expiratory volume in 1 s (FEV<sub>1</sub>), BSI stage and 6-min walk distance. Factors showing an association in the univariate analyses ( $p < 0.10$ ) were entered into two multivariable regression models, the first adjusted for steps-day<sup>-1</sup> and the second for sedentary time. The final variable selection was performed using the backward stepwise selection method (likelihood ratio;  $p_{\text{in}} < 0.05$ ,  $p_{\text{out}} > 0.10$ ), except for age and gender which had to appear in both models. Odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated. The Hosmer–Lemeshow goodness-of-fit test was performed to assess the overall fit of the final model. The areas under the curve (AUCs) for the ROC curves of the multivariable models for hospitalisation due to bronchiectasis were then calculated.

The internal validity of the final models was assessed using ordinary non-parametric bootstrapping with 1000 bootstrap samples and bias-corrected, accelerated 95% CIs.

We used the multiple imputation method [30] for missing data in the multivariable analyses. The level of significance was set at 0.05 (two-tailed). All analyses were performed using IBM SPSS Statistics version 25.0 (Armonk, NY, USA).

## Results

### Baseline clinical and physical activity data

Of the 72 patients with bronchiectasis recruited at baseline, 64 were included in the follow-up analysis (figure 1). The study population was classified into two groups according to the presence of hospitalisation due to an exacerbation during the 1-year follow-up: 1) hospitalised patients (n=15, 23%); and 2) non-hospitalised patients (n=49, 77%). Baseline clinical and physical activity characteristics are shown in table 1. Hospitalised patients were more likely to have chronic colonisation by *Pseudomonas aeruginosa*, more hospitalisations in the 12 months prior to the study, poor dyspnoea, worse lung function, worse QoL, a higher CCI score and a more severe BSI score.

The number of patients with COPD and bronchiectasis overlap was low. Of all patients, four (6%) had a smoking history of  $>10$  packs-year<sup>-1</sup> and a FEV<sub>1</sub>/forced vital capacity (FVC) ratio of  $<70\%$ . Distribution did not differ significantly between hospitalised (n=2, 13%) and non-hospitalised groups (n=2, 4%) (p=0.455).

In terms of physical activity, hospitalised patients took fewer of steps-day<sup>-1</sup>, spent more time sedentary and had lower levels of MVPA than non-hospitalised patients. Light physical activity and exercise capacity did not differ between groups.

