ORIGINAL RESEARCH All Types Obesity and Physical Inactivity Associated with the Risk of Activity of Daily Living Limitations Among People with Asthma

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Purpose: To examine the association between all types of obesity, physical inactivity, and the risk of activity of daily living limitations in people with asthma.

Patients and Methods: In this cross-sectional study, data from 2555 people aged between 25 and 74 years were acquired from the National Survey of Midlife Development in the United States Refresher conducted between 2011 and 2014. Self-reported questions were used to specify the presence or absence of asthma and physical inactivity. All participants were categorized as having no asthma or asthma. Obesity was defined based on three distinctive indicators: body mass index, waist circumference, and waist-to-hip ratio.

Results: Logistic regression analysis showed that people with asthma who had all types of obesity alone or both all types of obesity and physical inactivity were significantly (P <0.0001) almost more than three times more likely to have limitations in the activity of daily living than those without this condition, even after adjusting for all covariates. Moreover, the odds of activity of daily living limitations were 1.69 times increased in asthma patients with physical inactivity alone, but this increase in risk was not significant (P =0.465). In addition, the odds of activity of daily living limitations were significantly (P <0.0001) more than twice independently in people with asthma aged between 60 and 74 years, female, undergraduate level of education, smoking, and having joint/bone underlying diseases.

Conclusion: The results demonstrated that the presence of all types of obesity is related to a higher risk of activity of daily living limitations in people with asthma than in those without asthma. Having both all types of obesity and physical inactivity are also linked to a greater risk of activity of daily living limitations in these patients.

Keywords: asthma, obesity, physical inactivity, aging, older adults, body mass index, waist circumference, waist-to-hip ratio, activity of daily life

Introduction

The Global Initiative for Asthma (GINA) defines asthma as a chronic inflammatory disease of the airways that is characterized by a history of respiratory symptoms, such as wheezing, shortness of breath, chest tightness, and cough.¹ Asthma is a public health issue not only for high-income countries; it arises in all nations regardless of the level of growth.² Almost 300 million people of all ages and ethnic groups presently suffer from asthma worldwide.² Underdiagnosed and under-treated asthma makes a substantial burden on people and their families and often limits individuals' activities for a lifetime.³ The moderate cost per asthma-related hospital stay in the United States for adults raised from \$5200 to \$6600 from 2000 to 2010.⁴

Obesity, which affects the developed world, is both the main risk factor and a disease modifier of asthma.^{5–7} Although a dose-response relationship between obesity and asthma in adults has been encountered previously,⁸ body mass index (BMI) alone is not the most acceptable marker of obesity because the correlation between body fat and BMI is not stable.^{9,10} Assessing body fat distribution with measurements such as waist circumference (WC) or waist-to-hip ratio (WHR) may enhance the evaluation and diagnosis of obesity.⁹

Physical inactivity is a separate risk factor for numerous chronic diseases.¹¹ There is evidence pointing out that physical inactivity predisposes adults with asthma to long-term deconditioning.¹² As a result, maintaining the vicious cycle of inactivity, obesity, poorer asthma control, and difficulty performing daily activities sense trouble are frustrated, and report limitations in their social life.^{12,13}

As physical inactivity, obesity, or both are likely to be influential risk factors for the general health and well-being of adults with asthma, there is growing interest in these modifiable risk factors. The independent relationship between physical inactivity, obesity, and asthma has been studied broadly.^{14–16} However, previous work has outlined that the actual relationship between physical inactivity, obesity, and asthma has not been examined and is indistinct.¹⁷

Yet no study examined the association between all types of obesity, physical inactivity, or both with the risk of limitation in the activity of daily living (ADL) in people with asthma.¹⁸ To address this paucity in literature, the present study aimed to examine the association between obesity, physical inactivity, and the risk of ADL limitation in people with asthma. The study hypothesized that all types of obesity, physical inactivity, or both would be related to the risk of ADL limitations in this clinical population (Figure 1). Moreover, the suggested conceptual framework included the impact of aging within this clinical population. Aging may mediate the relationship between asthma-obesity phenotype and ADL limitation.¹⁹ On the other hand, aging may moderate the relationship between the reduction in physical activity and ADL limitation in people with asthma.²⁰

