

Persistent Uncontrolled Asthma: Long-Term Impact on Physical Activity and Body Composition

This article was published in the following Dove Press journal:
Journal of Asthma and Allergy

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Rationale: Asthma, obesity and physical activity (PA) are interrelated. However, longitudinal data with objective PA measures and direct assessment of body composition are still lacking.

Objective: To study the impact of symptom control on PA and body composition.

Methods: In a longitudinal cohort study of the German Center for Lung Research, we assessed the body composition of 233 asthma patients and 84 healthy controls using bioelectrical impedance analysis. PA (ie average daily steps and time of at least moderate activity, steps/min) was measured by accelerometry for one week. Asthma control was assessed by ACT score, ACQ-5 score and history of severe exacerbations. After two years of follow-up, we studied changes in physical activity and body composition in relation to asthma control.

Results: Patients with uncontrolled asthma had increased fat mass and decreased muscle mass compared to patients with controlled asthma or healthy controls. Both fat mass and muscle mass correlated better with asthma control than the body mass index (BMI). In multivariate regressions adjusted for age and sex, asthma control and physical activity were independent predictors of body composition ($R^2 = 0.61$, $p < 0.001$). Persistent uncontrolled asthma patients ($n=64$) had lower physical activity at both baseline (6614 steps/118 min) and follow-up (6195/115). Despite having stable BMI, they also had significant muscle loss (-1.2% , -0.88 kg, $p < 0.01$) and fat accumulation ($+1\%$, $+1.1$ kg, $p < 0.01$). By contrast, temporarily uncontrolled or controlled asthma patients had higher physical activity at baseline (8670/156) and follow-up (9058/153) with almost unchanged body composition.

Conclusion: Persistent uncontrolled asthma is associated with sustained physical inactivity and adverse changes in body composition that might be overlooked by relying solely on BMI. Physical activity is an independent predictor of body composition and reliable long-term marker of symptom control.

Keywords: symptom control, physical activity, body composition, fat mass, muscle mass, BMI

Background

Asthma is a common worldwide health problem affecting patients from all age groups.¹ In most patients, a proper therapy allows adequate symptom control. However, a subset of severe asthma patients remains persistently uncontrolled.² Uncontrolled asthma is often associated with obesity³ and physical inactivity^{4,5} in addition to corticosteroid induced comorbidities.⁶ While the relationship between asthma and obesity has been studied extensively, most of the studies have relied on the body mass index (BMI) as surrogate for body composition rather than the direct

measures of fat mass and muscle mass. Besides, the role of physical inactivity in this important association still remains uncertain, particularly, the long-term association of asthma control with physical activity and body composition. It has been suggested that functional impairments and physical inactivity in people with chronic lung diseases might adversely affect their body composition.⁷ For instance, physical inactivity and the associated muscle depletion are well established disease features of severe COPD.⁸ However, corresponding data in severe uncontrolled asthma are still lacking. Understanding the long-term consequences of asthma on physical activity and body composition is important as both might affect the overall health outcomes and are relevant for patients' quality of life.^{9,10}

In this context, the aims of this study were: 1) to study the association of asthma control with body composition, 2) to determine potential predictors of body composition in asthma, particularly, the role of physical activity and 3) to study the longitudinal changes in body composition and physical activity in patients with persistent uncontrolled asthma compared to asthma patients with better symptom control.

Methods

Study Design

The study subjects were adults with asthma and healthy controls who were recruited to the multicenter prospective longitudinal All Age Asthma Cohort (ALLIANCE), a cohort of pediatric and adult patients with asthma in Germany, initiated by the German Centre for Lung Research (DZL). The study was approved by the ethics committee at the university of Luebeck (Az.21–215) according with the Declaration of Helsinki and is registered at clinicaltrials.gov (adult arm: NCT02419274). Verbal and written informed consents were obtained from all subjects prior to enrollment.

The adult arm of the ALLIANCE cohort recruits patients with mild to severe asthma and healthy controls. Detailed information regarding recruitment, inclusion and exclusion criteria was described previously.¹¹ Patients had to have stable disease without acute exacerbations or respiratory tract infections within four weeks prior to study visit. In this analysis, we studied data from baseline and follow-up visits that took place 2 years later. An overview of the selection process for this analysis is given in ([Online Supplementary 1 and 2](#)).

Spirometry and Symptom Control

We measured forced expiratory volume in the first second (FEV1), forced vital capacity (FVC) and peak expiratory flow (PEF) from spirometry according to ERS standardizations.¹²

We defined asthma control based on European Respiratory Society/American Thoracic Society guidelines.² Asthma control was assessed by the asthma control test (ACT), asthma control questionnaire (ACQ5) and the annualized number of severe exacerbations 12 months prior to study visit, defined as a burst of systemic corticosteroids for ≥ 3 days. Uncontrolled asthma was defined as either ACQ ≥ 1.5 or ACT < 20 , or two or more severe exacerbations or one serious exacerbation with hospitalization, ICU stay or mechanical ventilation in the previous year.²

To study the long-term changes in body composition and its relation to asthma control, we compared the changes in body composition between patients with persistent uncontrolled asthma and patients with controlled or temporarily uncontrolled asthma. Persistent uncontrolled defines patients who had uncontrolled symptoms at baseline and at follow-up, while the rest of the patients had controlled asthma at both study visits or had uncontrolled symptoms at only one of the study visits.