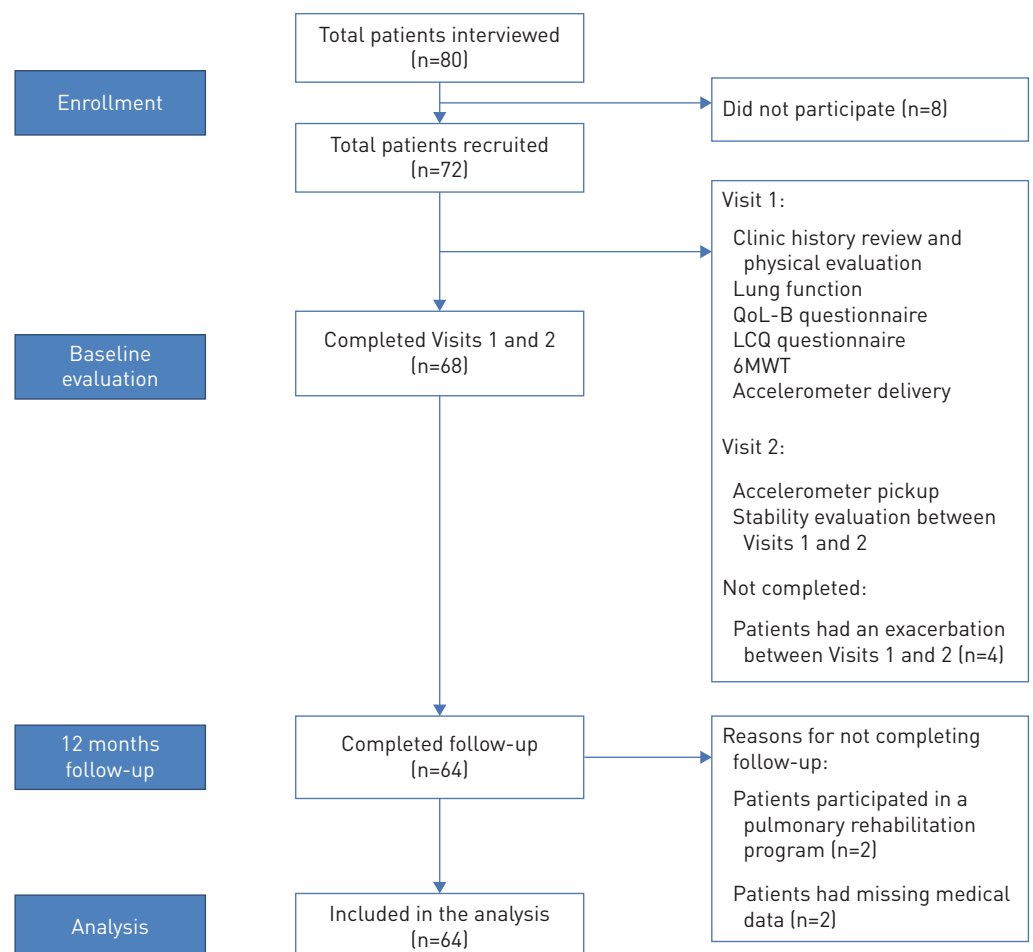


FIGURE 1 Enrolment flow chart. QoL-B: Quality of Life Bronchiectasis Questionnaire; LCQ: Leicester Cough Questionnaire; 6MWT: 6-min walk test.

TABLE 1 Baseline characteristics of hospitalised *versus* non-hospitalised bronchiectasis patients

