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Risk Factors and Clinical Outcomes Associated with Fixed Airflow Obstruction In Older Adults with Asthma

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Abstract

Background—Asthma in older adults is associated with increased morbidity and mortality compared to younger patients. Fixed airflow obstruction (FAO) is associated with decreased survival in younger patients, but its significance remains unclear in older adults with asthma.

Objective—To identify risk factors and outcomes related to FAO in older adults with asthma.

Methods—Subjects over age 55 with a physician diagnosis of persistent asthma were evaluated. Data collected included: participant demographic information; medications; asthma exacerbations; asthma control test (ACT); asthma quality of life (AQLQ); comorbidities; spirometry; atopic status; and fractional exhaled nitric oxide (FeNO). Clinical characteristics and outcomes associated with FAO (defined as FEV1/FVC post-bronchodilator value ≤ 70%) were assessed.

Results—A total of 186 participants were analyzed (48 males and 138 females, mean age 66 years). FAO was demonstrated in 30% of participants. Using regression analysis, predictors of

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Clinical Trial Registration

Database number NCT01979055. URL: https://clinicaltrials.gov/ct2/show/NCT01979055

Conflict of Interest

Dr. Bennett, Ms. Carpenter, Ms. Hao, Dr. Song, Dr. Steinberg, and Dr. Baptist have no potential conflicts of interest to disclose.

Authorship

Dr. Bennett participated in data generation; analysis and interpretation of the data; and preparation and critical revision of the manuscript.

Ms. Carpenter participated in: conception and design of the study; data generation; analysis and interpretation of data; and preparation and critical revision of the manuscript.

Ms. Hao participated in data generation; analysis and interpretation of the data; and preparation and critical revision of the manuscript.

Dr. Song participated in data generation; analysis and interpretation of the data; and preparation and critical revision of the manuscript.

Dr. Steinberg participated in data generation; analysis and interpretation of the data; and preparation and critical revision of the manuscript.

Dr. Baptist participated in: conception and design of the study; data generation; analysis and interpretation of data; and preparation and critical revision of the manuscript.

FAO included advanced age; African American race; male gender; and longer duration of asthma. In outcomes analysis, FAO was associated with a worsened ACT and AQLQ; however, after controlling for confounding factors, logistic regression revealed no association. No significant association was found amongst FAO and exacerbations, FeNO, atopy, rhinitis, education level, depression, smoking or BMI.

Conclusion—Risk factors associated with FAO in older adults with asthma include advanced age, African American race, increased asthma duration and male gender. Unlike younger patients, FAO is not independently associated with worsened asthma control, quality of life, or exacerbations in older asthmatic patients.

Keywords

asthma; fixed airflow obstruction; reversibility; older adults

Introduction

Asthma is a chronic disease resulting in episodic airflow obstruction secondary to inflammation and bronchospasm of the respiratory tract. The prevalence of asthma in the United States has continued to escalate, resulting in an increase in both healthcare costs and morbidity/mortality in the affected population[1]. At particular risk is an increasing proportion of older adults with asthma; it is estimated that 1 in 5 patients with asthma will be above age 65 by 2050, with prevalence increases in the older population continuing to outpace the younger[2]. It has been well-documented that morbidity and mortality in older adults with asthma is greater than that of the younger population, with a confluence of theorized contributing factors[3]. Patients above age 55 have higher rates of ED visits, hospitalization, and asthma-associated healthcare costs compared to those under age 55[4]. In fact, persons aged 55 and older demonstrate the highest asthma mortality rate compared to all other persons with asthma combined[5]. Despite this, asthma in older adults continues to be an under-recognized and under-treated epidemic[6].

While most patients initially demonstrate reversibility with bronchodilators and/or other asthma medications, known as reversible airflow obstruction (RAO), some patients will progress to irreversibility of airflow obstruction, deemed fixed airflow obstruction (FAO). The estimated prevalence of FAO has been previously reported between 8% and 49% in patients with asthma, a wide-ranging estimate[78]. In fact, a universal consensus has yet to be established in defining objective measures of FAO[79–19]. For the purposes of this study, the most commonly used and accepted definition of FAO (FEV1/FVC post-bronchodilator treatment value less than 70%) was utilized[121618].