Materials and Methods

Data for this cross-sectional study were obtained from the National Survey of Midlife Development in the United States (MIDUS) Refresher. The MIDUS Refresher was authorized by the institutional review board (IRB) of Harvard University, Georgetown University, the University of California at Los Angeles, and the University of Wisconsin. Written informed consent was obtained from all participants. The data accessed complied with data protection and privacy regulations of the National Archive of Computerized Data on Aging (NACDA). The data sets of MIDUS Refresher were collected between 2011 and 2014 as formerly explained.²¹ The MIDUS Refresher was supported by grants from the National Institute on Aging (P01AG020166, R37AG027343).²² The research was further supported by the following grants M01-RR023942 (Georgetown), M01-RR00865 (UCLA) from the General Clinical Research Centers Program, and 1UL1RR025011 (UW) from the Clinical and Translational Science Award (CTSA) program of the National Center for Research Resources, National Institutes of Health.²² Additionally, this study was approved for IRB exemption from the ethical committee at King Saud University (#E-22-6852).

A total of 2555 individuals aged between 25–74 was included in this study. Participants were categorized into two groups (with and without asthma) based on their self-report to the following question "In the past twelve months, have you experienced or been treated for asthma?". No asthma was defined if a person answered "no" to the question, whereas

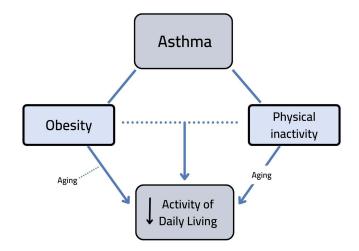


Figure I Hypothetical framework that demonstrates the association between asthma, obesity, physical inactivity, and the risk of activity of daily living (ADL) limitation.

having asthma was determined if they answered "yes" to the same question. This question is similar to the question asked in the previous study.²³

Obesity was assessed using its various indicators, such as BMI, WC, and WHR.^{24–26} BMI was calculated by dividing individuals' weight in kilograms (kg) by heights in meters (m) squared. The height measure (in inches) was multiplied by 0.0254 to obtain the height in "m". The weight (in pounds) was multiplied by 0.4536 to acquire the mass in "kg". To restrict the extremes, any heights more than 84-inch were set to 84-inch.

The subsequent questions were used to assess the WC and hip circumference (HC). "What is your waist size — that is, how many inches around is your waist?" Please measure at the level of your navel. "What is your hip size — that is, how many inches do your hips measure at the widest point?" Measured at the vastest point between your waist and your thighs. Individuals were taught to answer the above questions by measuring themselves while standing by using a non-stretchable tape. Participants were instructed to avoid measuring over clothing, including thin clothing and try to record answers to the nearest quarter (¹/₄) inch.

The WHR was computed by dividing the WC (in inches) by the HC (in inches). In computing WHR, the following rules were applied to handle extreme cases. To limit the extremes, any WC below 20 was assigned to 20, any HC below 22 was set to 22, and anything above 75 to 75. Any ratio that above or below exceeded 4 standard deviations from the mean within a gender was coded as "9" to be an extreme case and defined as a missing value.

All types of obesity were defined based on their indicators. First, having together BMI \geq 30kg/m², WC >40-inch, and WHR >0.9. Second, having a BMI greater than or equal to 30 kg/m².²⁴ Third, having a WC >40-inch for males and a WC >34.5 for females.²⁵ Fourth, having WHR >0.9 for males and WHR >0.85 for females.²⁶

Physical status was assessed based on the self-report question "How often do you engage in vigorous physical activity?"²⁷ Physical inactivity was determined if participants answered "once a month", "less than once a month", or "never" to the above question.²⁸ Physically active was defined if participants report "several times a week", "once a week", or "several times a month" to the question.

The outcome of interest was ADL limitations, assessed by asking

How much does your health limit you in lifting or carrying groceries, bathing or dressing, climbing several flights of stairs, climbing one flight of stairs, bending, kneeling, or stooping, walking more than a mile, walking several blocks, walking one block, doing a vigorous activity (eg running, lifting heavy objects)?^{29,30}

The response options were "a lot", "a little" and "not at all." The scales are constructed by calculating the mean of all the reverse-coded values of the items in each scale. Higher scores reflect a greater difficulty in performing each ADL.³¹ For missing, the scales are computed for cases that have at least one valid response to questions in the summary variable. The scale scores were not calculated for cases with no valid items on the scale and were coded as "not calculated due to missing data."

A series of covariates, such as age, sex, race, education, marital, employment, smoking, alcohol intake, and other diseases status were included. All these controlled variables were measured using dichotomous indicators for 25–59 years (reference) and 60–74 years; male and female (reference); white (reference) and minorities (black, mixed, Asian, and others); school/college and graduates (reference); married (reference) and unmarried/divorced/widow; employed and unemployed (reference); smoker and nonsmoker (reference) and alcohol consumption (yes and no). Consumption of alcohol was used as a reference. The status of other diseases was measured using dichotomous indicators yes and no (reference).