Characteristics	All patients (n=64)	Hospitalised (n=15)	Non-hospitalised (n=49)	p-value
<b>Demographics</b>				
Male	21 (33)	6 (40)	15 (31)	0.501
Age years	62.9±14.9	64.3±17.4	62.2±14.5	0.510
BMI kg·m <sup>-2</sup>	24.6±4.3	24.3±4.1	24.6±4.5	0.924
Retired	41 (64)	11 (73)	30 (61)	0.550
Former smoker	20 (31)	5 (33)	15 (31)	0.923
Smoking habit packs·year <sup>-1</sup>	30 (8.5–60)	40 (25.5–86.5)	19.2 (7–60)	0.119
Chronic colonisation	23 (36)	11 (73)	12 (24)	<b>0.001</b>
<i>Pseudomonas aeruginosa</i>	19 (29)	10 (66)	9 (18)	<b>0.000</b>
<i>Haemophilus influenza</i>	2 (3)	0 (0)	2 (4)	0.430
<i>Staphylococcus aureus</i>	2 (3)	1 (6)	1 (2)	0.371
Dyspnoea (MRC scale 1–5)	2 (2–2)	2 (2–3)	2 (2–2)	<b>0.004</b>
<b>Exacerbations and hospitalisations<sup>#</sup></b>				
Exacerbated patients	45 (70)	11 (73)	34 (70)	0.772
Number of exacerbations	1 (0–2)	2 (0–4)	1 (0–2)	0.171
Hospitalised patients	13 (20)	7 (47)	6 (12)	<b>0.004</b>
Number of hospitalisations	0 (0–0)	0 (0–1)	0 (0–0)	<b>0.004</b>
<b>Aetiology</b>				
Post-infectious	29 (45)	6 (40)	23 (47)	0.639
Idiopathic	14 (22)	5 (33)	9 (18)	0.224
Associated with COPD	4 (6)	2 (13)	2 (4)	0.455
Other	17 (26)	2 (13)	15 (30)	–
<b>Severity</b>				
CCI stage				<b>0.031</b>
Mild	51 (79)	9 (60)	42 (86)	
Moderate	9 (14)	4 (26)	5 (10)	
High	4 (6)	2 (13)	2 (4)	
BSI stage				<b>0.001</b>
Mild	23 (36)	2 (13)	21 (43)	
Moderate	22 (34)	3 (20)	19 (39)	
Severe	19 (29)	10 (66)	9 (18)	
<b>Pulmonary function and exercise capacity</b>				
FEV <sub>1</sub> % predicted	72±19.8	62.1±18.7	75.2±19.9	<b>0.020</b>
FEV <sub>1</sub> L	1.94±0.81	1.82±0.94	1.99±0.78	0.366
FVC % predicted	80.6±17.1	72.7±15.3	83.1±17.7	<b>0.026</b>
FVC L	2.82±0.83	2.6±0.75	2.89±0.86	0.342
FEV <sub>1</sub> /FVC %	86±18.6	82±22.1	86.92±17.7	0.495
6MWT m	512.7±93.5	467.7±116	522.7±83	0.063
<b>Respiratory medication<sup>¶</sup></b>				
Inhaled steroids	45 (70)	11 (73)	34 (69)	0.772
LABA	48 (75)	12 (80)	36 (73)	0.612
LAMA	28 (44)	12 (80)	16 (32)	<b>0.001</b>
Antibiotics	11 (17)	3 (20)	8 (16)	0.743
<b>QoL</b>				
QoL-B				
Physical function	57.3±33.8 (0–100)	53.3±35.2 (0–100)	58.5±33.7 (0–100)	0.588
Role function	75.5±28 (0–100)	53.3±32.9 (0–100)	82.3±22.7 (33.3–100)	<b>0.001</b>
Vitality	58.6±25.5 (0–100)	45.6±33.6 (0–100)	62.6±21.4 (16.7–100)	<b>0.033</b>
Emotional function	73.7±28.6 (0–100)	64.4±30.1 (0–100)	76.5±27.8 (0–100)	0.140
Social function	68.2±31.7 (0–100)	54.4±35.9 (0–100)	72.4±29.4 (0–100)	0.072
Treatment burden	69.8±40.6 (0–100)	75.5±36.6 (0–100)	68.0±41.9 (0–100)	0.670
Health perceptions	52.9±26.5 (0–100)	35.5±30.8 (0–100)	58.2±22.8 (0–100)	<b>0.007</b>
Respiratory symptoms	76.3±22.6 (33.3–100)	67.8±22.4 (33.3–100)	78.9±22.5 (33.3–100)	0.052
LCQ				
Physical	15.8 (11.8–19.4)	15 (10.4–18.7)	16.6 (12.4–19.5)	0.292
Psychological	15.3 (12–18.4)	14.2 (11.2–16.9)	15.7 (12–18.4)	0.115
Psychological	15.6 (11.1–19.3)	14.6 (9.4–18.4)	16.7 (12–19.9)	0.243
Social	18 (13–21)	18 (11.2–19.5)	18.7 (13.1–21)	0.582
<b>Physical activity</b>				
Light (1.6 to <3.0 METs) min·day <sup>-1</sup>	211.4±79	186±42.5	222.3±87.5	0.178
Moderate (3.0 to <6.0 METs) min·day <sup>-1</sup>	117±82	81.9±63	127.3±83.4	<b>0.015</b>
Vigorous (6.0 to <8.7 METs) min·day <sup>-1</sup>	0.78±1.86	0.55±1.6	0.9±2	0.546

Continued

TABLE 1 Continued

Characteristics	All patients (n=64)	Hospitalised (n=15)	Non-hospitalised (n=49)	p-value
MVPA min-day <sup>-1</sup>	115.5±78.5	82.4±64.2	125.3±78.6	<b>0.015</b>
Number of steps steps-day <sup>-1</sup>	6880±3447	4740±3196	7563±3382	<b>0.003</b>
Sedentary time h-day <sup>-1</sup>	7.17±1.8	8.22±1.48	6.83±1.74	<b>0.005</b>

Data are presented as n (%), mean±SD, median (interquartile range), or mean±SD (range). p-values in bold are statistically significant. BMI: body mass index; MRC: medical research council; COPD: chronic obstructive pulmonary disease; CCI: Charlson Comorbidity Index; BSI: Bronchiectasis Severity Index; PFT: pulmonary function test; FEV<sub>1</sub>: forced expiratory volume in 1 s; FVC: forced vital capacity; 6MWT: 6-min walk test; LABA: long-acting  $\beta$ -agonist; LAMA: long-acting muscarinic antagonist; QoL: quality of life; QoL-B: Quality of Life Bronchiectasis Questionnaire; LCQ: Leicester Cough Questionnaire; MET: metabolic equivalent task; MVPA: moderate-to-vigorous physical activity. #: exacerbations and hospitalisations in the 12 months prior to the study; †: patients may have had more than one medication.