Skeletal Muscle Mass and Body Composition

We performed whole body bioelectrical impedance analysis (BIA) using Nutribox analyzer (Data Input, Pöcking, Germany). BIA has shown to be a feasible tool that enables simple assessment of body composition in many clinical conditions.¹³ An alternating current was used at 50 kHz. We calculated the skeletal muscle mass (SM, [kg]) and its ratio to total body mass was expressed in percentage according to Janssen and colleagues.^{14,15} To study the relationship between SM, asthma control and physical activity, we classified asthma patients based on the SM quartiles into four groups for each gender. Further body composition measures were the fat mass (FM, [kg]) also in percent of the total body mass and the body mass index (BMI; [kg/m²]).

Physical Activity

Physical activity was measured over a period of one week by a multisensory activity monitor (SenseWear Pro Armband; BodyMedia, Pittsburgh, PA, USA) as previously described.^{16,17} Accelerometer outputs were:

average daily steps and the average daily minutes of at least moderate activity (any energy expenditure above 3 metabolic equivalents (METs)). A threshold of 94% of wearing time (22.5 h) for at least five days was set to identify valid analyses.¹⁷

Statistical Analysis

We used one-way analysis of variance ANOVA, or Fisher exact test to identify the significance of the differences of the measured clinical variables between asthma patients and healthy controls as well as between asthma patients in the different SM quartiles. For pairwise comparison, a post hoc analysis with Tukey's test was done. We used Spearman correlation to evaluate the association between measures of body composition and asthma control scores. We conducted multivariate regression analyses to study the association of muscle mass and fat mass with their potential predictors ie: sex, age, asthma control, corticosteroid therapy and physical activity. The statistical significance of the longitudinal changes in clinical variables was determined using paired Wilcoxon signed-rank test.

Statistical analyses were performed using R (version 3.6.2; R Foundation, Vienna, Austria). An alpha error of less than 5% was considered statistically significant.

Results

Body Composition in Asthma Patients versus Healthy Controls

For the cross-sectional analysis of baseline data, we included 106 patients with controlled asthma, 127 patients with uncontrolled asthma and 84 healthy controls. Detailed clinical characteristics and measures of physical activity and body composition are presented according to asthma control in [Table 1](#). The post hoc analysis revealed that the age difference was only significant between uncontrolled asthma and healthy controls ($p=0.012$), but neither between controlled and uncontrolled asthma patients ($p=0.75$), nor between controlled asthma and healthy controls ($p=0.088$). Expectedly, uncontrolled asthma patients had frequent daily symptoms, more severe exacerbations, worse lung function, higher demand for OCS and higher doses of ICS. Accordingly, uncontrolled asthma patients engaged in lower physical activity and were heavier, had increased fat mass and decreased muscle mass compared to controlled asthma patients or healthy controls. Although that both controlled asthma patients and

healthy controls had similar physical activity levels, controlled asthma patients were heavier, had lower muscle mass ($p=0.039$) and a tendency of fat mass accumulation ($p=0.061$) compared to healthy controls. Further, an age-matched analysis that included subjects who aged 40–64 years only, confirmed that uncontrolled asthma patients had significant decreased physical activity, increased fat mass and decreased muscle mass compared to controlled asthma patients or healthy control, ([Online Supplementary 3](#)).

Predictors of Body Composition in Asthma

The classification of asthma patients based on SM quartiles and gender is demonstrated in [Table 2](#). The first quartile represents the lowest SM values. Pairwise comparisons between all quartiles from both genders also revealed statistically significant differences in BMI and FM except for the BMI which was similar in the second and third male quartiles. Compared to other quartiles, the first quartiles in both males and females showed higher BMI, higher FM, higher ICS doses and higher proportion of female patients who were on regular OCS therapy ([Table 2](#)). We also found that the first quartiles are characterized with poorer symptom control compared to the other quartiles ([Table 2](#)). Interestingly, we observed that the correlations of the fat mass with ACT score ($R=-0.29$) and ACQ score ($R=0.28$), and between the muscle mass with ACT score ($R=0.26$) and ACQ score ($R=-0.28$) were better than the correlation of BMI with ACT score ($R=-0.19$) and ACQ score ($R=0.18$), (all p -values <0.05). Further, we found no statistically significant differences in lung function measures across all SM quartiles. In addition, measures of physical activity were closely associated with the SM as demonstrated in [Figure 1](#). First quartiles of both genders had a relatively low physical activity compared to the other quartiles. In female patients, the mean average daily steps and average daily time of at least moderate activity (steps/minutes) ranged from 6300/61 in the first quartile to 9653/226 in the fourth quartile ([Figure 1](#)). Likewise, in male patients the means of daily steps and time in at least moderate activity ranged from 5671/102 (steps/minutes) in the first quartile to 8349/186 (steps/minutes) in the fourth quartile.

