Identification of asthma phenotypes based on extrapulmonary treatable traits

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Cluster analysis based on extrapulmonary treatable traits in people with moderate-to-severe asthma indicates that physical inactivity, higher levels of sedentary time, symptoms of anxiety and depression, and obesity are associated with worse outcomes. https://bit.ly/2ATv1Ce

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ABSTRACT Asthma is a heterogeneous and complex disease, and a description of asthma phenotypes based on extrapulmonary treatable traits has not been previously reported.

The objective of this study was to identify and characterise clusters based on clinical, functional, anthropometrical and psychological characteristics in participants with moderate-to-severe asthma.

This was a cross-sectional multicentre study involving centres from Brazil and Australia. Participants (n=296) with moderate-to-severe asthma were consecutively recruited. Physical activity and sedentary time, clinical asthma control, anthropometric data, pulmonary function and psychological and health status were evaluated. Participants were classified by hierarchical cluster analysis and the clusters compared using ANOVA, Kruskal–Wallis and Chi-squared tests. Multiple logistic and linear regression models were performed to evaluate the association between variables.

We identified four clusters: 1) participants with controlled asthma who were physically active; 2) participants with uncontrolled asthma who were physically inactive and more sedentary; 3) participants with uncontrolled asthma and low physical activity, who were also obese and experienced anxiety and/or depression symptoms; and 4) participants with very uncontrolled asthma who were physically inactive, more sedentary, obese and experienced anxiety and/or depression symptoms. Higher levels of sedentary time, female sex and anxiety symptoms were associated with increased odds of exacerbation risk, while being more active showed a protective factor for hospitalisation. Asthma control was associated with sex, the occurrence of exacerbation, physical activity and health status.

Physical inactivity, obesity and symptoms of anxiety and/or depression were associated with worse asthma outcomes, and closely and inextricably associated with asthma control. This cluster analysis highlights the importance of assessing extrapulmonary traits to improve personalised management and outcomes for people with moderate and severe asthma.

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Introduction

Asthma is a major health concern, causing a high illness burden for individuals and health systems. Asthma is a heterogeneous and complex disease characterised by variability in disease expression and severity [1]. People with asthma have different clinical presentations, but, despite being partially explained by disease severity, these are insufficient to account for the recognised heterogeneity [2]. The current concept of airway diseases neither recognises the complexity of the disease nor promotes individualised management [3]. There is increasing appreciation of the impact of extrapulmonary features of asthma and associated comorbidities [4], highlighting the need to deconstruct and personalise asthma management by identifying measurable and modifiable traits [5]. "Treatable traits" is a taxonomy that has been proposed to recognise the complexity of chronic respiratory diseases. The approach seeks to characterise individuals by the presence of "potentially modifiable elements" that impact symptoms and prognosis [6, 7]. Traits are recognised within three domains: pulmonary, extrapulmonary and behavioural/risk factors [7]. To be considered a trait, the characteristic must be 1) identifiable, 2) clinically relevant and 3) modifiable [8].

Physical inactivity, high levels of sedentary time, psychological disturbances and obesity are extrapulmonary morbidities/traits frequently reported in people with moderate-to-severe asthma [9–12]. People with severe asthma are known to be less active and highly sedentary, and this is associated with worse exercise capacity, poor asthma control and increased systemic inflammation [13]. The lower aerobic capacity in people with asthma is associated with reduced health status and increased symptoms of depression, regardless of lung function and age [14]. Obesity in asthma is also associated with worse prognosis and severity, including increased asthma symptoms and exacerbations, worse lung function and higher use of oral corticosteroids (OCS) [1, 15]. Therefore, identifying asthma phenotypes that consider these treatable traits should be integral to asthma assessment to deliver the most appropriate treatments to patients [6].

Previous cluster analyses have identified asthma phenotypes focusing on characteristics related to disease severity, expiratory airflow limitation, inflammatory biomarkers and age of asthma onset [1, 16]. However, despite these well-conducted cluster analyses, a description of phenotypes based on extrapulmonary traits has not been previously reported. Thus, this study aimed to identify and characterise phenotypes based on clinical, functional, anthropometrical and psychological characteristics in people with moderate-to-severe asthma. We hypothesised that the severity of these clinical characteristics and modifiable behavioural risk factors can guide the classification of clinical asthma phenotypes (clusters).

Methods

A cross-sectional multicentre study involving centres from Brazil and Australia was conducted. Participants were recruited prospectively between July 2012 and March 2019 from tertiary care hospitals during routine medical consultations or using the clinics' research databases.

Adults (⩾18 years old) with a diagnosis of moderate-to-severe asthma according to the Global Initiative For Asthma criteria [17] who were clinically stable (free from exacerbation in the past 30 days) and receiving optimal treatment according to the international guidelines [17] were eligible for inclusion. Exclusion criteria included chronic obstructive pulmonary disease or other significant respiratory or cardiovascular diseases, active cancer, uncontrolled hypertension, diabetes or a musculoskeletal condition that could compromise participation in physical activity. The inability to understand the questionnaires, pregnancy and current or past history of smoking (⩾10 pack-years) were also listed as exclusions.

Written informed consent was obtained from all participants. Ethical approvals were granted by each centre's respective ethics committees.

Procedures

Data on demographics, anthropometrics (weight, height, body mass index (BMI)) [18], smoking history, comorbidities, lung function and asthma medication use were extracted from participants' medical records or through interview. Further assessments are listed below.

Asthma control

The Asthma Control Questionnaire (ACQ) [19, 20] consists of five questions relating to asthma symptoms, bronchodilator use and lung function (% predicted of forced expiratory volume in 1 s (FEV_1) before bronchodilation). Scores range from 0 to 6, where <0.75 and >1.5 are indicative of good and poorly controlled asthma, respectively [21].

Asthma-related health status

The Asthma Quality of Life Questionnaire (AQLQ) [22] comprises four asthma-related domains: activity limitations, symptoms, emotional function and environmental stimuli. Scores range from 0 to 7, with higher scores indicating better health status.

Asthma exacerbations

Exacerbations were defined as worsening of symptoms that led to ⩾3 days of OCS treatment or a temporary increase in their OCS maintenance dosage, an asthma-specific hospitalisation or an emergency department (ED) visit requiring systemic corticosteroids [23]. Exacerbations were elicited during standardised structured interviewing regarding the last 12 months.

