Asthma and Chronic Obstructive Pulmonary Disease Overlap in Women

Incidence and Risk Factors

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Abstract

Rationale: Women with asthma are at a high risk of developing chronic obstructive pulmonary disease (COPD) or asthma and COPD overlap syndrome (ACOS) as they age, which is a condition associated with a high mortality rate, low quality of life, and high healthcare costs. However, factors influencing the development of ACOS remain unclear.

Objectives: To quantify the risk of developing COPD in women in Ontario with asthma and identify factors that are associated with increased risk.

Methods: Data for women in Ontario with asthma who participated in the Canadian National Breast Screening Study from 1980 to 1985 were linked to health administrative databases, and participants were followed from 1992 to 2015. A competing risks survival model was used to measure the associations between sociodemographic, lifestyle, and environmental risk factors and time to COPD incidence, accounting for death as a competing risk.

Results: A total of 4,051 women with asthma were included in the study, of whom 1,701 (42.0%) developed COPD. The mean age at the study end date was 79 years. Low education, high body mass index, rurality, and high levels of cigarette smoking were associated with ACOS incidence, whereas exposure to fine particulate matter, a major air pollutant, was not.

Conclusions: Individual risk factors appear to play a more significant role in the development of ACOS in women than environmental factors, such as air pollution. Prevention strategies targeting health promotion and education may have the potential to reduce ACOS incidence in this population.

Keywords: asthma; COPD; women; risk factors; epidemiology

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Asthma and chronic obstructive pulmonary disease (COPD) overlap syndrome (ACOS) is a chronic respiratory condition associated with increased respiratory exacerbations, hospitalizations, and healthcare costs, compared with asthma or COPD alone (1–4). Compared with those with asthma or COPD alone, those with ACOS have been shown to have the lowest quality of life and the greatest number of comorbidities (4–6). ACOS is of particular concern for women, as several studies have identified sex differences in the incidence of ACOS, with women at a higher risk of developing the condition than men (6–10). Similarly, there is evidence of an alarming increase in ACOS prevalence in women in recent years (11, 12), the underlying reasons for which largely remain unexplained. Considering that ACOS is a relatively newly recognized classification, the increase in incidence and prevalence may be in part attributable to increased recognition and possible overdiagnosis. Women also have a higher mortality rate from ACOS than men (10). Thus, preventing the progression of asthma to ACOS continues to be an important public health problem (13).

Several other risk factors, in addition to female sex, have shown associations with ACOS diagnosis, such as older age, cigarette smoking, outdoor air pollution, occupational exposures, respiratory infections, and socioeconomic status (SES) (8, 13–15). However, much of the previous literature on risk factors for ACOS has compared clinical profiles of the three diseases (asthma, COPD, and ACOS), with a lack of attention to risk factors for disease development, especially independent of cigarette smoking (9, 14, 16). Research has shown that women make up a larger proportion of the nonsmoker COPD population than men, suggesting that they may be more vulnerable to risk factors other than cigarette smoking, compared with men (7, 17). Identifying the roles of modifiable risk factors in the progression from asthma to COPD is imperative for informing prevention strategies, while also providing an opportunity to further understand the potential origins of ACOS.

The objectives of this study were to determine the incidence of COPD in women in Ontario with asthma (thus, ACOS) and to characterize risk factors associated with the development of ACOS in women.

Methods

Study Population

Recruitment of study participants occurred between 1980 and 1985 as part of a randomized controlled trial: the Canadian National Breast Screening Study (CNBSS). The CNBSS examined whether regular mammography screening for breast cancer reduced breast cancer mortality (18, 19). A total of 89,835 women were recruited to the CNBSS from six Canadian provinces using several methods: personal invitation letters with follow-up phone calls, advertisements in newspapers and on local radio, and letters to employees of large organizations, recipients of social assistance checks, and members of professional associations.