Factors that correlated with body composition were integrated in multivariate regressions. The first

Table 1 Baseline Clinical Characteristics of Patients with Asthma and Healthy Controls

Characteristics	Healthy Controls	Controlled Asthma	Uncontrolled Asthma	P-value
n	84	106	127	–
Age, years	46.2 ±18.6	51.2 ±13.5	52.6 ±14.5	0.015*
Sex (% male)	53	45	41	0.20
BMI (kg/m ²)	24.9 ±4.0	26.7 ± 4.4	28.5 ±5.5	<0.0001
Smoking history, %	19	21	25	0.54
ICS (%)	–	12	8	0.08
ICS/LABA (%)	–	76	92	0.09
ICS dose (µg)	–	408 ±309	748 ±535	<0.0001
LAMA (%)	–	13	42	<0.0001
OCS (%)	–	14	32	<0.0001
Biological therapy (%)	–	8	16	<0.001
FEV1%	103 ±11	88 ±18	72 ±20	<0.0001
FEV1/FVC (%)	76 ±7	68 ± 11	60 ±13	<0.0001
PEF (l/s)	9.0 ±2.0	7.6 ±2.2	6.1 ± 2.0	<0.0001
ACT score	–	23.0 ±1.7	13.5 ±4.0	<0.0001
ACQ5 score	–	0.56 ±0.49	2.33 ±1.1	<0.0001
Severe exacerbations in the previous 12 months	–	0 (0.0–1.0)	2 (0.0–5.0)	<0.0001
Average daily steps	7839 (6577–9430)	7806 (6337–10,004)	6641 (4886–9280)	<0.001
Average daily time of at least moderate activity, min	132 (72–175)	133 (93–192)	108 (54–183)	0.012
SM (%)	36±7.0	34 ±6.0	32 ±6.0	<0.0001
FM (%)	30 ±7.0	32 ±7.0	35 ±7.0	<0.0001

Notes: Values are presented in mean and standard deviation or median and interquartile range. *Post hoc analysis: controlled asthma vs uncontrolled p=0.75, controlled asthma vs healthy controls p=0.088, uncontrolled asthma vs healthy controls p=0.012. Physical activity was similar between controlled asthma and healthy controls.

Abbreviations: BMI, body mass index (kg/m²); smoking history, current or former smoker >10 pack years; ICS dose, inhaled corticosteroids fluticasone equivalent (µg); LABA, long-acting β₂-adrenoceptor agonists; LAMA, long-acting muscarinic receptor antagonists; OCS, regular daily oral corticosteroid therapy; biological therapy, omalizumab or mepolizumab; FEV1, predicted forced expiratory volume in the 1 second; FVC, forced vital capacity; PEF, peak expiratory flow (l); ACT, asthma control test; ACQ, asthma control questionnaire; SM, skeletal muscle mass; FM, fat mass.

regression (R²=0.61, p< 0.0001) showed that main predictors of muscle mass were sex, followed by asthma control; age and physical activity, respectively (Table 3). The second regression showed that predictors of fat mass were sex, asthma control and physical activity (Table 3). In a further multivariate regression analysis, we did not include asthma control as predictor of body composition. This additional analysis revealed that the OCS use and ICS dose were also predictors of body composition that were exchangeable with asthma control and might be reflecting the demand of intensified

corticosteroid therapy in uncontrolled asthma patients ([Online Supplementary 4](#)).

Longitudinal Change of Body Composition in Persistent Uncontrolled Asthma

From 161 patients who attended their follow-up visit after two years, we identified 64 patients who had persistent uncontrolled asthma. While age and gender distribution of patients with persistent uncontrolled asthma were comparable to the remaining patients (56 ±11 vs 54 ±13, years,

Table 2 Clinical Characteristics of Asthma Patients Based on Skeletal Muscle Mass and Gender

Parameter	Males					Females				
	First Quartile	Second Quartile	Third Quartile	Fourth Quartile	P-value	First Quartile	Second Quartile	Third Quartile	Fourth Quartile	P-value
SM quartile	<33.5	33.5–36.9	37.0–40.9	≥41	–	<26.3	26.4–28.8	28.9–32.6	>32.6	–
n	22	30	27	21	–	28	40	27	38	–
Age, years	59.9 ±11.4	54.4 ±14.6	54.0 ±11.1	49.0 ±13	0.06	54.3 ±11	54.4 ±14	48.7 ±12.9	43.7 ±16	<0.01
SM (%)	31 ±2	35 ±1	39 ±1	44 ±2	<0.01	24 ±2	28 ±1	30 ±1	36 ±4	<0.01
BMI (kg/m ²)	32.8 ±3.8	28.2 ±2.6	27.4 ±3.7	25.2 ±2.9	<0.01	34.7 ±5.0	27.5 ±4.1	25.6 ±2.8	22.3 ±2.8	<0.01
FM (%)	37 ±3	31 ±1	27 ±2	21 ±2	<0.01	46 ±3	39 ±3	36 ±2	29 ±6	<0.01
ACQ5 score	1.9 ±1.2	1.44 ±1.2	1.20 ±1.0	0.96 ±0.9	0.03	2.3 ±1.5	1.8 ±1.5	1.3 ±1.1	1.2 ±1.1	<0.01
ACT score	15.9 ±4.8	18.0 ±6.1	19.2 ±4.8	20.0 ±5.2	0.06	14.7 ±5.4	17.2 ±5.9	18.4 ±5.8	18.9 ±5.4	0.02
FEV1 (%)	72 ±14	81 ±24	77 ±18	99 ±20	0.52	73 ±20	81 ±28	83 ±18	85 ±21	0.14
FEV1/FVC (%)	59 ±13	64 ±11	60 ±11	62 ±12	0.41	62 ±12	65 ±14	66 ±12	68 ±13	0.39
PEF (l/s)	7.4 ±2.6	8.00 ±2.5	8.1 ±2.3	8.2 ±2.5	0.74	5.9 ±1.7	5.9 ±1.7	5.8 ±1.1	6.0 ±1.6	0.9
ICS dose (µg)	775 (400–1000)	500 (250–900)	500 (250–1000)	400 (250–500)	0.04	695 (460 –1000)	500 (500–1000)	500 (250–500)	450 (118–500)	0.01
OCS, (%)	22	14	30	27	0.55	48	25	22	10	0.02