Relatively few studies have been performed to evaluate risk factors for FAO, with significant heterogeneity amongst inclusion/exclusion criteria[79–19]. Some proposed risk factors for FAO include adult-onset asthma, older age, African American race, male gender, and a history of smoking based on analyses of patient populations 18 years and older. Paradoxically, the presence and absence of allergic rhinitis has also been highlighted as a risk factor [78131418]. Despite these findings, there have been no prior studies exclusively related to older adults with asthma, the population at greatest risk for morbidity and mortality[16].

The significance of FAO with regard to clinical outcomes in older adults with asthma also remains unclear. Poorer prognoses have been associated with FAO in younger populations[9], but no studies have evaluated the significance of FAO in older adults with asthma related to NIH core asthma outcomes recommendations[1620]. It is currently unknown if older adults with FAO experience poorer outcomes, as is seen in younger adults.

The goal of this study was to examine clinical characteristics, including risk factors and clinical outcomes, associated with FAO in older adults with asthma.

Methods

Participants and Protocol

As part of a blinded, randomized controlled study of older adults with asthma (NCT01979055), participants were recruited from two academic institutions in Michigan serving a diverse population of older adults. Investigators recruited subjects above the age of 55 with a physician diagnosis of persistent asthma, the age above which asthma mortality rates are the greatest[21]. Based on previous data collection from the Centers for Disease Control and Prevention (CDC), in addition to other prospective trials, the age of 55 years was used as a threshold for older adults in our study[22–25]. An additional analysis was performed limiting patient age to 65 years or greater and is included in the supplementary materials section. Persistent asthma was defined according to NIH guidelines, including answering yes to the following questions: “Has a doctor or health care provider ever told you that you have asthma?”; “Do you still have asthma?”; and “Do you take any medicine or inhalers for your asthma every day?”. Exclusionary criteria included any other significant cardiopulmonary disease (including chronic obstructive pulmonary disease or emphysema); current smokers; a greater than 20 pack-year smoking history (as this level has been associated with the development of COPD)[26]; a lack of telephone access; or significantly impaired cognitive capacity. Computed tomography scans to assess for emphysematous changes were not performed. Institutional review board approval and written informed consent were obtained.

Data Collection

Demographics—A baseline questionnaire was administered to all study participants. Items assessed included: age; gender; race; self-reported ethnicity; education level; asthma medications (including dose and frequency); smoking history; age at diagnosis of asthma; exacerbations over the past year; depression screening; health comorbidities; and body mass index (BMI). To identify depression in asthma patients, the short-form Geriatric Depression Scale (GDS) was utilized; a score greater than 5 is suggestive of depression[27]. To assess education level, participants identified their highest level of completed education. Choices included below high school; high school completion; 2-year college completion; 4-year college completion; and post-graduate completion. To assess concomitant medical conditions (comorbidities), participants identified the presence or absence of previously diagnosed medical conditions consisting of heart disease; hypertension; stroke; or cancer.

Asthma-related assessments—To assess perceptions of quality of life in asthma patients, the mini Asthma Quality of Life Questionnaire (AQLQ) was utilized. The AQLQ questionnaire is the most commonly used measure of quality of life in those with asthma[28]. Subjective perceptions of asthma control were evaluated using the Asthma Control Test (ACT). A score less than 20 is suggestive of a patient perception of poor asthma control[29]. Asthma exacerbations were defined as self-reported medical care usage (with asthma as the primary reason) over the previous 12 months for 1) hospitalization; 2) emergency department visits; 3) unscheduled doctor/clinic visits for urgent asthma treatment; 4) systemic glucocorticoid use; this is consistent with NIH core asthma outcomes[20]. Asthma severity was determined using the NIH NAEPP guidelines[30]. These guidelines, based on asthma medication use, classify asthma severity on a scale of 1 (mild) to 6 (severe) (Supplemental Table 1.).