Inclusion criteria for this cohort study were: CNBSS participants who resided in Ontario, who gave consent for their health card number to be used for data linkage, and who had prevalent asthma observed in Ontario health administrative databases between 1992 and 2015. Women were considered to have prevalent asthma if they were present in the Ontario Asthma Surveillance Information System—a cohort of individuals with asthma in Ontario, captured using a validated health administrative definition of one or more asthma hospitalizations and/or two or more asthma ambulatory care claims in 2 consecutive years. *International Classification of Diseases, Ninth Revision* (ICD-9) code 493, ICD-10 codes J45 and J46, and Ontario Health Insurance Plan billing code 493 were used to capture claims for asthma. In adults, this health administrative definition has been demonstrated to have 84% sensitivity and 76% specificity compared with a clinical reference standard (20). Study exclusion criteria were: women with onset of COPD before their first known date of asthma prevalence, those without a valid health card number, or those who moved out of Ontario during the study period.

Participants' data were linked to Ontario health administrative databases housed at the Institute for Clinical Evaluative Sciences (ICES) in Toronto, Ontario. Participants' data were linked using an encrypted unique health card number given to all Ontario residents. The health administrative databases used in this study were the National Ambulatory Care Reporting System, Discharge Abstract Database, Ontario Health Insurance Plan Claims Database, and Same Day Surgery Database to capture health services use, and the Provincial Registered Persons Database to capture participant characteristics, such as age, sex, and geographic location. Participants were followed prospectively from their asthma prevalence date (index date) to outcome, death, or end of study.

Risk Factors

Potential risk factors for ACOS incidence were identified through a review of the published literature. Variables of interest included: age, history of cigarette smoking, education, income, body mass index (BMI), air pollution, marital status, employment status, rurality, and history of other health conditions (hypertension, diabetes, congestive heart failure, acute myocardial infarction, lung cancer, non-lung cancer, angina, ischemic heart disease, and stroke). As part of the CNBSS, detailed self-reported risk factor data were collected using questionnaires administered at baseline (between 1980 and 1985) (18, 19). Cigarette smoking was measured in pack-years (never-smoker, $<$5 yr, 5 to $\leq$15 yr, 15 to $<$25 yr, or $\geq$25 yr), using self-reported history. Other baseline self-reported characteristics included: age at study enrollment (years), education (less than high school, high school, college/business, or university), marital status (married, never married, or divorced/widowed/separated), employment status (unemployed or employed), BMI (calculated as kg/m^2 using self-reported height and weight), and mean annual household income. History of congestive heart failure, hypertension, cancer, diabetes, and acute myocardial infarction were measured using disease cohort databases housed at ICES. History of angina, stroke, and ischemic heart disease were identified through health administrative databases using ICD-9 and ICD-10 codes. Rurality (residing in a community with a population of $\leq$10,000 people) was measured at time of asthma prevalence using residence postal code.

Satellite data were used to estimate the earth's surface concentration of fine particulate matter (particulate matter with an aerodynamic diameter $\leq$ 2.5 μm [$PM_{2.5}$]) from 1998 to 2006 (21, 22). The satellite-based concentrations were calculated based on aerosol optical depth data from the Moderate Resolution Imaging Spectroradiometer and Multiangle Imaging

Spectroradiometer instruments onboard the National Aeronautics and Space Administration's Terra satellite (21, 22). Long-term average surface concentrations of $PM_{2.5}$ were derived at a resolution of approximately 10×10 km. Exposure surface concentrations of $PM_{2.5}$ were then assigned to participants using the centroids of their postal codes at baseline.