### Cut-off points (steps-day<sup>-1</sup> and sedentary time) and hospitalisation risk

Table 2 presents the best cut-off points for steps-day<sup>-1</sup>, sedentary time, moderate physical activity and MVPA for predicting hospital admission during follow-up. Light and vigorous physical activity had very low sensitivity and specificity, without presenting statistically significant differences. Kaplan–Meier curves evaluating the time to first hospitalisation due to bronchiectasis exacerbation (according to steps-day<sup>-1</sup> and sedentary time) are represented in figure 2. Patients with  $\leq 6290$  steps-day<sup>-1</sup> or  $\geq 7.8$  h-day<sup>-1</sup> of sedentary behaviour had a higher risk of hospital admission due to bronchiectasis exacerbation at 1-year follow-up than patients with more steps-day<sup>-1</sup> or less sedentary time ( $p < 0.001$ ).

### Association between physical activity outcomes and hospitalisation due to an exacerbation of bronchiectasis

In accordance with the proposed cut-off values, the logistic regression model showed a higher risk of hospitalisation for bronchiectasis patients with low levels of physical activity ( $\leq 6290$  steps-day<sup>-1</sup>) and high sedentary behaviour ( $\geq 7.8$  h-day<sup>-1</sup>). After adjusting for all relevant confounders (age, gender, chronic colonisation by *Pseudomonas aeruginosa* and hospitalisations during the 12 months prior to the study), sedentary behaviour raised the risk of hospitalisation by 5.91 times (table 3 and supplementary table S1). When the final model was adjusted for gender and BSI, sedentary behaviour also raised the risk of hospitalisation by 5.34 times (supplementary table S1). After excluding patients with a smoking history of  $\geq 10$  packs-year<sup>-1</sup> and after adjusting for all relevant confounders, low physical activity ( $\leq 6290$  steps-day<sup>-1</sup>) raised the risk of hospitalisation by 8.7 times (supplementary table S2).

The sensitivity analyses including weekend data showed reductions in the cut-off points and the size of the associations, although the significance of the effect remained unchanged with regard to the analyses including only weekdays (supplementary tables S3–S5 and supplementary figures S1a and S1b). Internal validation of the final models was conducted using bootstrapping with 1000 samples. All variables remained significant after a bootstrapping procedure, with small 95% CIs around the original coefficients.

### Discussion

To our knowledge, this is the first study to investigate the association between physical activity, sedentary time and risk of hospitalisation in patients with bronchiectasis. We confirmed that patients hospitalised for an exacerbation of bronchiectasis during the 1-year follow-up period presented poor clinical characteristics, higher severity and lower levels of physical activity at baseline compared than those not hospitalised. This study is the first to propose cut-off points for number of steps ( $\leq 6290$  steps-day<sup>-1</sup>) and time spent in sedentary behaviour ( $\geq 7.8$  h-day<sup>-1</sup>) in order to objectively identify patients with bronchiectasis who are at a higher risk for hospital admission in the next year. Finally, the risk for

TABLE 2 Cut-off points for hospitalisation variables (number of steps, sedentary time and physical activity)

Variable	AUC (95% CI)	Sensitivity %	Specificity %	Best cut-off value	p-value
Number of steps steps-day <sup>-1</sup>	0.75 (0.60–0.89)	61	73	6290	0.003
Sedentary time h-day <sup>-1</sup>	0.74 (0.59–0.88)	73	74	7.8	0.005
Moderate physical activity min-day <sup>-1</sup>	0.71 (0.55–0.87)	67	73	84.4	0.015
MVPA min-day <sup>-1</sup>	0.71 (0.55–0.87)	85	53	66.3	0.015

AUC: area under the curve; CI: confidence interval; MVPA: moderate-to-vigorous physical activity.