Anxiety and depression symptoms

The Hospital Anxiety and Depression Scale (HADS) [24] consists of 14 items divided into two domains, seven for anxiety (HADS-A) and seven for depression (HADS-D). Each item is scored from 0 to 3, with a maximum score of 21 for each domain. A score of ⩾8 in either domain indicates possible anxiety or depression [25].

All questionnaires were validated and applied in the appropriate language (English or Portuguese).

Physical activity and sedentary time

Movement behaviours were objectively measured by the accelerometer Actigraph GT3X (Actigraph, Pensacola, FL, USA) [26]. The device was initialised *via* a computer interface to collect data in 60-s epochs on the three axes using specific software (ActiLife 6.13.3 Firmware version). Participants wore the device on their waist (using an elastic belt) during wake time for seven consecutive days. Data from valid days (⩾4 days and ⩾10 h of recording) were presented as the average number of steps per day, the time spent (min·day^{-1}) in moderate-vigorous physical activity (MVPA; defined as ⩾1951 counts·min^{-1}) and the time spent (min·day^{-1}) in sedentary time (defined as <100 counts·min^{-1}) [27]. Participants performing ⩾10 000, ⩾7500 and ⩾5000 steps·day^{-1} were classified as "physically active", "somewhat active" and "low-level active", respectively [28].

Statistical analysis

Data were analysed using the Statistical Package for Social Sciences version 18.0 for Windows (SPSS Inc., Chicago, IL, USA).

A hierarchical cluster analysis was performed to identify the number of clusters and cluster centroids using principal component analysis (PCA) [29, 30]. The Shapiro–Wilk test evaluated data normality. The between-cluster differences were analysed by the Chi-squared test, ANOVA (plus Holm–Sidak test) or Kruskal–Wallis test (plus Dunn's multiple comparison test). Significance was set at $p<0.05$.

The association analyses were performed using multiple logistic regression between the dependent outcomes (exacerbation, hospitalisation, ED visit and temporary systemic corticosteroid) and the clinical and behavioural characteristics included in the cluster analysis. The stepwise forward process was used to add variables into the model. Multiple linear regression analysis was performed to identify the independent factors associated with ACQ-7 (dependent variable), sex, BMI, the occurrence of exacerbation, inhaled corticosteroid (ICS) use, daily physical activity, sedentary time, HADS and AQLQ score. Detailed statistical analyses are presented in the supplementary material.

Results

Patient characteristics

A total of 414 participants were assessed for eligibility, and 118 excluded. The final study population consisted of 296 participants with moderate-to-severe asthma (243 from Brazil and 53 from Australia). Participants were mostly female, overweight, had low physical activity and high sedentary time levels, and had mild airway obstruction (table 1). The majority (68%) of the participants had uncontrolled asthma, and 64% had experienced at least one exacerbation in the last 12 months (10% hospitalisations, 49% visits to the ED, 60% used systemic corticosteroids). Participants from Australia were older, more physically inactive and spent more time engaged in sedentary time. However, they had better health status and fewer symptoms of anxiety and depression (table 1).

There were 15 comorbidities identified: osteoporosis, vocal cord dysfunction, dyslipidaemia, bowel disease, hypothyroidism, diabetes, dermatitis, obstructive sleep apnoea syndrome, sinusitis, musculoskeletal impairment, psychological disturbance, hypertension, obesity, gastro-oesophageal reflux disease (GORD) and rhinitis. The frequency of comorbidities ranged from 3% to 78%. Rhinitis, GORD, obesity, hypertension and psychological disturbance were the most prevalent comorbidities (figure 1a). Almost all participants (98%) had at least one comorbidity and >50% had more than three comorbidities (figure 1b).

Cluster analysis and description

The Kaiser–Meyer–Olkin (0.6) and the Bartlett's Test of Sphericity ($p<0.001$) confirmed that the cluster analysis was appropriate. The PCA identified two components: component 1 encompassed the variables BMI, ACQ-7, AQLQ and HADS; component 2 encompassed physical activity levels and sedentary time (supplementary table S1).

TABLE 1 Participant characteristics

	Brazilian cohort	Australian cohort	All participants
Participants n	243	53	296
Anthropometric data			
Female	203 (84)	28 (53)*	231 (78)
Age years	46.0 (39.0–53.0)	54.0 (41.0–64.2)*	47.0 (39.0–45.0)
BMI kg·m^{-2}	30.4 (26.7–34.7)	28.8 (25.2–33.8)	29.9 (26.6–34.6)
Physical activity			
Steps steps·day^{-1}	6480 (5024–8425)	5402 (3951–7744)*	6246 (4808–8103)
MVPA min·day^{-1}	20.0 (13.1–35.1)	22.7 (12.8–36.9)	20.4 (12.9–35.5)
Sedentary time h·day^{-1}	8.5±1.8	11.2±1.4*	8.9±1.9
Pulmonary function			
FEV_1 % predicted	70.4±18.6	66.8±23.3	69.8±19.5
FVC % predicted	84.0±16.3	79.8±18.9	83.3±16.8
FEV_1/FVC	0.69 (0.62–0.75)	0.62 (0.56–0.71)*	0.68 (0.60–0.75)
Asthma medication			
ICS dose µg·day^{-1}	1600 (1600–2400)	2000 (2000–2000)	1600 (1600–2400)
LABA use	231 (95)	47 (87)	287 (94)
Asthma control			
ACQ-7 score	1.8 (1.2–2.6)	2.1 (1.4–2.6)	2.0 (1.3–2.6)
Uncontrolled asthma	162 (67)	37 (71)	199 (67)
Exacerbation			
Hospitalisation	15 (7)	15 (28)*	30 (10)
Emergency department visit	117 (52)	17 (32)*	134 (49)
Systemic corticosteroid burst	119 (53)	46 (87)*	165 (60)
Exacerbation[#]	141 (58)	47 (88)*	188 (64)
Health status			
AQLQ total score	4.0 (3.1–5.0)	5.4 (4.3–6.2)*	4.2 (3.2–5.2)
HAD-A total score	9.0 (5.7–12.0)	6.0 (4.0–9.0)*	8.5 (5.0–11.0)
HAD-D total score	7.0 (4.0–10.2)	4.0 (2.0–6.0)*	6.0 (4.0–10.0)

Data are presented as mean±SD, median (25th–75th) or n (%), unless otherwise indicated. BMI: body mass index; MVPA: moderate and vigorous physical activity; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; ICS: inhaled corticosteroids (total daily dose beclomethasone equivalent); LABA: long-acting β_2-agonists; ACQ-7: Asthma Control Questionnaire with seven questions; AQLQ: Asthma Quality of Life Questionnaire; HAD-A: Hospital Anxiety and Depression Scale-Anxiety; HAD-D: Hospital Anxiety and Depression Scale-Depression. [#]: exacerbation defined as hospitalisation, emergency department visit and temporary systemic corticosteroid; *: p<0.05 between countries.