Outcome

The primary outcome was time between first documented date of prevalent asthma and the date of incident COPD. Incident COPD was measured using the COPD database housed at ICES. The COPD database was created using a validated health administrative definition of COPD based on ICD-9 codes 491, 492, and 496 and ICD-10 codes J41, J42, J43, and J44. Individuals were defined as having COPD if they were 35 years of age or older and had one or more COPD hospitalizations and/or one or more COPD ambulatory care claims. This case definition has a sensitivity of 85% and a specificity of 78% (23). To account for the possibility of misclassification between asthma, COPD, and ACOS, in a sensitivity analysis, those with a diagnoses of COPD within 2 years of their asthma prevalence date were excluded from the analysis.

Death was considered a competing risk event in the study. The date of death (if applicable) was obtained from the Provincial Registered Persons Database.

Statistical Analysis

Descriptive statistics. Counts and percentages of incident COPD were calculated for the study population. Risk factors were described and compared between those with asthma only and those who developed ACOS. For categorical variables, numbers and percentages were presented for each category. For continuous variables, mean values were presented with standard deviations (SDs), and median values were presented with interquartile ranges. Chi-square or two-sided *t* tests were used to assess the statistical significance of differences between groups. A two-sided P value < 0.05 was considered statistically significant in all analyses. All analyses were performed using SAS Enterprise Guide 6.1 (SAS Institute Inc.).

Survival analysis. A competing risks survival model was used to measure the association between risk factors and time from asthma prevalence date to incident COPD, while taking into account risk of death. In this model, onset of COPD was considered a failure, and death before onset of COPD was a competing risk. Women who were lost to follow-up or who reached the end of the observation period (December 31, 2015) event free were censored. To assess the associations between multiple risk factors and the development of COPD, multivariable competing risk regression models for the subdistribution hazards were performed according to the method of Fine and Gray (16). The subdistribution hazard is a function of the cumulative incidence for the corresponding cause of failure. The strength of the association between each predictor variable and the outcome was assessed using the subhazard ratio (SHR), which is the ratio of hazards associated with the cumulative incidence function in the presence of and in the absence of a prognostic factor. These subdistribution hazard regression models describe the contribution of the exposures to the hazard of experiencing one type of failure (e.g., incident ACOS), while acknowledging that other kinds of failure (e.g., death) exist.

Ethics

Ethics approval for this study was obtained from the Hospital for Sick Children Research Ethics Board (Toronto, ON, Canada). Individual informed study consent was received from each study participant at the time of enrollment in the CNBSS, and permission was given for participant data to be used in data linkage.

Results

Among the 89,835 CNBSS participants, 4,051 met the inclusion criteria for this study, including residing in Ontario and having prevalent asthma (Figure 1). Mean observation time from prevalent asthma (mean age, 64 yr) to study end was 13.78 years (SD, 7.08 yr) for those who did not develop COPD. Those who developed COPD were followed from a mean age of 63 years for an average of 5.95 years (SD, 5.60). In the study population, 1,701 women (42.0%) went on to develop COPD. Figure 2 shows the cumulative incidence of ACOS over the course of the study period, with death as a competing risk. When we considered the time between asthma prevalence date and incidence of COPD, we found that 385 (22.6% of those with incident COPD) developed COPD within a year of their first prevalent asthma date, 180 (10.6%) developed COPD between 1 and 2 years after their first prevalent asthma date, and the majority (1,136; 66.8%) developed COPD more than 2 years after their first prevalent asthma date. A total of 1,040 women died during the study period: 34.3% of those who developed ACOS and 19.4% of those who did not.

Women with ACOS differed significantly from women with only asthma on several sociodemographic and lifestyle risk factors and exposure to air pollution (Table 1). Women with ACOS tended to be older, had a higher BMI, and were exposed to a higher level of air pollution. Fewer of those with ACOS had a university education (19.5%) than those with asthma only (27%). A higher proportion of the ACOS population were ever-smokers (62.3%), compared with the asthma-only population (47.6%). Those with ACOS had a lower mean household income and more often lived in a rural area (12.1%) than those with asthma only (9.0%).