The Farrington-Manning Score test was used to estimate the required sample size for each group to prove true results by using the level of significance (alpha =0.05), power (0.8), and proportion between groups (0.36, 0.26).³² The required minimum sample for each group was yielded as 264. Shapiro–Wilk test was utilized to determine the data normality.^{33,34}

Descriptive statistics, such as mean (standard deviation) and number (percentage) were shown for constant and definite variables, respectively. The average distribution of BMI, WC, WHR, and ADL was presented for both groups. Inferential statistics, such as chi-square for categorical and independent Student's t-tests for continuous variables were used for comparisons between groups (with and without asthma).

Linear regression models were used to predict the association between obesity, physical inactivity, and the risk of ADL limitations in people with asthma compared to those with no asthma. Model 1 was unadjusted by including groups along with age, sex, race, education, marital, employment, smoking, and alcohol intake status. Model 2 was adjusted for other diseases (joint/bone, cardiovascular, and diabetes) status along with model 1. Odds ratio (OR) with associated confidence interval (95% CI) were calculated for each model.

Sensitivity analyses were conducted to test the robustness of our results by assessing the interaction between the presence of asthma and selected parameters, such as age (60–74 vs 25–59) sex (female vs male), race (Caucasian vs African American), education (undergraduate vs graduates/master), marital status (not married/divorced vs married), employment (unemployed vs employed), smoking status (smoker vs nonsmoker), alcohol intake status (yes vs no), joint/ bone disease (yes vs no), cardiovascular disease (yes vs no), and diabetes (yes vs no). All statistical analyses were accomplished using Stata 14.1 statistical software (Stata Corp, 2015). The statistical significance was determined if the P-value is <0.05.

Results

Of the 3577 participants, 2555 were included in the study. Data missing/refusal were excluded from the analysis (n =1022). Of the 2555 participants, 314 had asthma (Figure 2). People with asthma were significantly more than 2 years old than those who did not. Most patients were female (65.3%), white (79.3%), and had a Ph.D. level of education (60.2%). The participants were married (51.9%), employed (56.1%), or smokers (70.6%). A higher percentage of the participants had no alcohol intake (66.7%) or other diseases, such as joint/bone (63.7%), cardiovascular diseases (92%), and diabetes (79.3%) (Table 1).

The distribution of average scores for BMI, WC, WHR, and ADL was higher in people with asthma than in those without asthma. The average BMI, WC, and ADL scores differed significantly between groups. However, the average WHR score between the groups was not statistically significant (P = 0.641) (Figure 3).

Compared to people with no asthma, those with asthma who had obesity (defined using BMI, WC, and WHR) were significantly associated (P <0.0001) with almost 6-fold higher odds of ADL limitation even after adjusting for all covariates. Obesity defined using BMI or WC was also significantly associated with almost 5-fold and 3-fold odds of ADL limitation, respectively. Age between 60–74 years, female sex, undergraduate-level of education, smoking, and having joint/bone underlying diseases were independently more often significantly (P <0.0001) had more than 2-fold odds of ADL limitation (Table 2).

In people with asthma, physical inactivity was associated with 1.69-fold odds of ADL limitation, but this increase in risk was not significant (95% CI =0.74, 3.17) even after controlling for all covariates (95% CI =0.80, 3.54). Age between

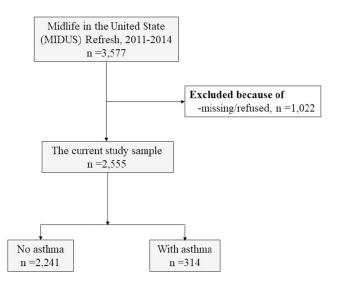


Figure 2 Flowchart of the study participants.