Notes: Values are in mean ±sd except for ICS due to skewness are represented in median and IQR. A post hoc analysis showed statistically significant differences in age only between the first and fourth/first and third quartiles in females. In females, the differences in the ACQ5 score were significant between the first and fourth, first and third quartiles, while the difference of ACT score was significant only between the first and fourth quartiles. In males, the ACQ5 was significantly different only between the first and fourth quartiles.

Abbreviations: SM, skeletal muscle mass; BMI, body mass index (kg/m²); FM, fat mass; ACQ, asthma control questionnaire; ACT, asthma control test; FEV1, predicted forced expiratory volume in the 1 second; FVC, forced vital capacity; PEF, peak expiratory flow (l); ICS dose, inhaled corticosteroids fluticasone equivalent (µg); OCS, oral corticosteroid.

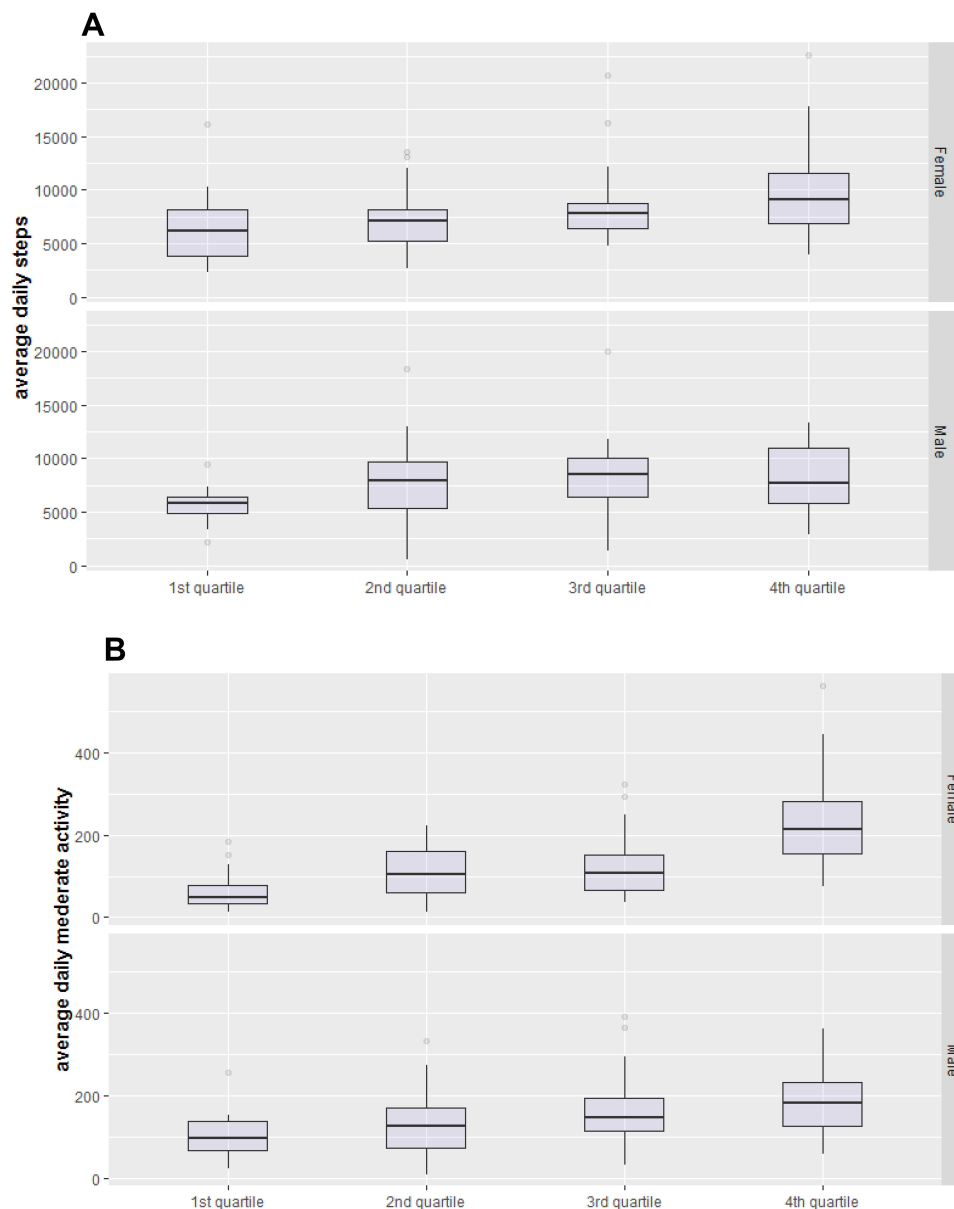


Figure 1 Physical activity in asthma patients in relation to skeletal muscle mass quartiles and gender: **(A)** the distribution of average daily steps in muscle mass quartiles. **(B)** the distribution of at least daily time in moderate activity according to muscle mass quartiles. In females, the post hoc analysis showed statistically significant differences in means of average daily steps between the first and fourth quartiles ($p<0.0001$), first and third quartiles ($p=0.005$), and second and fourth quartiles ($p=0.01$), **(A, upper panel)**. The average daily time of at least moderate activity was significantly different between all quartile ($p<0.001$) except between the second and third quartiles ($p=0.08$) **(B, upper panel)**. In males, average daily steps were only significantly different between the first and fourth quartiles ($p=0.031$), and between the second and fourth quartiles ($p=0.002$) **(A, lower panel)**. Likewise, the average daily time of at least moderate activity was also significantly different between the first and fourth ($p=0.031$), and between the second and fourth quartiles ($p=0.026$) **(B, lower panel)**.

$p=0.16$) and (45% vs 49, %male, $p=0.63$), the proportion of patients with regular OCS intake (20% vs 7%, $p=0.02$) and the ICS doses (795 μg vs 530 μg , $p<0.01$), were significantly higher in persistent uncontrolled asthma at follow-up.