Table 2 shows that, when compared with those aged 40 to 44 years at recruitment (youngest age category), being older at recruitment was associated with a greater cumulative incidence of ACOS (SHR, 1.18; 95% confidence interval [CI], 1.03–1.36; SHR, 1.77; 95% CI, 1.55–2.02; SHR, 2.02; 95% CI, 1.74–2.35 for those aged 45–49, 50–54, and 55–59 yr at recruitment, respectively). Compared with a university education, there was a higher cumulative incidence of ACOS for those with less than a high school education (SHR, 1.39; 95% CI, 1.18–1.63), with a high school/trade school/vocational school education (SHR, 1.26; 95% CI, 1.08–1.48), or with college/business school (SHR, 1.20; 95% CI, 1.04–1.38) as their highest level of education. Being employed was associated with a lower cumulative incidence of ACOS compared with being unemployed (SHR, 0.86; 95% CI, 0.77–0.96). A BMI of greater than or equal to 30 (obese), compared with less than 25 (normal), was associated with a greater cumulative incidence of ACOS (SHR, 1.22; 95% CI, 1.06–1.41). Cigarette smoking was associated in a dose–response fashion with an increased cumulative incidence of ACOS (SHR, 1.05; 95% CI, 0.89–1.24; SHR, 1.33; 95% CI, 1.14–1.55; SHR, 1.98; 95% CI, 1.70–2.31; SHR 2.51; 95% CI, 2.17–2.89 for those

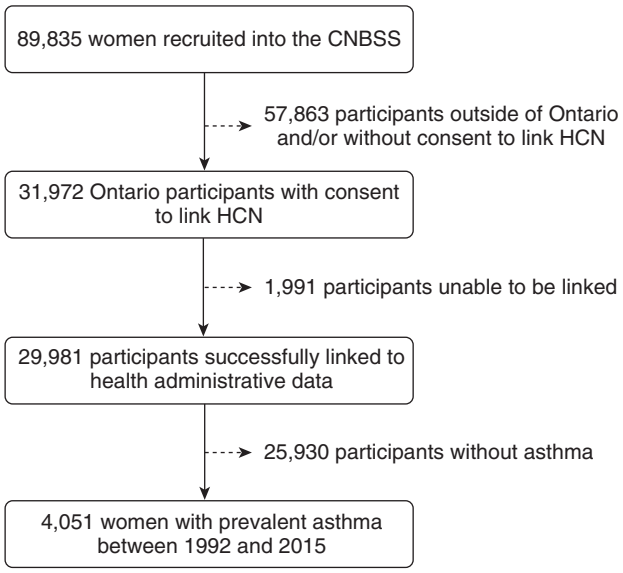

Figure 1. Flow diagram depicting assembly of the study population. CNBSS = Canadian National Breast Screening Study; HCN = Health Card Number.

smoking <5 pack-years, 5 to <15 pack-years, 15 to <25 pack-years, and >25 pack-years, respectively, compared with never-smokers). Rural residence was associated with a greater incidence of ACOS than urban residence (SHR, 1.22; 95% CI, 1.04–1.43). Exposure to $PM_{2.5}$ was not significantly associated with cumulative incidence of ACOS in this study population.

In the sensitivity analysis, 565 participants (14%) who developed COPD within 2 years of their asthma prevalence date were excluded. Running the same analyses in this subpopulation produced similar results to what was observed in the full cohort; however, employment status and BMI were no longer associated with ACOS incidence.

Discussion

In this large cohort study of women followed prospectively between 1992 and 2015, we investigated the role of several sociodemographic, lifestyle, and environmental risk factors on the progression from asthma to COPD (ACOS incidence). In our study population of women with asthma, more than one in three women went on to develop COPD during the study period. Significant risk factors associated with ACOS incidence included older age, lower educational attainment, unemployment, obesity, rural residence, and a history of cigarette smoking (>5 pack-years).