Ward's cluster analysis was based on the significant components identified by the PCA. Using the hierarchical cluster analysis described in the Methods, a dendrogram was generated and four clusters were identified. The four clusters differed significantly by sex, BMI, asthma medication, asthma control, physical activity levels, sedentary time, health status and symptoms of anxiety and depression (table 2). Although all clusters had a high frequency of rhinitis (>60%), they differed in the frequency for most other comorbidities (figure 2).

Cluster 1, "High movers"

This cluster comprised 76 participants (25%), of whom 88% were from the Brazilian population. The cluster had the largest percentage of physically active participants (41% classified as "physically active", 79% as "somewhat physically active") and engaged in less sedentary time than other cluster participants. Additionally, most of the participants (62%) had controlled asthma symptoms, were female, were overweight and used lower doses of ICS compared with the other clusters.

Cluster 2, "Poorly active"

This cluster comprised 80 participants (27.3%, with 60% from the Brazilian cohort), and 99% were classified as low-level active and more sedentary. This cluster had fewer female patients, who were overweight, but with a smaller number of obese patients than clusters 3 and 4 (respectively, 37% *versus* 69% and 64%). Most participants (65%) presented with uncontrolled asthma symptoms.

Cluster 3, "Moderately active, obese and distressed"

This cluster comprised 69 patients (23%) who were mostly female, and 75% presented with uncontrolled asthma. Obesity was present in 71% of participants; they were more physically active, and engaged in less sedentary time than clusters 2 and 4, and had higher anxiety and depression scores than clusters 1 and 2.

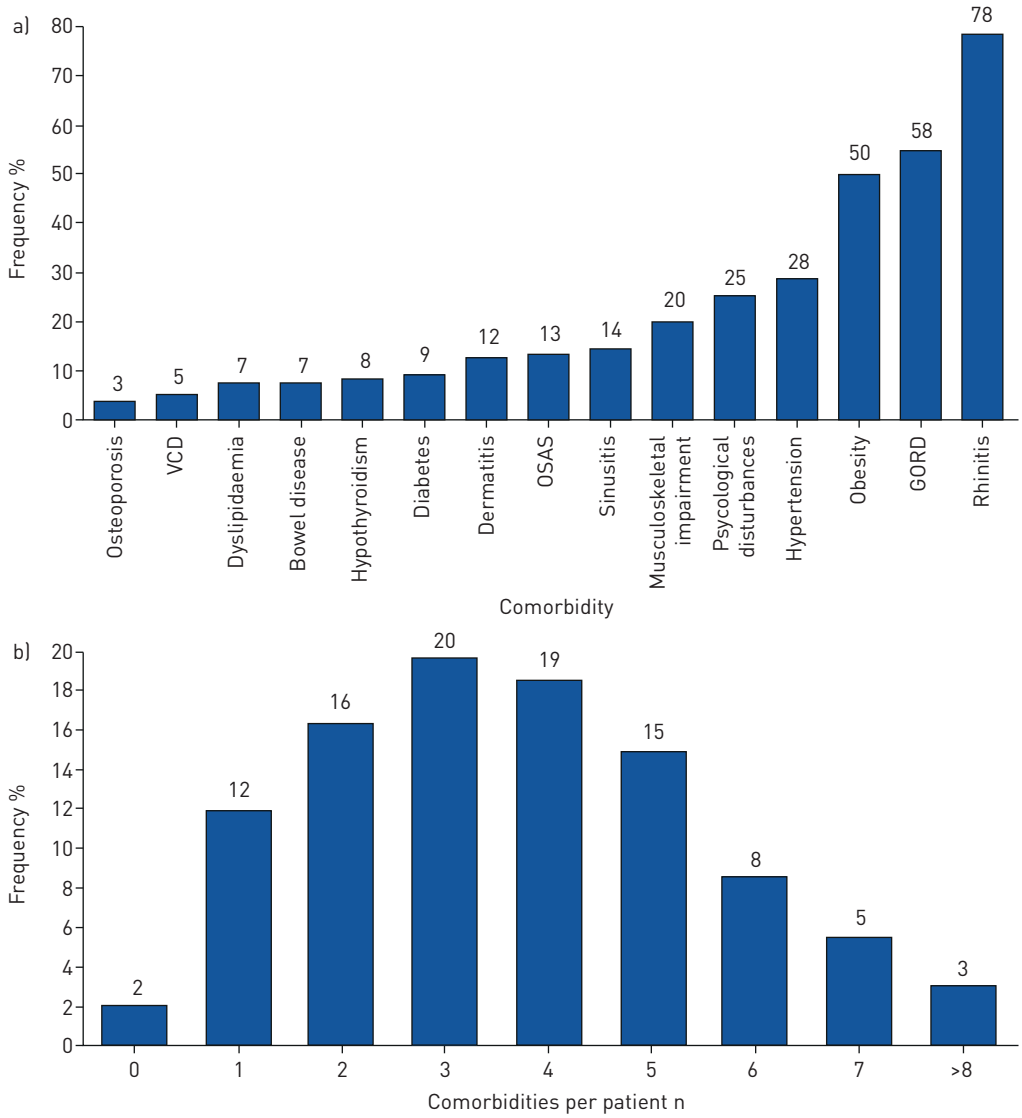

FIGURE 1 Comorbidities in 296 participants with moderate-to-severe asthma. a) Distribution of 15 comorbidities identified; b) distribution of the number of comorbidities per patient. VCD: vocal cord dysfunction; OSAS: obstructive sleep apnoea syndrome; GORD: gastro-oesophageal reflux disease.

Cluster 4, "Inactive, obese and distressed"

This cluster comprised 71 participants (24%, with 83% from the Brazilian cohort). Obesity was present in 64% of participants, and all were classified as physically inactive and accrued a high volume of sedentary time. Participants in cluster 4 presented with increased anxiety and depression symptom scores compared with those in clusters 1 and 2. They used higher doses of ICS and long-acting β_2-agonists. Most participants (91%) presented with uncontrolled asthma.