Despite having unchanged BMI, patients with persistent uncontrolled asthma had a statistically significant loss of muscle mass with a mean loss of 1.2% (0.88 kg) over two years. In contrast, patients with controlled or

temporarily uncontrolled asthma had almost unchanged muscle mass with a reduction of only 0.3% (0.1 kg), **(Table 4 and Figure 2A)**. In addition to the decrease in muscle mass, there was a significant increase in fat mass in persistent uncontrolled asthma whereas patients with controlled or temporarily uncontrolled asthma showed no statistically significant changes in body composition **(Table 4)**.

Table 3 Predictors of Body Composition in Asthma

Predictors of Skeletal Muscle Mass			
Factor	Estimator	Standard Error	P-value
Male sex	2.748 e ⁻⁰²	4.774e ⁻⁰³	<0.001
ACT score	1.186 e ⁻⁰³	5.139 e ⁻⁰⁴	0.021
Age	-6.497 e ⁻⁰⁴	1.646 e ⁻⁰⁴	<0.001
Physical activity	2.913 e ⁻⁰⁴	2.738 e ⁻⁰⁵	<0.001
OCS use	-9.242 e ⁻⁰³	6.142 e ⁻⁰³	0.16
ICS dose	-5.031 e ⁻⁰⁶	5.073e ⁻⁰⁶	0.40
Intercept	2.748 e ⁻⁰¹	1.031 e ⁻⁰²	<0.001
Predictors of Fat Mass			
Male sex	-7.77 e ⁻⁰²	5.994 e ⁻⁰³	<0.001
ACT score	-1.452 e ⁻⁰³	6.237 e ⁻⁰⁴	0.021
Age	3.355 e ⁻⁰⁴	2.089 e ⁻⁰⁴	0.15
Physical activity	-3.993 e ⁻⁰⁴	3.419 e ⁻⁰⁵	<0.001
OCS use	1.369 e ⁻⁰²	9.083 e ⁻⁰³	0.080
ICS dose	6.385 e ⁻⁰⁵	8.533 e ⁻⁰⁶	0.38
Intercept	4.292 e ⁻⁰¹	1.451 e ⁻⁰²	<0.001

Notes: Multivariate regressions including predictors of SM: multiple R²=0.61, p<0.0001, and predictors of fat mass: multiple R²=0.61, p<0.0001. Age in years, sex: being male. In alternative regressions that did not include the ACT score as predictors, OCS use and ICS dose were significant predictors of muscle mass and fat mass ([Online Supplementary 3](#)).

Abbreviations: ACT, asthma control test; OCS, regular oral corticosteroid use (categorical variable); physical activity, average daily time in moderate activity in minutes; ICS dose, fluticasone equivalent in µg.

At follow-up, levels of physical activity of both asthma groups remained relatively unchanged. However, we observed a constantly reduced physical activity in persistent uncontrolled asthma patients ([Figure 2B](#) and [C](#)). They also had a numeric reduction in the average daily steps by -445/day compared to a slight numeric increase of step counts (+195 steps/day) in the rest of patients at follow-up. Minutes of physical activity did not differ between baseline and follow-up in either asthma group.