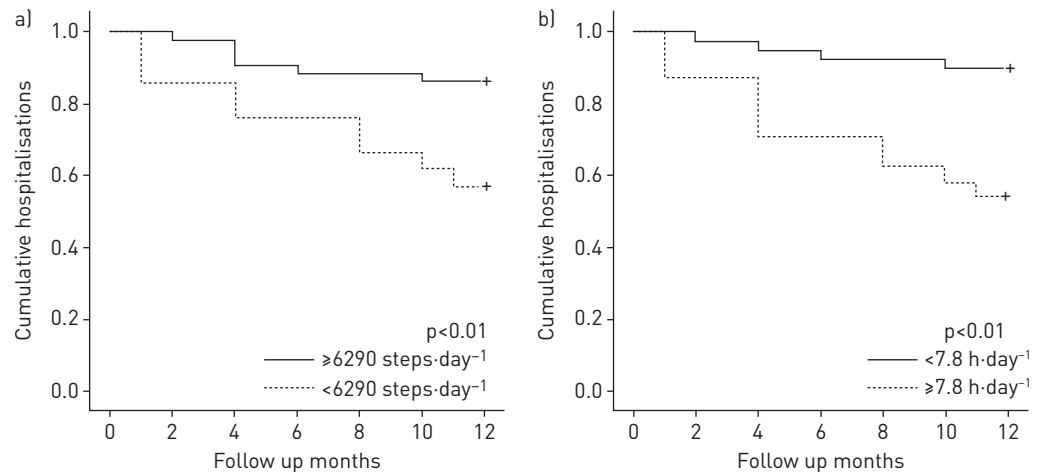


FIGURE 2 Kaplan-Meier graphics according to receiver operating characteristic (ROC) curve cut-off points: a) 6290 steps-day<sup>-1</sup>; b) 7.8 h-day<sup>-1</sup> of sedentary behaviour.

hospitalisation in patients with bronchiectasis due to exacerbation was significantly higher (5.91 times) in those who spent  $\geq 7.8$  h-day<sup>-1</sup> in sedentary behaviour.

Little is known about physical activity behaviour in bronchiectasis populations. In a recent study, José *et al.* [31] measured physical activity with a pedometer and demonstrated that patients with bronchiectasis showed lower physical activity levels than healthy controls. They also concluded that patients affected by bronchiectasis who appeared to be more active in daily life were the ones with better pulmonary function, functional capacity and lower dyspnoea. In fact, this Brazilian bronchiectasis population was surprisingly active (with a mean 8007 steps-day<sup>-1</sup> versus 10994 steps-day<sup>-1</sup> in healthy peers).

In 2015, BRADLEY *et al.* [18] analysed physical activity in 63 patients with bronchiectasis using an ActiGraph GT3X+ accelerometer (ActiGraph, Pensacola, FL, USA). The mean was 6001 steps-day<sup>-1</sup> versus 6880 steps-day<sup>-1</sup> in our population and the mean time spent in sedentary behaviour in those subjects was 10.5 h-day<sup>-1</sup> compared to 7.2 h-day<sup>-1</sup> in our study. We stress that this finding is unlikely to be related to disease severity, as the population analysed by BRADLEY *et al.* presented lower severity levels (BSI score: 49% mild, 33% moderate and 18% severe) than ours (BSI score: 36% mild, 35% moderate and 29% severe). A point to be considered is that the patients with lower physical activity levels were the ones with greater severity. Consequently, lower physical activity may have been due to physical impairment in the more severe patients, who in turn had more exacerbations.

Regarding BSI [20], the item “hospitalisations in the previous 2 years” had the highest score of all, and is a recognised predictor of 4-year mortality, further hospital admissions, exacerbations and worse QoL. The history of hospitalisations due to a bronchiectasis exacerbation is an important clinical outcome because of

TABLE 3 Crude and adjusted associations between level of physical activity (measured in steps) and sedentary time, and bronchiectasis hospitalisations

Variable	n	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
<b>Number of steps<sup>#</sup> steps-day<sup>-1</sup></b>					
High physical activity ( $\geq 6290$ )	43	1.00		1.00	
Low physical activity ( $<6290$ )	21	4.62 (1.36–15.68)	0.014	4.20 (0.82–21.47)	0.085
<b>Sedentary time<sup>¶</sup> h-day<sup>-1</sup></b>					
Not sedentary ( $<7.8$ )	40	1.00		1.00	
Sedentary ( $\geq 7.8$ )	24	7.62 (2.06–28.18)	0.002	5.91 (1.26–27.81)	0.024