Our results suggest that only those patients with controlled asthma were physically active, suggesting that the two outcomes are firmly linked. There were no between-cluster differences in age, smoking history, asthma onset, lung function or the frequency of participants treated with long-acting β_2-agonists in combination with ICS (table 2).

Comorbidities, asthma control, health status, psychological symptoms and exacerbations within clusters

The most prevalent comorbidities in all clusters were GORD, obesity and rhinitis (figure 2). Diabetes, obesity and psychological disturbances were most prevalent in clusters 3 and 4. Cluster 3 had a lower prevalence of musculoskeletal disorders than all the other clusters.

TABLE 2 Cluster characteristics of participants with moderate-to-severe asthma

	1) High movers	2) Poorly active	3) Moderately active, obese and distressed	4) Inactive, obese and distressed
Participants n	76	80	69	71
Brazilian %	88	60	100	83
Australian %	12	40	0	17
Anthropometric/asthma data				
Female	60 (79)	48 (60)[#]	62 (90)[¶]	61 (86)[#,¶]
Age years	45.0 (38.5–53.5)	47.5 (36.5–58.0)	49.0 (40.7–54.0)	46.0 (41.0–55.0)
BMI kg·m^{-2}	27.6±4.9	29.3±5.7	33.1±5.8[#,¶]	33.2±6.2[#,¶]
Ex-smoker	18 (24)	18 (23)	15 (22)	17 (24)
Onset of childhood asthma	56 (74)	46 (58)	44 (64)	45 (63)
Pulmonary function				
FEV_1 % predicted	72.8±19.1	69.3±20.8	71.4±18.1	65.6±19.6
FVC % predicted	86.2±14.7	82.3±17.6	85.1±16.5	79.5±17.9
FEV_1/FVC	0.68±0.11	0.67±0.12	0.69±0.09	0.66±0.10
Asthma medication				
ICS dose µg·day^{-1}	1600 (1100–1600)	2000 (1600–2000)[#]	1600 (1600–2400)[#]	2000 (1600–2400)[#]
LABA use	69 (90.7)	75 (93.7)	67 (97.1)	67 (94.3)
Asthma control				
ACQ-7 score	1.3 (0.7–1.8)	1.7 (1.3–2.4)[#]	2.0 (1.5–2.7)[#]	2.7 (2.2–3.4)[#,¶,+]
Uncontrolled asthma	29 (38)	53 (67)[#]	52 (75)[#]	64 (92)[#,¶,+]
Physical activity				
Steps steps·day^{-1}	9249 (7814–10 998)	5193 (4309–6206)[#]	7380 (6113–9281)[#,¶]	4606 (3669–5569)[#,+]
MVPA min·day^{-1}	33.7 (20.3–54.8)	19.6 (12.8–28.2)[#]	27.2 (14.7–42.2)[#]	13.6 (8.2–19.0)[#,¶,+]
Sedentary time h·day^{-1}	7.9±1.6	10.1±1.8[#]	7.8 ±1.4[¶]	9.8±1.8[#,+]
Health status				
AQLQ total score	4.9 (4.1–5.8)	5.3 (4.5–5.8)	3.2 (2.7–3.9)[#,¶]	3.5 (2.9–4.1)[#,¶]
AQLQ symptoms score	5.2 (4.3–6.0)	5.1 (4.4–5.8)	3.7 (2.9–4.4)[#,¶]	3.6 (2.8–4.6)[#,¶]
AQLQ activity limitation score	4.5 (3.8–5.5)	5.3 (4.5–6.0)	3.2 (2.5–3.7)[#,¶]	3.4 (2.8–4.1)[#,¶]
AQLQ emotional function score	5.1 (3.4–6.4)	5.6 (4.6–6.4)	3.0 (2.0–3.8)[#,¶]	3.8 (2.6–4.6)[#,¶]
AQLQ environmental stimuli score	4.9 (3.2–5.7)	5.5 (4.2–6.2)	2.5 (1.7–3.5)	3.2 (2.5–4.8)
HAD-A score	6.0 (4.0–9.0)	5.0 (3.0–7.0)	13.0 (10.0–15.0)[#,¶]	10.0 (8.0–12.0)[#,¶,+]
HAD-D score	4.0 (3.0–6.0)	4.0 (2.0–6.0)	13.0 (10.0–15.0)[#,¶]	9.0 (6.0–11.0)[#,¶,+]

Data are presented as mean±SD, median (25th–75th) or n (%), unless otherwise indicated. BMI: body mass index; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; ICS: inhaled corticosteroids (total daily dose beclomethasone equivalent); LABA: long-acting β_2-agonists; ACQ-7: Asthma Control Questionnaire with seven questions; MVPA: moderate and vigorous physical activity; AQLQ: Asthma Quality of Life Questionnaire; HAD-A: Hospital Anxiety and Depression Scale-Anxiety; HAD-D: Hospital Anxiety and Depression Scale-Depression. [#]: p<0.05 *versus* cluster 1; [¶]: p<0.05 *versus* cluster 2; [+]: p<0.05 *versus* cluster 3.

Clusters 3 and 4 reported worse asthma control than clusters 1 and 2 (figure 3). The use of short-acting bronchodilators was higher in cluster 4. No between-cluster differences were observed for lung function. The odds of uncontrolled asthma were higher in clusters 2 and 3 compared to cluster 1 (respectively, OR 3.3, 95% CI 1.7–6.4 and OR 4.6, 95% CI 2.4–10.1). Cluster 4 presented even higher odds of uncontrolled asthma (OR 17.6, 95% CI 6.7–45.6) (figure 4a).

Cluster 4 reported the highest exacerbation rate. No difference in the odds of exacerbations and hospitalisations was observed between clusters 1, 2 and 3 (figure 4b, c). Cluster 4 presented 2.3 (95% CI 1.1–4.6) higher odds of exacerbation compared with cluster 1 and 5.5 (95% CI 1.5–20.0) higher odds of hospitalisation compared with clusters 1 and 3. Clusters 3 and 4 presented higher odds of ED visits (respectively, OR 1.8, 95% CI 1.0–3.6 and OR 1.9, 95% CI 1.0–3.7) compared with cluster 2. No between-cluster differences were observed for the odds of requiring systemic corticosteroid use for asthma exacerbation.