Characteristics	Without Asthma n =2241 (87.7%)	With Asthma n =314 (12.3%)	P value
Age in year, mean (SD)	52.0 (14.2)	54.5 (14.1)	0.0026
Age group, n (%)			0.0068
25–59 years	1419 (63.3)	174 (55.4)	
60–74 years	822 (36.7)	140 (44.6)	
Sex, n (%)			<0.0001
Female	1160 (51.8)	205 (65.3)	
Male	1080 (48.2)	109 (34.7)	
Race, n (%)			0.0096
White	1896 (85.1)	246 (79.3)	
Minorities	333 (14.9)	64 (20.7)	
Educational level, n (%)			0.0015
School/college	122 (5.4)	20 (6.4)	
Graduates/masters	989 (44.2)	105 (33.4)	
Ph.D.	1127 (50.4)	189 (60.2)	
Employment status, n (%)			0.0029
Employed	1446 (64.8)	175 (56.1)	
Unemployed	787 (35.2)	137 (43.9)	
Marital status, n (%)			<0.0001
Married	1487 (66.6)	163 (51.9)	
Separated/divorced/ widow	453 (20.3)	94 (29.9)	
Never married	293 (13.1)	57 (18.2)	
Smoking status, n (%)			0.0073
Yes	909 (61.2)	154 (70.6)	
No	576 (38.8)	64 (29.4)	
Alcohol intake, n (%)			0.0015
Yes	555 (24.9)	103 (33.3)	
No	1676 (75.1)	206 (66.7)	
Joint/bone disease, n (%)			<0.0001
Yes	414 (18.5)	114 (36.3)	
No	1827 (81.5)	200 (63.7)	

 Table I Basic Characteristics of the Study Sample, n =2555

(Continued)

Characteristics	Without Asthma n =2241 (87.7%)	With Asthma n =314 (12.3%)	P value
Cardiovascular disease, n (%)			0.0002
Yes	78 (3.5)	25 (8)	
No	2162 (96.5)	289 (92)	
Diabetes, n (%)			<0.0001
Yes	232 (10.4)	65 (20.7)	
No	2009 (89.6)	249 (79.3)	

Table I (Continued).

60-74 years, female sex, undergraduate-level of education, smoking, and having joint/bone underlying diseases were independently more often significantly (P < 0.0001) had nearly 2-fold or more odds of ADL limitation (Table 3).

Compared to adults with no asthma, those with asthma who had both obesity (defined using BMI, WC, and WHR) and physical inactivity were significantly associated (P <0.0001) with 5-fold the odds of ADL limitation even after adjusting for all covariates. Additionally, obesity (defined using either BMI or WC) and physical inactivity were significantly associated with more than 3-fold and 2-fold the odds of ADL limitation, respectively. Age between 60–74 years, female sex, undergraduate level of education, smoking, and having joint/bone underlying diseases were independently more often significantly (P <0.0001) had more than 2-fold odds of ADL limitation (Table 4).

Discussion

The present study examined the association between all types of obesity, physical inactivity, and the risk of ADL limitation in people with asthma compared with those without asthma. The results of this study revealed that a higher risk

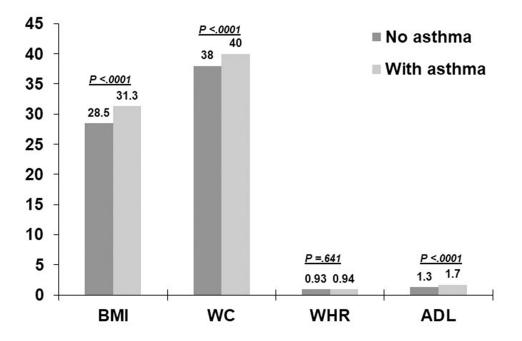


Figure 3 The average score by asthma status.

Abbreviations: ADL, the activity of daily life; BMI, body mass index; WC, waist circumference; WHR, waist-to-hip ratio.

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	Model I		M	odel 2
	OR	95% CI	OR	95% CI
Obesity [†]	6.16	2.82, 13.4	5.79	2.65, 12.6
Obesity [‡]	5.09	2.22, 11.6	4.77	2.07, 10.9
Obesity ^π	3.50	1.20, 10.1	2.76	1.01, 8.09
Obesity [€]	1.46	0.61, 3.51	1.53	0.64, 3.66
60–74 years	3.24	1.79, 5.87	3.18	1.76, 5.74
Female	2.57	1.29, 5.12	2.34	1.18, 4.61
Caucasians	1.13	0.55, 2.29	1.16	0.56, 2.36
Undergraduates	2.55	1.38, 4.72	2.43	1.30, 4.54
Unemployed	1.45	0.83, 2.51	1.29	0.74, 2.25
Not married/divorced	1.65	0.95, 2.86	1.61	0.93, 2.80
Smoker	2.13	1.11, 4.07	2.12	1.01, 4.09
Alcohol intake	1.34	0.75, 2.39	1.34	0.74, 2.42
Joint/bone disease			2.35	1.34, 4.11
Diabetes			0.83	0.42, 1.64
Cardiovascular disease			1.53	0.66, 3.57

able 2 Association Between Obes	ty and the Risk of Activity of Daily	y Living in People with Asthma
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of ADL limitation is linked to the presence of all types of obesity in people with asthma than in those without asthma. Moreover, the findings showed a greater risk of ADL limitation is linked to all types of obesity and physical inactivity in this clinical population. It is noteworthy that age between 60 and 74 years, female sex, undergraduate level of education, smoking, and joint/bone underlying diseases were independently linked to the risk of ADL limitation.