Measures of lung function—To assess lung function parameters, a spirometer was utilized (EasyOne Plus Model 2001; Zurich, Switzerland) and results were compared to published predicted values at baseline and after combination short-acting beta-agonist/anticholinergic administration[31]. The maximal bronchodilator response was determined 10 minutes after inhaling nebulized ipratropium bromide and albuterol (0.5 mg/3 mg per 3 mL) after discontinuation of a short-acting beta agonist (SABA) for at least six hours and long-acting beta-agonist (LABA) for at least twelve hours. FAO was defined as FEV1/FVC post-bronchodilator treatment value less than 70%, the most commonly used and accepted definition[121618]. Fractional exhaled nitric oxide was measured with a pre-calibrated nitric oxide monitor (Aerocrine AB Model 510(k); Solna, Sweden).

Atopy—To assess atopic status, participants underwent skin-prick testing at baseline evaluation after discontinuation of antihistamine medications for at least 5 days. Atopy was defined by the presence of at least one positive skin-prick test, administered via ComforTen® applicator, to the tested aeroallergens (house dust mite, mixed grass pollen, mixed tree pollen, mixed weed pollen, mold mix, cockroach, cat dander, dog dander). Positive histamine and negative saline controls were also placed. A positive skin-prick test was defined by a wheal at least 3 mm greater than the negative saline control.

Statistical Analysis

To compare the differences between the FAO and RAO groups, two sample t-test and chi-square tests were carried out for continuous and dichotomized variables. The logistic regression analysis was conducted to fit the dichotomized response, being FAO or RAO, with demographic covariates adjusted as indicated. The estimated odds of FAO compared to the odds of RAO were also calculated and provided. SAS version 9.3 (SAS Institute Incorporated; Cary, NC) was utilized for the analyses.

Results

A total of 186 participants were analyzed. The mean age of participants was 66 years (range 58.6 to 73.4 years) with a 25.8% male and 32.3% African American distribution. The average asthma duration was 32.1 years, with average BMI 31.2. Of the 186 older adults

with asthma, 56 (30%) demonstrated FAO according to study criteria. The majority of participants (n=113; 60.8%) demonstrated atopy, and the mean FeNO value was 28.7 parts per billion. Participants with RAO demonstrated a significant post-treatment improvement in FEV1/FVC compared to those with FAO (Table 1.).

When limiting the analysis to those aged 65 years and above, a total of 97 participants were included. The mean age of participants was 71.3 years with a similar gender, race, asthma duration, and BMI distribution. Of the 97 older adults with asthma, 34 (35%) demonstrated FAO.

Risk Factors for FAO

As compared to those with RAO, stratified group comparison revealed a significant association between FAO and African American race, male gender, increased duration of asthma and increased comorbidities (Table 1.). Patient age revealed borderline significance ($p = 0.07$) in association to those with FAO. After controlling for confounding factors, regression analysis identified independent risk factors associated with FAO to include male gender, increased duration of asthma, older participants, and African American race (Table 2.). Male gender was recognized as an independent risk factor for the development of FAO, with an almost 4-fold increased risk (OR= 3.98). FAO was independently associated with a longer duration of asthma in older adults. For every decade with asthma, the risk for FAO in older adults with asthma increased by 36%. African American race in older adults with asthma was linked with an increased risk of FAO by a factor of more than 4. FAO was also correlated with age. For every decade of life in older adults with asthma, their risk of FAO was increased by 85%. Asthma severity, smoking, atopy, depression, comorbidities, education level, rhinitis and BMI were not independently associated with FAO using regression analysis.

When limiting to those aged 65 years and above, stratified group comparison revealed a significant association between FAO and African American race, increased duration of asthma, and increased comorbidities (Supplemental Table 2.). After controlling for confounding factors, regression analysis identified independent risk factors associated with FAO to include increased duration of asthma; male gender and African American race revealed borderline significance (Supplemental Table 3.). For every decade with asthma, the risk for FAO in older adults above 65 increased by 53% (OR= 1.53, 95% CI: 1.13–2.08). Asthma severity, smoking, atopy, depression, comorbidities, education level, rhinitis and BMI were not independently associated with FAO using regression analysis.