Clusters 3 and 4 reported lower health status, more symptoms, greater activity limitation and impaired mental health compared with clusters 1 and 2 (table 2).

Clusters 3 and 4 presented with increased anxiety and depression symptom levels compared with clusters 1 and 2. However, patients in cluster 3 presented even higher anxiety and depression symptoms than those in cluster 4 (table 2).

Tree diagram

The tree diagram was performed using discriminatory variables for cluster assignment (physical activity, obesity and anxiety symptoms) using subsets of these variables to assess the classification of participants

0–20% >20–40% >40–60% >60%	Osteoporosis %	VCD %	Dyslipidaemia %	Bowel disease %	Hypothyroidism %	Diabetes %	Dermatitis %	OSAS %	Sinusitis %	MSK impairment %	Psychological disturbance %	Hypertension %	Obesity %	GORD %	Rhinitis %
1) High movers (n=76)	4	4	4	5	8	3	9	9	15	18	13	16	33	42	78
2) Poorly active (n=80)	1	3	3	8	8	6	21#	10	14	31	21	31#	30	42	61
3) Moderately active, obese and distressed (n=69)	3	3	17#,¶	6	12	15#	6	15	17	7¶	32#	38#	70#,¶	54	80
4) Inactive, obese and distressed (n=71)	6	10	6	10	4	14#	13	20	11	21+	35#	30	62#,¶	72#,¶,+	80

FIGURE 2 Frequency of comorbidities per cluster. Data are presented as the percentage of each comorbidity in the four clusters. VCD: vocal cord dysfunction; OSAS: obstructive sleep apnoea syndrome; MSK: musculoskeletal; GORD: gastro-oesophageal reflux disease. #: p<0.05 *versus* cluster 1; ¶: p<0.05 *versus* cluster 2; +: p<0.05 *versus* cluster 3.

(figure 5). The results of this analysis demonstrate that a greater number of comorbidities/risk factors (*e.g.* inactivity, obesity and anxiety) identifies clusters with worse asthma control. The proportion of participants in each cluster is presented in figure 6. These figures suggest that a simple method for phenotyping of asthma subclasses can be based on these clinical variables.

Clinical associations

The associations between the dependent outcomes (exacerbation, hospitalisation, ED visit and bursts of systemic corticosteroids) with the characteristics sex, BMI, ACQ-5, sedentary time, daily physical activity, HADS-A, HADS-D, AQLQ and ICS dose are described in supplementary table S2. Higher levels of sedentary time were significantly associated with increased odds of exacerbation (OR 1.83, 95% CI 1.02–3.30, p=0.04) and hospitalisation (OR 1.23, 95% CI 1.01–1.50, p=0.04) and with greater systemic corticosteroids bursts (OR 1.16, 95% CI 1.02–1.32, p=0.02) (supplementary table S2). Being more active was a protective factor for hospitalisation (OR 0.81, 95% CI 0.67–0.97, p=0.03) (supplementary table S2). Female sex was also a risk factor for exacerbation (OR 1.14, 95% CI 1.01–1.30, p=0.04), ED visits (OR 1.90, 95% CI 1.02–3.53, p=0.04) and for greater systemic corticosteroid bursts (OR 1.95, 95% CI 1.06–3.60,

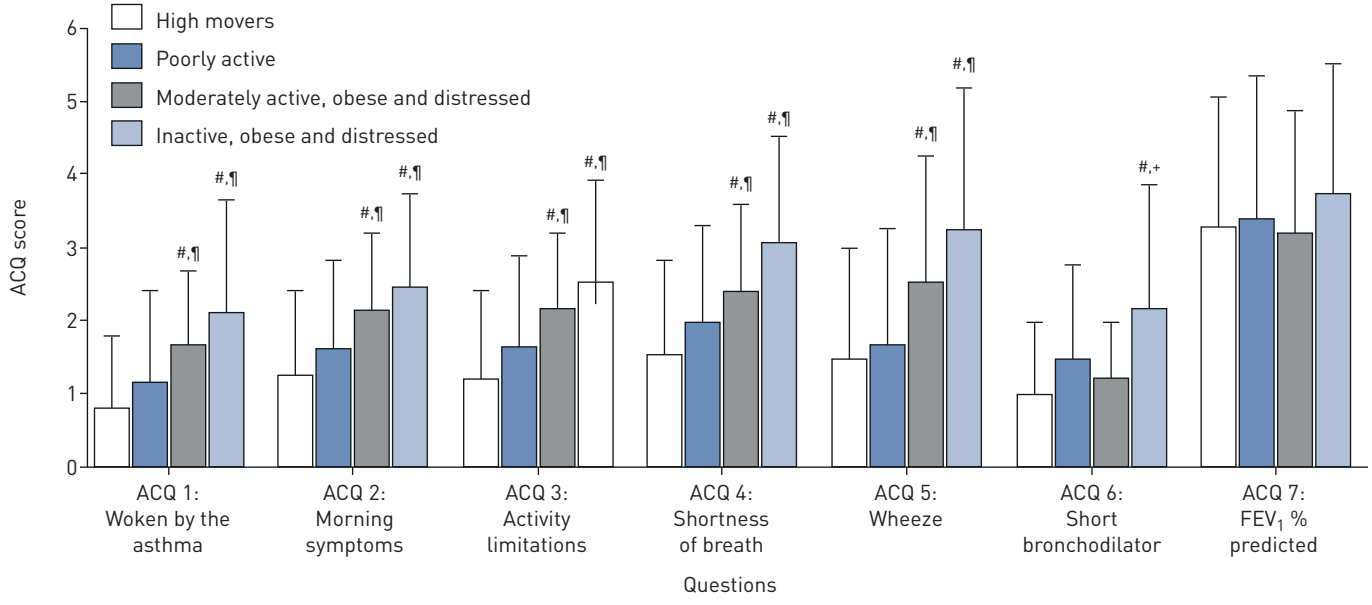

FIGURE 3 Comparison between clusters of each Asthma Control Questionnaire-7 (ACQ-7) question. Data are presented as mean±SD. FEV_1: forced expiratory volume in 1 s. #: p<0.05 *versus* cluster 1; ¶: p<0.05 *versus* cluster 2; +: p<0.05 *versus* cluster 3.