These results seem to be consistent with another research that found that older adults with poor asthma control were near twice the odds to have ADL limitations in bathing, dressing, walking, toileting, and transferring than older adults with well-controlled asthma.²⁰ That study findings have also shown that patients with one or more ADL limitations were more likely to be female, have less than high school education, have an income \leq \$1350 per month, and are unmarried. Another recent longitudinal study found that abdominal obesity measured using WC remained associated with disability incidence (reported difficulty in at least one ADL), even after controlling for BMI, gender, age, low grip strength, cognitive impairment, physical inactivity, and chronic diseases.³⁵ However, those studies were limited to older adults who lived in New York City, Chicago, or São Paulo, had somewhat methodologically issues in design, study population, and differed in outcome studied.

Findings from the present study are contrary to that of older studies that found no significant difference in ADL items among asthmatic older patients compared to those without asthma.^{36,37} However, that study had shown that adults with asthma significantly had a higher dependence on instrumental ADL, such as telephone use, shopping, and cooking in comparison with a control group matched for age and sex. However, these studies had methodological limitations in study design, setting, population, and outcome.

In contrast to the aforementioned studies, the current study findings were homogeneous concerning people with asthma who had obesity, physical inactivity, or both. In this study, widely used and well-validated self-reported and

Notes: Bolded values are significant. [†]Obesity was defined as having together BMI ≥30kg/m², WC >40-inch, and WHR >0.9. [‡]Obesity was defined as having BMI ≥30kg/m for both genders. ^πObesity was defined as having WC >40-inch for males and WC >34.5 for females. [€]Obesity was defined as having WHR >0.9 for males and WHR >0.85 for females. **Abbreviations**: OR, odds ratio; CI, confidence interval.

	Model I		Model 2	
	OR	95% CI	OR	95% CI
Physical inactivity	1.54	0.74, 3.17	1.69	0.80, 3.54
60–74 years	2.95	1.64, 5.32	2.56	1.41, 4.66
Female	1.88	1.04, 3.39	1.90	1.03, 3.49
Caucasians	1.08	0.53, 2.22	1.13	0.54, 2.35
Undergraduates	2.47	1.35, 4.52	2.33	1.26, 4.30
Unemployed	1.24	0.71, 2.16	1.10	0.63, 1.94
Not married/divorced	1.48	0.85, 2.58	1.42	0.81, 2.49
Smoker	2.09	1.09, 3.99	2.15	1.11, 4.16
Alcohol intake	1.27	0.69, 2.32	1.24	0.67, 2.29
Joint/bone disease			2.31	1.32, 4.05
Diabetes			0.95	0.48, 1.90
Cardiovascular disease			2.20	0.94, 5.11

Table 3 Association Between Physical Inactivity and the Risk of Activity of Daily Living in People with	
Asthma	

Note: Bolded values are significant.

Abbreviations: OR, odds ratio; Cl, confidence interval.

objective measures of asthma, physical inactivity, ADL, and all kinds of obesity for adult populations were used. Moreover, analyses that are appropriately adjusted for key confounders, such as age, gender, race, education, employment, marital status, smoking, alcohol intake, and comorbidity, mainly joint/bone diseases. Thus, the present study findings are the first and new that firmly establish an independent association of all kinds of obesity, physical inactivity, and both (all kinds of obesity and physical inactivity) with the risk of ADL limitation in people with asthma. Similar to findings from this study, other research has suggested that the risk of ADL limitation in asthma patients is associated with aging, being female, having less education, poor income per month, being unmarried, current smoker, and having joint/bone diseases.^{20,38–40}