Data are shown as estimated odds ratios (ORs) [95% confidence intervals (CIs)] of the explanatory variables in the low physical activity group. The OR represents the odds that low physical activity will occur given exposure to the explanatory variable, compared to the odds of the outcome occurring in the absence of that exposure. The p-values are based on the null hypothesis that all ORs relating to an explanatory variable are equal to unity (no effect). <sup>#</sup>: multivariable model adjusted for age, gender, chronic colonisation by *Pseudomonas aeruginosa* and hospitalisations in the 12 months prior to the study. A Hosmer-Lemeshow goodness-of-fit test is used ( $p=0.85$ ). For the receiver operating characteristic (ROC) curve, the area under the curve (AUC)=0.86 (95% CI 0.76–0.97). <sup>¶</sup>: multivariable model adjusted for age, gender, chronic colonisation by *Pseudomonas aeruginosa* and hospitalisations in the 12 months prior to the study. A Hosmer-Lemeshow goodness-of-fit test is used ( $p=0.78$ ). For the ROC curve, the AUC=0.87 (95% CI 0.76–0.97).

its negative consequences for the prognosis of the disease. In a recent cohort of 651 patients, 23.2% were defined as “frequent exacerbators” and presented poorer severity scores, more systemic inflammation and a greater use of antibiotic and anti-inflammatory therapies. The authors concluded that a history of at least 2 exacerbations-year<sup>-1</sup> or 1 hospitalisation-year<sup>-1</sup> was the variable with the best prognostic value for 5-year all-cause mortality (AUC 0.75, 95% CI 0.69–0.81;  $p < 0.001$ ) [32]. However, no information was available about physical activity levels in that population.

Considering our results, the groups did not differ in terms of exercise capacity or light physical activity, and time spent in sedentary behaviour was the only factor that raised the risk of hospitalisation (by 5.91 times). Although the differences in exercise capacity were not statistically significant, they were greater than the minimal important difference defined for patients with bronchiectasis [33]. We believe that breaking the sedentary habit in the population with bronchiectasis might have a significant clinical impact on reducing the number of hospitalisations and on improving QoL.

Previous studies have sought to find cut-off points for time spent in sedentary behaviour and steps-day<sup>-1</sup> in chronic respiratory diseases. In 2017, FURLANETTO *et al.* [12] were the first to propose an objective cut-off point for sedentarism in subjects affected by COPD and to investigate the association of this variable with long-term mortality. They demonstrated that the mortality risk was 4.09 times higher in patients who spent  $\geq 8.5$  h-day<sup>-1</sup> seated (with AUC=0.76, sensitivity=84% and specificity=65%). It has also been shown that the longer the time spent in sedentary behaviour per day, the higher the number of COPD exacerbations, although this was not analysed in terms of hospitalisation [34]. Our results are in line with previous studies in patients with COPD, perhaps due to similarities in physical activity behaviour in patients with these two chronic respiratory diseases. The risk of hospitalisation during follow-up in our population remained in the same direction after excluding patients who had a smoking history of  $>10$  packs-year<sup>-1</sup>. However, these findings should be interpreted carefully, as after excluding these patients the sample size fell by 25%.

It is well known that increased sedentary behaviour is associated with worsened health effects, which may differ from those caused by reduced physical activity in daily life [35], in both healthy subjects and patients with chronic respiratory diseases [10]. Strategies for reducing sedentary behaviour and for increasing physical activity will be key components of future bronchiectasis management in order to improve outcomes such as QoL and to reduce the risk of hospitalisation.

The main strengths of our study were the fact that physical activity was measured with an objective and validated tool such as an accelerometer, and the reduction of bias due to seasonality thanks to the inclusion and follow-up of patients over a whole year. One limitation of our study might be the analyses of the physical activity parameters on weekdays; however, since the significance of the effect remained unchanged with regard to the analyses including weekends, we are confident that the magnitude of the association was not overestimated. Another possible limitation is the fact that the number of hospitalisations was calculated using only medical history data and we might have missed some patients hospitalised at different centres.

Future studies should consider the inclusion of patients with bronchiectasis from other countries and other ethnicities in order to compare and contrast the results reported here. It will also be important to determine whether reducing the time spent in sedentary behaviour can significantly lower the percentage of hospitalised patients.