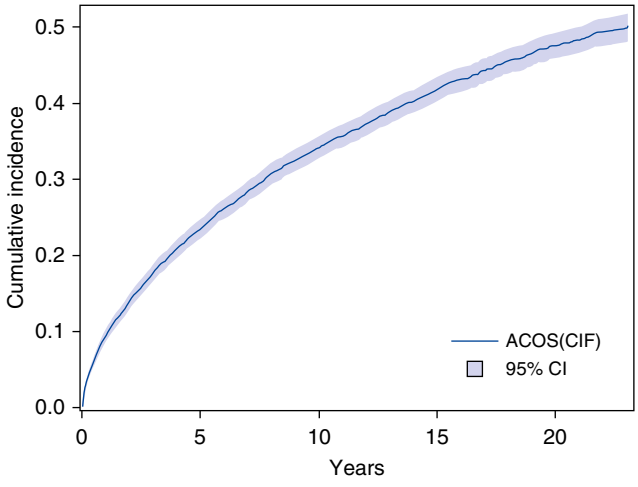

Figure 2. Cumulative incidence of asthma and chronic obstructive pulmonary disease overlap syndrome (ACOS), with death as a competing risk. CI = confidence interval; CIF = cumulative incidence function.

Few cohort studies have investigated risk factors for incident COPD in people with asthma (15). Our previous cohort study found that cigarette smoking, a high BMI, and a higher exposure to $PM_{2.5}$ were significantly associated with increased ACOS incidence in adults (>18 yr of age) in Ontario, Canada, which are results that are somewhat different than what was observed in this study (15). However, in that study, the cohort was younger in age, included both men and women, and adjusted for neighborhood-level SES measures, rather than individual-level SES, which may have had weaker associations with ACOS (15). In cross-sectional studies, older age, history of cigarette smoking, obesity, and lower education levels have also been shown to be significantly associated with ACOS diagnosis (8, 9, 14, 24). In addition, similar to our study, one other study found that exposure to heavy traffic was not more prevalent in the ACOS population than in those without ACOS (8).

In the general population, obesity typically is associated with a higher risk of death; however, in some chronic diseases, such as heart failure and COPD, overweight and obesity are, paradoxically, associated with better outcomes (25–28), a phenomenon referred to as the "obesity paradox." On the other hand, advanced COPD, particularly in the form of emphysema, is instead typically associated with weight loss and muscle wasting and is associated with increased rates of death (29–31). Overweight or obesity is more prevalent among individuals with asthma or COPD with chronic bronchitis rather than COPD with emphysema (32). This may be in part due to a more sedentary lifestyle, which would contribute to the development of obesity. Our study findings showed that BMI of greater than or equal to 30 (obese), compared with less than 25 (normal) was associated with a greater cumulative incidence of COPD among women with asthma. This observation may be a marker of sedentary lifestyle associated with prevalent asthma and/or COPD.

Table 1. Characteristics of the Ontario Canadian National Breast Screening Study women with asthma only or with asthma and chronic obstructive pulmonary disease overlap syndrome