Unexpectedly, there was no significant association between obesity (defined using WHR) and ADL limitation in people with asthma. The reason for this is not clear, but it may have something to do with study design because an earlier study has shown that abdominal fat and obesity were positively associated with ADL limitation approximately 9 years later among African American, white men, and women.⁴¹ In addition, no differences were found between physical inactivity and the risk of ADL limitation in people with asthma compared to those with no asthma. A possible explanation for this result may be physical activity was assessed based on the self-report. A reporting bias may have occurred. Thus, an objectively measured physical activity level may be necessary to establish a reliable relationship with the risk of ADL limitation in people with asthma. Another possible reason is that airflow limitation and shortness of breath while doing physical activity may lead to physical inactivity. Particularly, the adults with asthma had more than a 3-fold greater risk of persistent airflow limitation than the people with severe asthma that began before the age of 18 years has been reported in the previous study.⁴²

The findings of this study must be interpreted with caution because somewhat limited due to the cross-sectional design. In this design, the data limits making causal inferences regarding the association between obesity, physical inactivity, and ADL limitation in people with asthma.⁴³ Another limitation was the potential bias of self-reporting of asthma, physical inactivity, and the outcome of ADL limitation. Although this study showed a strong association between all types of obesity, physical inactivity, and ADL limitations, these results may be biased by self-reported asthma. In

	Model I		Mo	del 2
	OR	95% CI	OR	95% CI
Obesity [†] and physical inactivity	5.06	2.44, 10.4	5.04	2.41, 10.5
Obesity [‡] and physical inactivity	3.40	1.55, 7.46	3.47	1.57, 7.66
Obesity $^{\!$	2.58	1.01, 7.18	2.53	1.00, 7.15
Obesity [€] and physical inactivity	1.06	0.43, 2.62	1.37	0.55, 3.42
60–74 years	3.52	1.97, 6.31	3.17	1.76, 5.71
Female	2.13	1.14, 4.00	2.01	1.06, 3.82
Caucasians	1.06	0.52, 2.13	1.07	0.53, 2.17
Undergraduates	2.79	1.50, 5.17	2.73	1.46, 5.12
Unemployed	1.34	0.77, 2.32	1.15	0.65, 2.00
Not married/divorced	1.66	0.96, 2.88	1.62	0.93, 2.82
Smoker	2.16	1.13, 4.11	2.18	1.13, 4.19
Alcohol intake	1.24	0.69, 2.21	1.25	0.69, 2.26
Joint/bone disease			2.37	1.35, 4.16
Diabetes			0.89	0.45, 1.74
Cardiovascular disease			1.81	0.78, 4.18

Table 4 Association of Obesity	Indicators and Physical	Inactivity with the	e Risk of Activity of	of Daily
Living in People with Asthma				

Notes: Bolded values are significant. [†]Obesity was defined as having together BMI ≥ 30 kg/m², WC >40-inch, and WHR >0.9. [‡]Obesity was defined as having BMI ≥ 30 kg/m for both genders. [#]Obesity was defined as having WC >40-inch for males and WC >34.5 for females. [€]Obesity was defined as having WHR >0.9 for males and WHR >0.85 for females. **Abbreviations:** OR, odds ratio; CI, confidence interval.

addition, this study cannot examine the longitudinal association of obesity and physical inactivity on the risk of ADL limitation in people with asthma. However, the primary strength of this is the larger sample size with more than 80% power has shown a statistically significant relationship.⁴⁴

The results of this study, while preliminary, suggest that obesity and a sedentary lifestyle are associated with functional impairment and negative health consequences in people with asthma. This study's findings have important implications for developing lifestyle interventions in asthma care and pulmonary rehabilitation that address all kinds of obesity, physical inactivity, and ADL limitation. Previous studies presented herein the promising lifestyle interventions emerging in asthma care and the role of pulmonary rehabilitation that target weight loss, physical inactivity, lifestyle interventions.^{45,46}

Conclusion

The present study aimed to examine the association between all types of obesity, physical inactivity, and risk of ADL limitation in people with asthma. This study showed that the presence of all types of obesity was associated with a greater risk of ADL limitations in people with asthma than in those without asthma. The second finding was that both all types of obesity and physical inactivity were associated with a higher risk of ADL limitation in these patients. The study also showed that age between 60 and 74 years, female sex, undergraduate level of education, smoking, and joint/bone underlying diseases were independently linked to the risk of ADL limitations. Moreover, the current study findings highlight the importance of developing lifestyle interventions in asthma care and pulmonary rehabilitation that address all kinds of obesity, physical inactivity, and ADL limitation in this clinical population. Future studies are needed to

determine the longitudinal relationship of modifiable behaviors, such as obesity (normal, central, abdominal, etc.) and physical inactivity in preventing or delaying the onset of ADL limitation in people with asthma in addition to aging, smoking, and/or comorbidities.

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Disclosure

The authors report no conflicts of interest in this work.

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1583