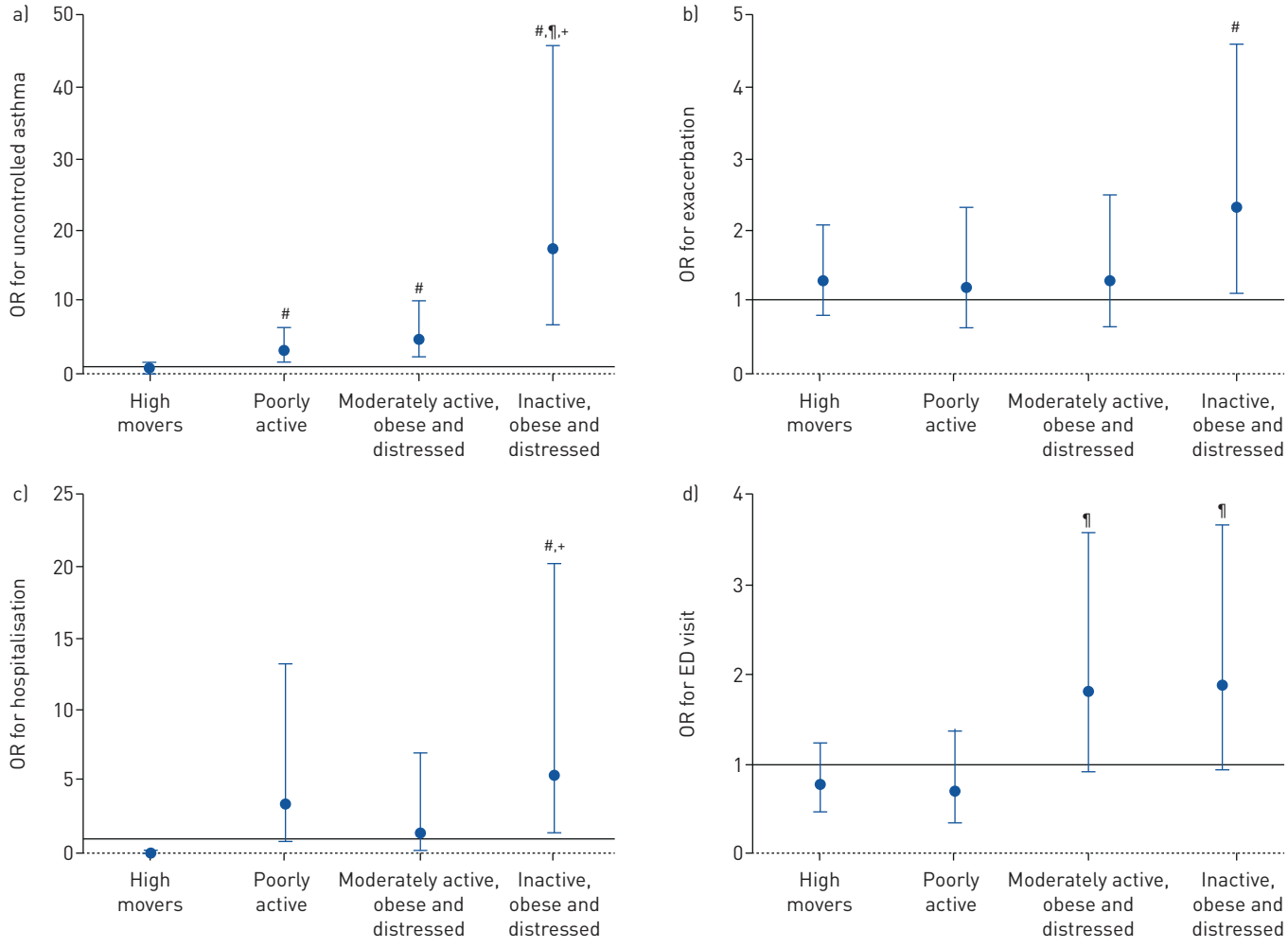

FIGURE 4 Adjusted odds ratios (OR) between clusters. a) Uncontrolled asthma; b) exacerbation; c) hospitalisation; d) emergency department (ED) visit. Data are presented as the median (95% CI). #: p<0.05 *versus* cluster 1; ¶: p<0.05 *versus* cluster 2; +: p<0.05 *versus* cluster 3.

p=0.03) (supplementary table S2). Higher levels of anxiety symptoms were also significantly associated with increased ED visits (OR 1.06, 95% CI 1.02–1.14, p=0.01).

Multiple linear regression

The ACQ-7 total score was significantly associated with sex, the occurrence of exacerbation, daily physical activity and AQLQ total score (supplementary table S3):

$$\text{ACQ-7}=4.13+(0.33\times\text{exacerbation})-(0.35\times\text{sex})-(0.08\times\text{steps}\cdot\text{day}^{-1})-(0.34\times\text{AQLQ})$$

Discussion

In this study, we performed a hierarchical cluster analysis to identify clinical asthma phenotypes based on extrapulmonary traits and behavioural/risk factors in patients with moderate-to-severe asthma, and to describe the clinical characteristics associated with these phenotypes. We included two populations, from Brazil and Australia. Our analysis identified four distinct phenotypes with relatively even representation of patients within each cluster. These were 1) participants with controlled asthma who were physically active; 2) participants with uncontrolled asthma who were physically inactive and more sedentary; 3) participants with uncontrolled asthma with low physical activity, who were also obese and experienced anxiety and/or depression symptoms; and 4) participants with very uncontrolled asthma, who were physically inactive, more sedentary, obese and experienced anxiety and/or depression symptoms. We examined the clinical associations of each of these clusters and determined cluster 4 to be associated with worse outcomes in terms of exacerbation; they also had the poorest asthma control.