Clinical Outcomes Associated with FAO

As compared to those with RAO, stratified group comparison revealed that those with FAO had lower subjective asthma scores (Table 3.). In older adults who demonstrated FAO, ACT scores were lower (16.3 vs. 18.2, $p = 0.01$). In those older adults with FAO, AQLQ scores were also lower (4.8 vs. 5.3, $p = 0.008$); these lower AQLQ scores correlate with a perception of a worsened quality of life in participants with FAO. However, after controlling for confounding factors using regression analysis, there was no significant difference amongst the groups (Table 4.). Logistic regression did reveal systemic glucocorticoid use,

rhinitis, education level, and BMI as independent risk factors associated with poor perception of asthma control and quality of life. There was no significant difference in clinical outcomes pertaining to exacerbations (hospitalization; ED visits; unscheduled doctor/clinic visits for urgent treatment; or systemic glucocorticoid use) between FAO and RAO (Table 3.). Logistic regression revealed asthma severity as the only independent risk factor associated with exacerbations in older adults with asthma (OR= 1.86, 95% CI = 1.36 – 2.54) (Supplemental Table 4.).

When limiting to those aged 65 years and above, similar findings were demonstrated. As compared to those with RAO, stratified group comparison revealed that those with FAO had lower subjective asthma quality of life scores, but not asthma control (Supplemental Table 5.). However, after controlling for confounding factors using regression analysis, there was no significant difference amongst the groups (Supplemental Table 6.). Logistic regression did reveal systemic glucocorticoid use as an independent risk factor associated with poor perception of asthma quality of life. There was no significant difference in clinical outcomes pertaining to exacerbations (hospitalization; ED visits; unscheduled doctor/clinic visits for urgent treatment; or systemic glucocorticoid use) between FAO and RAO.

Discussion

Our findings identify the prevalence of FAO in older adults with asthma at a rate of 30%, compared to previously reported incidence rates for all age groups between 8% and 49%[8]. Using regression analysis, in older adults, FAO is associated with older participants, male gender, African American race, and a longer duration of asthma. No significant association was found amongst FAO and asthma severity; smoking; atopy; or FeNO, which is disparate from previous studies of younger populations[8–19]. Additionally, no association was found amongst FAO and BMI or education levels.

Compared to those with RAO, there was no difference in exacerbations (hospitalization; ED visits; unscheduled doctor/clinic visits for urgent treatment; systemic glucocorticoid use) in those with FAO; this lack of association differs from that seen in younger patients with FAO[9]. A similar discordance was recently demonstrated when assessing obesity and asthma morbidity in older versus younger asthmatic patients[32]. While bivariate group comparison did show differences in subjective asthma scores, after controlling for confounding factors ACT and AQLQ scores were not significantly different. Asthma severity, rhinitis, education level, and BMI were identified as independent predictors of worsened outcomes in older asthmatic patients, which are consistent with prior reports[133334]. Although depression did not impact outcomes in our study, it has been previously noted to do so in older adults with asthma[3536].

To our knowledge, this is the first study to evaluate predictors and outcomes associated with FAO in older adults diagnosed with persistent asthma, the population with the highest asthma morbidity and mortality. Previous studies have demonstrated an association amongst FAO and potentially poorer healthcare outcomes in younger populations with asthma[916]. However, in our study of older adults with asthma, lung function assessments (FEV1, FeNO, FAO) did not play a role in predicting ACT, AQLQ, or asthma exacerbations. In fact, as

opposed to younger patients, lung function optimization may be a misguided goal for older populations with asthma. Other investigators have demonstrated no advantage in asthma outcomes with the use of peak flow monitoring in older adults with asthma[37]. Therefore, healthcare providers should focus on other previously established risk factors including asthma severity (determined by medication use, *not* lung function tests), systemic corticosteroid use, socioeconomic status with education as a proxy, depression and BMI to improve outcomes for older adults[3,32–38].