### Conclusions

For the first time we demonstrate an association between hospitalisation due to bronchiectasis exacerbation and physical activity behaviour. Hospitalised bronchiectasis patients had lower physical activity and higher sedentary behaviour than their non-hospitalised counterparts. Patients who walked  $\leq 6290$  steps-day<sup>-1</sup> or spent  $\geq 7.8$  h-day<sup>-1</sup> in sedentary behaviour increased the risk of hospitalisation during 1-year follow-up. Moreover, sedentary behaviour alone increased the risk of hospital admission by 5.91 times. Objectively measured sedentary behaviour could be an independent predictor of hospitalisation due to an exacerbation in patients with bronchiectasis. If this finding is validated in future studies, it may be appropriate to include physical activity and sedentary behaviour as an item in severity scores.

**Acknowledgements:** The authors would like to thank the patients for taking part in the study.

**Author contributions:** V. Alcaraz-Serrano had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. V. Alcaraz-Serrano designed and developed the study protocol. V. Alcaraz-Serrano and A. Navarro collected the data from patients. V. Alcaraz-Serrano, E. Gimeno-Santos and A. Gabarrus participated in the statistical analysis and data interpretation. V. Alcaraz-Serrano, E. Gimeno-Santos and G. Scioscia participated in the writing of the manuscript. All the authors have read the final version of the manuscript, fully approve it and qualify for authorship.