Discussion

Our main study findings were: first, uncontrolled asthma patients have a reduced skeletal muscle mass and increased fat mass compared to controlled asthma patients or healthy controls. Second, asthma control and physical activity were independent predictors of body composition irrespective of age and gender. Third, persistent

uncontrolled asthma results in sustained physical inactivity which might lead to further unfavorable changes in body composition on the long-term.

So far, studying the relationship between asthma and obesity has mainly relied upon the BMI. Several studies have shown a modest overall increase in asthma incidence and prevalence in obese individuals,¹⁸ in addition to the negative impact of obesity on asthma outcomes.¹⁹ Interestingly, our data revealed that significant changes in body composition including the increase in fat mass can be observed in patients with persistent uncontrolled asthma despite having stable BMI. Our findings indicate that the measurement of body composition by BIA provides additional information on the relation between asthma control and body composition that cannot be obtained by the crude measure of BMI.

Unlike in asthma, the impact of COPD on physical activity and body composition has been studied extensively, particularly the progressive loss of muscle mass as important marker of morbidity and mortality.^{20,21} Furthermore, these studies also demonstrated an association between sustained physical inactivity and the accelerated loss of muscle mass.²² Here, we report for the first-time longitudinal changes in body composition in asthma patients considering the long-term status of symptom control and the objectively measured physical activity. Persistent uncontrolled asthma was associated with sustained physical inactivity which appears to be an important contributor to the long-term adverse changes in body composition including the loss of muscle mass.

Furthermore, our data indicate that physical activity is a reliable long-term marker of asthma control. We found that persistent uncontrolled asthma patients had mean daily steps of (6614 and 6195) versus (8670 and 9058) in controlled asthma patients at baseline and follow-up, respectively. Interestingly, we observed a numeric decline of only 445 daily steps over two years in persistent uncontrolled asthma, however, with a sustained difference of at least 2000 daily steps between both groups. In line with the difference in step counts, the time in at least moderate activity remained constantly lower in patients with persistent uncontrolled asthma with a difference of 38 minutes at both baseline and follow-up. Therefore, our findings also indicate that the long-term changes of physical activity in persistent uncontrolled asthma are modest compared to the significant decline of physical activity in severe progressive COPD where we showed a decline of nearly 400 steps per year.²² Accordingly, in contrast to severe COPD,

Table 4 Measures of Body Composition, Physical Activity and Symptom Control at Baseline and Follow-Up

Parameter	Persistent Uncontrolled			Controlled or Transitionally Uncontrolled				
	Baseline	Follow-Up	Mean Difference	P-value	Baseline	Follow-Up	Mean Difference	P-value
BMI (kg/m ²)	28.5 ±4.9	28.7 ±5.0	+0.20	0.39	26.6 ±4.6	26.7 ±4.5	+0.10	0.66
FM (%)	34.6 ±7	35.8 ±7	+1%	0.015	32.3 ±6	32.7% ±6	0.0	0.29
FM (kg)	30.1 ±10.0	31.2 ±10.0	+1.06	0.012	25.8 ±8.51	26.2 ±8.2	+0.4	0.45
SM (%)	32.2 ±6	31.0 ±6	-1.2%	<0.01	33.8 ±5	33.5% ±5	-0.3%	0.30
SM (kg)	27.39 ±6.7	26.51 ±6.4	-0.88	<0.01	26.8 ±6.7	26.7 ±6.9	-0.1	0.53
Daily steps	6614 ±2854	6195 ±2642	-445	0.14	8670±3723	9058 ±3610	+195	0.56
Moderate activity	118 ±75	115 ±79	-3.0	0.11	156 ± 85	153 ±81	-3.0	0.43
FEV1 (%)	73 ±20.0	71 ±20.0	-1.9%	0.33	86 ±20	84 ± 20	-2%	0.11
ACQ5 score	2.27 ±1.13	2.47 ±1.13	+0.17	0.29	0.85 ±0.8	0.81 ±0.7	-0.06	0.54
ACT score	13.12 ±4.24	14.14 ±3.5	+1.02	0.08	21.1 ±3.8	21.8 ±2.9	+0.69	0.10

Notes: Values are presented in mean and standard deviation. P-values are from either paired t-test or paired Wilcoxon test and represent the statistical significance of the longitudinal change of the tested measures.
Abbreviations: SM, skeletal muscle mass (skeletal muscle mass/total body mass x %); BMI, body mass index kg/m²; FM, fat mass to total body mass %; ACQ, asthma control questionnaire; ACT, asthma control test; FEV1, predicted forced expiratory volume in the 1 second.