Limitations of the study include a patient population limited to the Midwestern United States; exclusion of participants with prior diagnoses of COPD and emphysema, which has the potential for excluding those with the Asthma COPD Overlap Syndrome (ACOS); and baseline data obtained at a single visit, non-reflective of the potential vacillating nature of asthma. While it is possible that the study had potential for misdiagnosis of asthma by healthcare providers, asthma was defined using commonly accepted criteria for diagnosis[37,39]. It is possible that asthma severity could be misclassified based on the criteria of asthma medication use, but other large-scale studies have also used asthma medications to classify asthma severity[35,40]. Additionally, although characteristic associations were identified in our study, causality cannot be inferred in a cross-sectional study. While it is possible that the study was underpowered to find differences in asthma exacerbations, this is unlikely, as the p-value was 0.997, and the specific components of asthma exacerbations were equally split between the two groups. While the demographic of patients aged 55 and above is broad, future studies are required to further analyze select patient populations, including those categorized as the “very old” (>80 years) and ACOS[41].

Despite limitations, the results suggest that independent risk factors associated with FAO in older adults with asthma include male gender, older participants, African American race, and increased duration of asthma. Unlike younger patients, our results suggest that FAO is not implicated in poorer asthma outcomes in older adults, placing less emphasis on lung function maximization for optimal care outcomes in this population. Asthma is a complex disease, and further isolation of germane risk factors is paramount for optimal evaluation, diagnosis, management and counseling related to the treatment of older adults with asthma.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

FAO	fixed airflow obstruction
NIH	National Institutes of Health

NAEPP	National Asthma Education and Prevention Program
COPD	chronic obstructive pulmonary disease
FeNO	fractional exhaled nitric oxide
ppb	parts per billion
BMI	body mass index
GDS	geriatric depression scale
AQLQ	asthma quality of life
ACT	asthma control test
FEV1	forced expiratory volume in 1 second
FVC	forced vital capacity
SABA	short-acting β2-agonist
LABA	long-acting β2-agonist
OR	odds ratio
ER	emergency room
SD	standard deviation

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Table 1

Baseline participant data *

	FAO	RAO	p-value
Number of participants	56	130	
African American	55.4 (31)	22.3 (29)	<0.0001
Male gender	37.5 (21)	21.5 (28)	0.04
Asthma duration, yr (SD)	40.8 (21.3)	28.4 (19.5)	0.0001
Comorbidities [1]	1.1	0.8	0.005
Age, yr (SD)	67.7 (9.0)	65.2 (6.4)	0.07
Smoking duration, pack-years (SD)	2.9 (6.2)	2.3 (5.4)	0.46
Education level [2]	3.4	3.6	0.26
Atopy	62.5 (35)	60 (78)	0.75
Rhinitis	76.8 (43)	72.3 (94)	0.52
Depression	23.3 (13)	23.9 (31)	0.93
BMI	31.1	31.2	0.94
Asthma severity score [3]	3.5	3.6	0.66
FeNO value [4]	33	26.9	0.2
FEV1 pre-treatment, % predicted (SD)	54.5 (16.1)	77.1 (18.4)	<0.0001
FEV1 post-treatment, % predicted (SD)	61.1 (16.3)	81.8 (16.8)	<0.0001
FEV1 difference (post - pre), % (SD)	6.5 (9.8)	4.7 (9.4)	0.22
FEV1/FVC, pre-treatment value (SD)	61.1 (10.6)	76.1 (6.8)	<0.0001
FEV1/FVC, post-treament value (SD)	61.1 (8.2)	79.4 (5.2)	<0.0001
FEV1/FVC difference (post - pre), % (SD)	0.007 (9.6)	3.3 (5.7)	0.02

* Data presented as % (n) unless otherwise indicated

FAO = fixed airflow obstruction; RAO = reversible airflow obstruction; BMI = body mass index; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity

[1] Average number of comorbidities including heart disease; hypertension; stroke; or cancer

[2] 1 = below high school; 2 = high school; 3 = 2-yr college; 4= 4-yr college; 5= post-graduate degree

[3] NIH NAEPP severity score on a scale of 1 (mild) to 6 (most severe)

[4] FeNO = fractional exhaled nitric oxide (in parts per billion)

Table 2

Logistic regression of factors associated with FAO

	p-value	OR	95% Confidence Interval
Male gender	0.005	3.98	(1.51, 10.54)
Asthma duration by decade	0.004	1.36	(1.10, 1.67)
African American race	0.009	4.29	(1.45, 12.76)
Age (by decade)	0.050	1.85	(1.01,3.40)

OR = odds ratio

Table 3

Outcomes in older adults with asthma *

	FAO	RAO	p-value
Asthma control test score - ACT (SD)	16.3 (4.7)	18.2 (4.5)	0.01
Asthma quality of life score - AQLQ (SD)	4.8 (1.3)	5.3 (1.1)	0.008
Asthma exacerbations	55.4 (31)	55.4 (72)	0.997
Hospitalization	14.6 (8)	9.2 (12)	0.29
ER visit	23.2 (13)	14.6 (19)	0.15
Unscheduled medical visit	32.1 (18)	34.4 (44)	0.77
Glucocorticoid use	42.9 (24)	49.2 (62)	0.43

* data presented as % (n) unless otherwise indicated

Table 4

Linear regression of predictors of ACT and AQLQ

	β	95% Confidence Interval	p−value
ACT			
Race	−2.37	(−4.0, −0.78)	0.004
Systemic glucocorticoid use	−1.89	(−3.16, −0.62)	0.004
Rhinitis	−1.92	(−3.33, −0.51)	0.008
Education level	0.65	(0.06, 1.24)	0.03
Fixed airflow obstruction (FAO)	0.04	(−1.61, 1.69)	0.96
Gender	−0.43	(−1.90, 1.04)	0.57
Age	−0.07	(−0.97, 0.83)	0.87
Asthma severity score[1]	−0.47	(−1.0, 0.06)	0.09
Asthma duration	−0.05	(−0.38, 0.28)	0.75
Atopy	0.66	(−0.65, 1.97)	0.33
Depression	−0.63	(−2.10, 0.84)	0.4
BMI	−0.05	(−0.13, 0.03)	0.31
Comorbidities[2]	−0.47	(−1.37, 0.43)	0.31
Fractional exhaled nitric oxide (FeNO)	−0.01	(−0.03, 0.01)	0.21
FEV1, %	0.03	(−0.01,0.07)	0.09
AQLQ			
Race	−0.86	(−1.25, −0.47)	0.0001
Systemic glucocorticoid use	−0.49	(−0.80, −0.18)	0.002
Rhinitis	−0.56	(−0.89, −0.23)	0.001
BMI	−0.02	(−0.04, 0.01)	0.03
Asthma severity score[1]	−0.14	(−0.28, −0.01)	0.04
Education level	0.15	(0.01,0.29)	0.05
Fixed airflow obstruction (FAO)	−0.17	(−0.56, 0.22)	0.41
Gender	−0.31	(−0.66, 0.04)	0.09
Age	0.06	(−0.16, 0.28)	0.6
Asthma duration	0.02	(−0.06, 0.10)	0.57
Atopy	0.01	(−0.30, 0.32)	0.95
Depression	−0.14	(−0.49, 0.21)	0.45
Comorbidities[2]	−0.08	(−0.30, 0.14)	0.47
Fractional exhaled nitric oxide (FeNO)	0.002	(−0.01,0.01)	0.51
FEV1, %	0.005	(−0.01,0.02)	0.28

ACT = asthma control test; AQLQ = asthma quality of life

FEV1 = forced expiratory volume in 1 second, pre-treatment (% predicted)

[1] NIH NAEPP severity score on a scale of 1 (mild) to 6 (most severe)

[2]Comorbidities including heart disease; hypertension; stroke; or cancer