**Conflict of interest:** None declared.



## References

- 1 Flume PA, Chalmers JD, Olivier KN. Advances in bronchiectasis: endotyping, genetics, microbiome, and disease heterogeneity. *Lancet* 2018; 392: 880–890.
- 2 Watt AP, Brown V, Courtney J, *et al.* Neutrophil apoptosis, proinflammatory mediators and cell counts in bronchiectasis. *Thorax* 2004; 59: 231–236.
- 3 Menéndez R, Méndez R, Polverino E, *et al.* Factors associated with hospitalization in bronchiectasis exacerbations: a one-year follow-up study. *Respir Res* 2017; 18: 176.
- 4 Ringshausen FC, de Roux A, Pletz MW, *et al.* Bronchiectasis-associated hospitalizations in Germany, 2005–2011: a population-based study of disease burden and trends. *PLoS One* 2013; 8: e71109.
- 5 Sánchez-Muñoz G, López de Andrés A, Jiménez-García R, *et al.* Time trends in hospital admissions for bronchiectasis: analysis of the Spanish national hospital discharge data (2004 to 2013). *PLoS One* 2016; 11: e0162282.
- 6 Seitz AE, Olivier KN, Steiner CA, *et al.* Trends and burden of bronchiectasis-associated hospitalizations in the United States, 1993–2006. *Chest* 2010; 138: 944–949.
- 7 Hill AT, Haworth CS, Aliberti S, *et al.* Pulmonary exacerbation in adults with bronchiectasis: a consensus definition for clinical research. *Eur Respir J* 2017; 49: 1700051.
- 8 Cantón R, Máiz L, Escribano A, *et al.* Consenso español para la prevención y el tratamiento de la infección bronquial por *Pseudomonas aeruginosa* en el paciente con fibrosis quística [Spanish consensus on the prevention and treatment of *Pseudomonas aeruginosa* bronchial infections in cystic fibrosis patients]. *Arch Bronconeumol* 2015; 51: 140–150.
- 9 Gimeno-Santos E, Frei A, Steurer-Stey C, *et al.* Determinants and outcomes of physical activity in patients with COPD: a systematic review. *Thorax* 2014; 69: 731–739.
- 10 Lewthwaite H, Effing TW, Olds T, *et al.* Physical activity, sedentary behaviour and sleep in COPD guidelines: a systematic review. *Chron Respir Dis* 2017; 14: 231–244.
- 11 Demeyer H, Donaire-Gonzalez D, Gimeno-Santos E, *et al.* Physical activity is associated with attenuated disease progression in chronic obstructive pulmonary disease. *Med Sci Sports Exerc* 2019; 51: 833–840.
- 12 Furlanetto KC, Donária L, Schneider LP, *et al.* Sedentary behavior is an independent predictor of mortality in subjects with COPD. *Respir Care* 2017; 62: 579–587.
- 13 Flume PA, Robinson KA, O'Sullivan BP, *et al.* Cystic fibrosis pulmonary guidelines: airway clearance therapies. *Respir Care* 2009; 54: 522–537.
- 14 Spruit MA, Singh SJ, Garvey C, *et al.* An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med* 2013; 188: e13–e64.
- 15 Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. *Public Health Rep* 1985; 100: 126–131.
- 16 Hill K, Gardiner PA, Cavalheri V, *et al.* Physical activity and sedentary behaviour: applying lessons to chronic obstructive pulmonary disease. *Intern Med J* 2015; 45: 474–482.
- 17 Sedentary Behaviour Research Network. Letter to the Editor: standardized use of the terms “sedentary” and “sedentary behaviours”. *Appl Physiol Nutr Metab* 2012; 37: 540–542.
- 18 Bradley JM, Wilson JJ, Hayes K, *et al.* Sedentary behaviour and physical activity in bronchiectasis: a cross-sectional study. *BMC Pulm Med* 2015; 15: 61.
- 19 Charlson ME, Pompei P, Ales KL, *et al.* A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; 40: 373–383.
- 20 Chalmers JD, Goeminne P, Aliberti S, *et al.* The bronchiectasis severity index. An international derivation and validation study. *Am J Respir Crit Care Med* 2014; 189: 576–585.
- 21 Hester KLM, Macfarlane JG, Tedd H, *et al.* Fatigue in bronchiectasis. *QJM* 2012; 105: 235–240.
- 22 Miller MR, Hankinson J, Brusasco V, *et al.* Standardisation of spirometry. *Eur Respir J* 2005; 26: 319–338.
- 23 Holland AE, Spruit MA, Troosters T, *et al.* An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. *Eur Respir J* 2014; 44: 1428–1446.
- 24 Oliveira C, Oliveira G, Espildora F, *et al.* Validation of a quality of life questionnaire for bronchiectasis: psychometric analyses of the Spanish QOL-B-V3.0. *Qual Life Res* 2014; 23: 1279–1292.
- 25 Muñoz G, Buxó M, De Gracia J, *et al.* Validation of a Spanish version of the Leicester Cough Questionnaire in non-cystic fibrosis bronchiectasis. *Chron Respir Dis* 2016; 13: 128–136.
- 26 Ainsworth BE, Haskell WL, Whitt MC, *et al.* Compendium of physical activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc* 2000; 32: Suppl. 9, S498–S504.
- 27 Marrugat J, Vila J, Pavesi M, *et al.* Estimation of the sample size in clinical and epidemiological investigations. *Med Clin (Barc)* 1998; 111: 267–276.
- 28 Demeyer H, Burtin C, Van Remoortel H, *et al.* Standardizing the analysis of physical activity in patients with COPD following a pulmonary rehabilitation program. *Chest* 2014; 146: 318–327.
- 29 Youden WJ. Index for rating diagnostic tests. *Cancer* 1950; 3: 32–35.
- 30 Sterne JA, White IR, Carlin JB, *et al.* Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009; 338: b2393.
- 31 José A, Ramos TM, de Castro RAS, *et al.* Reduced physical activity with bronchiectasis. *Respir Care* 2018; 63: 1498–1505.
- 32 Martínez-García MÁ, Athanazio R, Grambliska G, *et al.* Prognostic value of frequent exacerbations in bronchiectasis: the relationship with disease severity. *Arch Bronconeumol* 2019; 55: 81–87.
- 33 Lee AL, Hill CJ, Cecins N, *et al.* Minimal important difference in field walking tests in non-cystic fibrosis bronchiectasis following exercise training. *Respir Med* 2014; 108: 1303–1309.
- 34 Hartman JE, Marike Boezen H, De Greef MH, *et al.* Physical and psychosocial factors associated with physical activity in patients with chronic obstructive pulmonary disease. *Arch Phys Med Rehabil* 2013; 94: 2396–2402.
- 35 Tremblay MS, Colley RC, Saunders TJ, *et al.* Physiological and health implications of a sedentary lifestyle. *Appl Physiol Nutr Metab* 2010; 35: 725–740.