Previous cluster analyses have been performed in asthma, aiming to identify clinical phenotypes in patients with severe disease. Despite the importance of these clinical phenotypes, alternative approaches

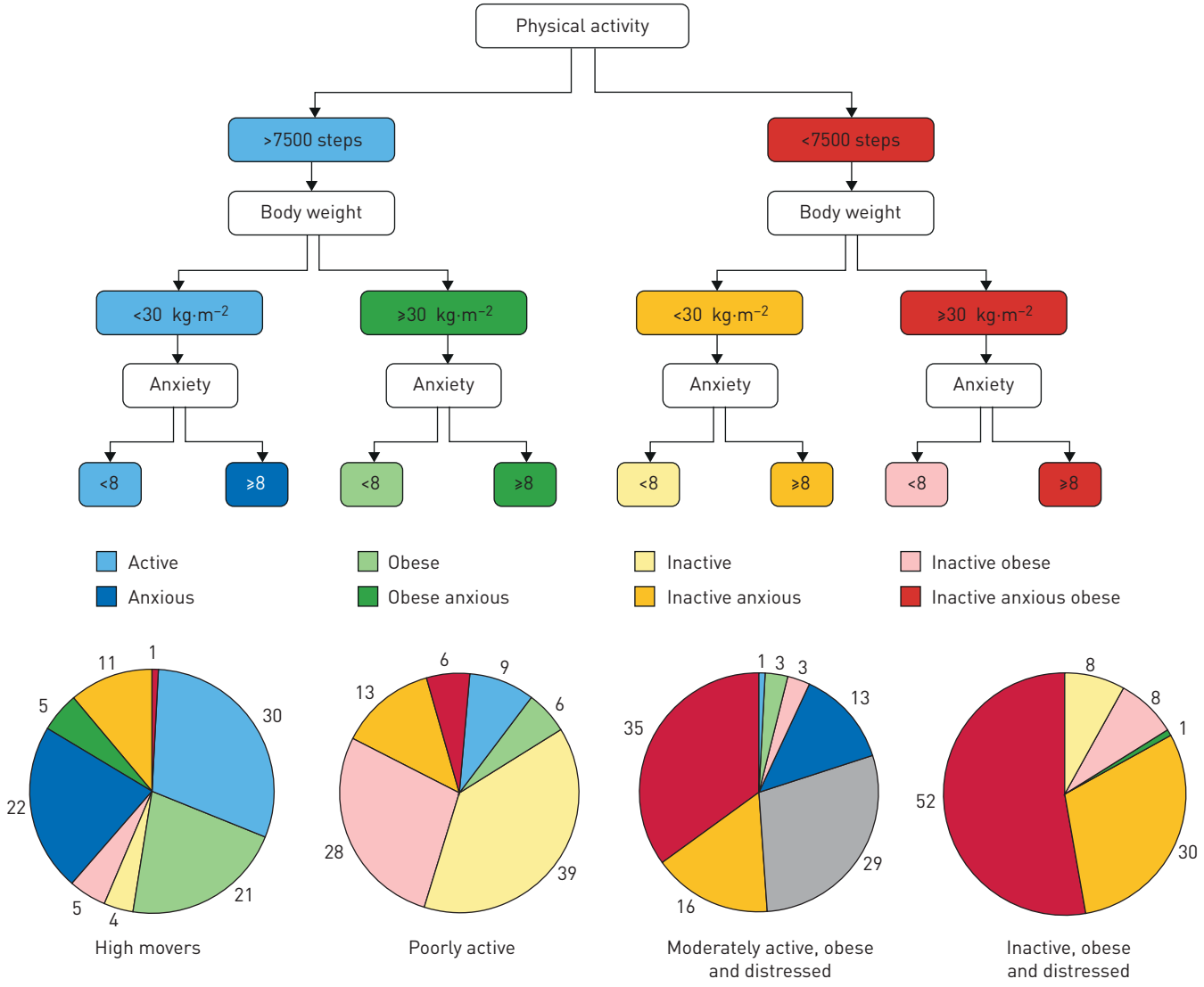

FIGURE 5 Tree analysis reporting the distribution of each comorbidity in the clusters considering clinical cut-points (darker colour) for physical activity (in step counting) [28], body mass index [43] and anxiety symptoms (Hospital and Anxiety and Depression Scale subscale) [24]. Participants were assigned to one of the four clusters that range from controlled asthma (cluster 1) to very uncontrolled asthma disease (cluster 4).

have been recommended for the classification of asthma. Moore *et al.* [16] identified five clusters of patients with different clinical, physiological and inflammatory characteristics. Of the 11 most important variables that determined assignment to individual clusters, six were based on pulmonary function tests, two were age-related, two reflected medication use and one was sex. In another analysis, Haldar *et al.* [1] defined four clusters in patients from secondary care; the variables included airway inflammation, lung function, symptoms, atopy and obesity. Patients were classified as having "early-onset symptoms" and "late-onset inflammation", and there was observed discordance between asthma symptoms and eosinophilic airway inflammation [1]. To the best of our knowledge, no prior asthma cluster analyses have attempted to phenotype patients based on extrapulmonary treatable traits and risk factors. This analysis is necessary for several reasons. Traits such as physical inactivity and high sedentary time are common in patients with asthma, especially in severe disease [13], and they are significantly associated with poor clinical outcomes and poor health status [4]. Evidence from the general population and in other chronic diseases has confirmed that these traits are importantly modifiable [31, 32]. Therefore, understanding the impacts of these traits and how they cluster is important for the development of treatment interventions beyond the current asthma management paradigm [33, 34].

There have been advances in asthma management for patients with severe asthma over the last decade, including monoclonal antibody therapies [35] and macrolide antibiotics for exacerbation reduction [36].