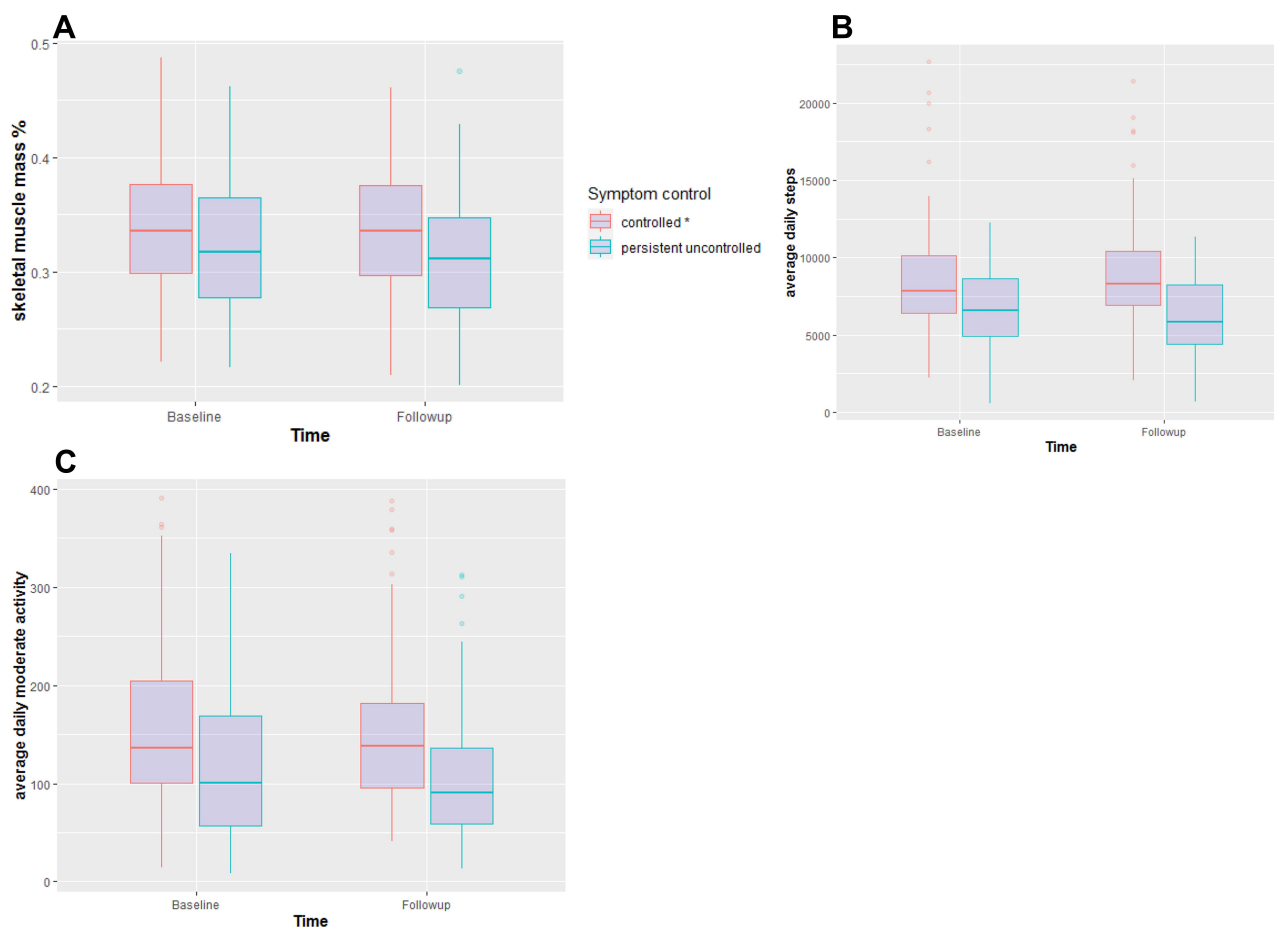


Figure 2 Longitudinal differences in muscle mass (A) average daily steps (B) and time of at least moderate activity (C) between persistent uncontrolled and controlled asthma patients at baseline and follow-up. Patients with persistent uncontrolled asthma had lower muscle mass (A), lower average daily steps (B) and time in at least moderate activity (C) at baseline and at follow-up $p < 0.01$ compared to the rest of patients.

Note: Controlled*: patients with controlled asthma at both study visits or uncontrolled symptoms at only one of the study visits.

persistent uncontrolled asthma is characterized by sustained low rather than continuous declining physical activity. Furthermore, our findings regarding the longitudinal association between asthma control and physical activity confirm previous comparable findings of cross-sectional studies from Holland, Australia and Brazil.^{4,5}

The association of physical activity with asthma outcomes, ie symptom control and body composition, supports the potential role of physical activity in asthma management. In COPD, the benefits of physical activity on disease outcomes have been addressed adequately.^{23,24} In asthma however, corresponding data are scarce. Dogra and co-workers demonstrated improvements in symptom control and quality of life of 21 asthma patients who were enrolled in a 12-week supervised exercise intervention.²⁵ Indeed, further prospective studies with larger samples are needed to establish the role of physical activity in asthma outcome.

Interestingly, we also found that both high dose ICS and long-term OCS therapy are predictors of increased fat mass and low muscle mass in asthma. However, the impact of corticosteroid therapy as predictor of body composition was exchangeable with asthma control in multivariate regressions. Therefore, based on our multivariate regression analysis, it is hard to determine whether the impact of corticosteroid therapy on body composition is to explain by the effect of corticosteroid only or whether it is attributable to other factors associated with uncontrolled asthma. While systemic corticosteroids are known to cause muscle mass depletion and fat accumulation,^{26,27} less is known about the impact of higher doses of ICS on body composition. Nevertheless, it is unlikely that the longitudinal changes in body composition are caused by systemic corticosteroid therapy only, as we observed an overall decline in the proportion of patients who were on OCS from baseline (46%) to follow-up (27%).

Our study has limitations. First, we have no follow-up data from healthy controls which might have helped demonstrating the longitudinal changes in body composition in comparison to asthma patients. However, we were able to demonstrate long-term differences of body composition among asthma patients based on asthma severity and symptom control. Second, we used BIA to study muscle mass. BIA-measured muscle mass is dependent on the relations between body composition, body water and BMI. Despite of that, BIA is a simple, feasible tool that was found to be reasonably valid compared to other standardized methods used in the assessment of body composition such like the dual X-ray absorptiometry.²⁸ Finally, we did not assess the muscle function, which might have emphasized the impact of severe uncontrolled asthma on muscle dysfunction that known to be associated with muscle depletion in COPD.²⁶ However, we used the objectively measured physical activity to correlate skeletal muscle mass with the physical performance. Further, for all we know, this is the first study to demonstrate the longitudinal association between symptom control, physical activity and body composition.

In summary, persistent uncontrolled asthma is associated with adverse changes in the body composition. Direct measures of body composition appear to be more appropriate for studying the relationship between asthma and body composition rather than the crude BMI measure. Moreover, persistent uncontrolled asthma is closely associated with sustained physical inactivity. Physical activity appears to be an independent predictor of body composition and reliable long-term marker of symptom control.

Abbreviations

ACT, asthma control test; ACQ, asthma control questionnaire; BIA, bioelectrical impedance analysis; BMI, body mass index; SM, skeletal muscle mass; FM, fat mass.

Data Sharing Statement

The datasets used during the current study are available from the corresponding author on reasonable request.

Ethics Approval

The study is a part from the prospective longitudinal All Age Asthma Cohort (ALLIANCE). The study was approved according with the Declaration of Helsinki by the ethics committee at Medical School Luebeck, Germany, and is registered at clinicaltrials.gov (pediatric arm: NCT02496468; adult arm: NCT02419274).

Acknowledgments

We thank Regine Wieland, Petra Hundack-Winter, Margret Gleiniger, Zaklina Hinz, Susann Prange, Corinna Derwort (LungClinic Grossshansdorf, Grossshansdorf, Germany) for their excellent support in study logistics.

Funding

The ALLIANCE infrastructure is provided by the participating sites of the German Centre for Lung Research (DZL) and associated study centers and hospitals. Direct costs of the ALLIANCE Cohort are being paid by project grants from the German Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung, BMBF), grant number “82DZL001A4”.

Disclosure

Mustafa Abdo reports no conflict of interest. Frederik Trinkmann received travel support from Actelion, Berlin Chemie, Boehringer Ingelheim, Chiesi, Novartis, Mundipharma and TEVA as well as speaker or consultation fees from AstraZeneca, Berlin Chemie, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, GlaxoSmithKline, Novartis and Roche, Sanofi aventis, all outside the submitted work. Anne-Marie Kirsten, Heike biller, Frauke Pedersen and Christian Herzmann report no conflict of interest. Erika von Mutius reports personal fees from Pharmaventures, personal fees from OM Pharma S. A., personal fees from Springer-Verlag GmbH, personal fees from Elsevier GmbH and Elsevier Ltd., personal fees from Peptinnovate Ltd., personal fees from Turun Yliopisto, personal fees from Tampereen Yliopisto, personal fees from Helsingin Yliopisto, personal fees from European Respiratory Society, personal fees from Deutsche Pharmazeutische Gesellschaft e. V., personal fees from Massachusetts Medical Society, personal fees from Chinese University of Hongkong, personal fees from European Commission, personal fees from Böhringer Ingelheim International GmbH, personal fees from Universiteit Utrecht, Faculteit Diergeneeskunde, personal fees from Universität Salzburg, personal fees from Georg Thieme Verlag, personal fees from Japanese Society of Pediatric Allergy and Clinical Immunology (JSPACI), outside the submitted work; In addition, Dr. von Mutius has a patent LU101064 - Barn dust extract for the prevention and treatment of diseases pending, a patent EP2361632: Specific environmental bacteria for the protection from and/or the treatment of allergic, chronic inflammatory and/or autoimmune disorders with royalties paid to

ProtectImmun GmbH, a patent EP 1411977: Composition containing bacterial antigens used for the prophylaxis and the treatment of allergic diseases licensed to ProtectImmun GmbH, a patent number EP1637147: Stable dust extract for allergy protection licensed to ProtectImmun GmbH, and a patent EP 1964570: Pharmaceutical compound to protect against allergies and inflammatory diseases licensed to ProtectImmun GmbH. Matthias V. Kopp, Gesine Hansen, Benjamin Waschki, Klaus F. Rabe and Henrik Watz reports no relevant conflict of interest. Thomas Bahmer reports grants from BMBF: Unrestricted research grant for the German Center for Lung Research (DZL), during the conduct of the study; personal fees from AstraZeneca, personal fees from GlaxoSmithKline, personal fees from Novartis, and personal fees from Roche, outside the submitted work. The authors report no other conflicts of interest in this work.

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