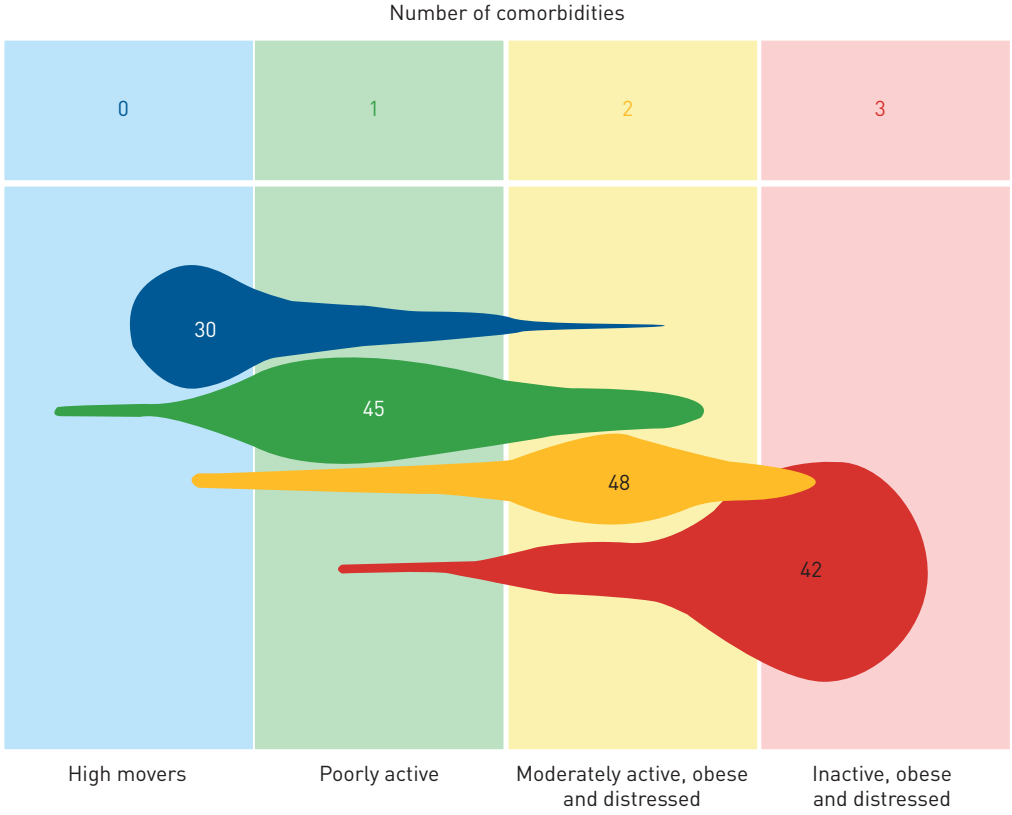

FIGURE 6 Tree performance. Using the algorithm generated by the tree analysis, 80% of participants were assigned to the correct cluster according to the number of comorbidities. Colours are in line with the tree diagram (blue: high movers; green: poorly active; yellow: moderately active, obese and distressed; red: inactive, obese and distressed). The number of comorbidities (inactive, obese and distressed/higher anxiety scores) ranges from zero to three. The percentage of participants from that cluster that are correctly assigned is indicated numerically within the shape.

Nevertheless, patients with severe disease continue to experience poor health status [37], and have a higher comorbidity and risk-factor burden than those with controlled disease [6]. Therefore, a current priority is to develop interventions that target clinically important extrapulmonary traits [6]. Our cluster analysis has identified four clusters based on these traits. We have also determined the clinical relevance of these clusters by assessing their associations with important clinical outcomes such as exacerbations, health status and asthma control. Targeting these traits may improve these outcomes. The treatable traits paradigm proposes the application of multidimensional assessment to identify traits that are clinically important, measurable and modifiable, followed by targeted interventions for each trait identified. A randomised controlled trial of this approach in severe asthma demonstrated its efficacy in terms of improving health status and airway and systemic inflammation and in reducing primary care visits [8]. In this study, all of the traits identified were treated. The presence of the traits of anxiety, depression and obesity are common and tend to be associated with poorer asthma outcomes independent of the clinical features of the disease. In clusters 2 and 4, the age of asthma onset and lung function were relatively similar; however, the outcomes in cluster 4 were worse. The difference was the presence of these additional traits. This finding highlights the importance of these traits on disease outcomes.

The impact of obesity and symptoms of anxiety and depression warrants consideration. Cluster 4 (very uncontrolled asthma, highly physically inactive and sedentary with obesity) and cluster 3 (more active with better asthma control than cluster 4, but still obese with anxiety and depression) were associated with the poorest clinical outcomes. This further highlights the importance of these extrapulmonary traits in terms of their additive deleterious effects on people with moderate and severe asthma. Obesity is common in more severe asthma and is a recognised risk factor for increased asthma exacerbations and worse asthma control [1, 10]. The synergistic relationship between obesity and reduced physical activity is also well characterised [38]. Previous studies in obese [39, 40] and non-obese [41] people with asthma have shown that dietary restriction plus exercise programmes have promising effects on asthma control and health status, highlighting their potential as treatable traits.

This is the first study to identify asthma phenotypes considering clinical, functional, anthropometrical and psychological characteristics collectively, in people with moderate-to-severe asthma. Our findings reinforce the need for an individualised multidimensional assessment of asthma to facilitate the implementation of personalised management [8]. For instance, a behaviour-change intervention aimed at increasing physical activity could lead to improved asthma control for patients of cluster 2 (poorly active) [33], while weight-loss and psychological interventions may be proposed for patients within cluster 3 (moderately active, obese and distressed). Regarding cluster 4 (physically inactive, obese and distressed), a more comprehensive approach, including physical training and programmes that address techniques, may be more effective in improving asthma control [8, 39, 42]. In addition, we have proposed cut-points that allow the identification of these clusters (figure 5), which may be applied in clinical practice. However, further studies are required to validate these cut-points to endorse or refute their applicability.

Asthma phenotypes have been applied in clinical practice to allow more precise endpoints according to the main underlying pathology, with the aim of reducing exacerbations and corticosteroid treatment and improving clinical control, pulmonary function and quality of life [1, 16]. Despite this, people with moderate-to-severe asthma continue to experience frequent symptoms and attacks, suggesting that current pharma- and non-pharmacotherapies are insufficient given the complexity of more severe disease. If the phenotypes identified in this current study are considered in the overall management of people with moderate-to-severe asthma, there may be greater gains in asthma control and outcomes for this population.

Our study has strengths and some limitations. In terms of strengths, we quantified physical activity and sedentary outcomes using objective measures, which are scarce in these populations. Second, the inclusion of participants from two continents increases the generalisability of our findings, even though these populations were not matched in terms of age, lung function or the impact of the disease. Another limitation may be the higher proportion of women; however, this is also reflective of a more severe asthma population. Despite the multicentre nature of this study, the sample size is relatively small, indicating the need for further validation of these clusters. We also acknowledge the imbalance in the number of patients between Brazilian and Australian cohorts; however, this imbalance takes into account the populations of each country (210 and 25 million inhabitants, respectively). Finally, due to the cross-sectional nature of the study design, we cannot establish causality. Further studies are needed to understand the bidirectional nature of these traits in this population.

In conclusion, we have identified four asthma phenotypes based on extrapulmonary characteristics through hierarchical cluster analysis. These distinct clusters based on physical activity levels, obesity and depressive and anxiety symptoms were associated with important clinical asthma outcomes. Our data reinforce the importance of evaluating extrapulmonary traits in clinical practice to individualise treatments with the goal of improving clinical outcomes in people with moderate-to-severe asthma.

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