Characteristic	Asthma Only (*n* = 2,350)	ACOS (*n* = 1,701)
Age at entry into CNBSS, yr		
40–44	759 (32.3)	406 (23.9)
45–49	673 (28.6)	394 (23.2)
50–54	545 (23.2)	521 (30.6)
55–59	373 (15.9)	380 (22.3)
Age at asthma prevalence, yr	64.4 (8.4)	63.4 (7.5)
Age at study end, yr	78.7 (6.0)	79.7 (6.3)
Cigarette smoking		
Never	1,231 (52.4)	641 (37.7)
<5 pack-years	365 (15.5)	203 (11.9)
5 to <15 pack-years	320 (13.6)	226 (13.3)
15 to <25 pack-years	202 (8.6)	256 (15)
⩾25 pack-years	142 (6.0)	315 (18.5)
Unknown pack-years	81 (3.4)	54 (3.2)
Unknown smoking status	9 (0.4)	6 (0.4)
Highest level of educational attainment		
Less than HS	380 (16.2)	383 (22.5)
HS/trade/vocation school	485 (20.6)	372 (21.9)
College or business school	850 (36.2)	615 (36.2)
University	635 (27.0)	331 (19.5)
Annual household income, thousands, mean ± SD	$30.1 ± $9.9	$29.1 ± $9.4
BMI group		
<25	1,318 (56.1)	869 (51.1)
⩾25 to <30	649 (27.6)	506 (29.7)
⩾30	352 (15.0)	300 (17.6)
Unknown	31 (1.3)	26 (1.5)
$PM_{2.5}$ exposure from 1998 to 2006		
Mean ± SD	12.5 ± 2.4	12.7 ± 2.4
Median (interquartile range)	12.7 (10.0–14.6)	13.1 (11.1–14.6)
Marital status		
Never married	145 (6.2)	87 (5.1)
Married	1,861 (79.2)	1,326 (78.0)
Divorced/separated/widowed	344 (14.6)	288 (16.9)
Occupation		
Homemaker or unemployed	726 (30.9)	577 (33.9)
Employed	1,564 (66.0)	1,076 (63.3)
Unknown	60 (2.6)	48 (2.8)
Rural		
Yes	212 (9.0)	205 (12.1)
No	2,090 (88.9)	1,482 (87.1)
Missing	48 (2.0)	14 (0.8)
Place of birth		
Canada	1,699 (72.3)	1,286 (75.6)
United Kingdom	316 (13.4)	234 (13.8)
European (excluding UK)	187 (8.0)	107 (6.3)
United States	63 (2.7)	45 (2.6)
Other	85 (3.6)	29 (1.7)

Definition of abbreviations: ACOS = asthma and chronic obstructive pulmonary disease overlap syndrome; BMI = body mass index; CNBSS = Canadian National Breast Screening Study; HS = high school; $PM_{2.5}$ = particulate matter with an aerodynamic diameter ⩽ 2.5 μm; SD = standard deviation.
Data presented as *n* (%) unless otherwise noted.

Overall, findings of this study suggest that lifestyle risk factors, rather than air pollution, play a significant role in ACOS development in this population of women with asthma. Several studies on the association between air pollution and COPD support these results (33, 34). For example, one study from England found inconsistent evidence for an association between air pollution and COPD incidence in their large cohort aged 40 to 89 years (33). In another study investigating long-term exposure to ambient air pollution using four cohorts from the ESCAPE (European Studies on Chronic Air Pollution Effects) project, analysis of individual cohorts and meta-analysis showed no significant associations between $PM_{2.5}$ and incidence or prevalence of COPD (34).

Another important finding of this study was the high incidence of ACOS in the population of women with asthma in Ontario. More than 40% of women with asthma developed ACOS over the study period. Also surprising was the finding that more than one-third (38%) of the women who developed ACOS were never-smokers. This result suggests that more proactive prevention strategies are needed, especially those that address risk factors outside of cigarette smoking. Fortunately, most of the significant risk factors for ACOS development identified are modifiable; thus, health promotion efforts such as health education, increased physical activity, maintaining a healthy diet, and smoking cessation have the potential to make a difference in ACOS incidence in this population.

Furthermore, these results may suggest that there are barriers to receiving adequate respiratory care for women with asthma. One way ACOS is theorized to arise is from airway remodeling, resulting in irreversible airway obstruction in people with asthma (35). Some of the factors identified in this study may be directly linked to poor respiratory health, such as obesity and cigarette smoking, whereas others, such as education, unemployment, and rural living, may be more indirectly associated. For example, socioeconomic barriers may result in undertreatment of asthma over time, leading to more frequent/severe asthma attacks. Although we hypothesize that our results may be related to asthma severity and/or poor management over time, we did not have data to investigate this association directly. However, efforts should still be made to improve access to adequate asthma treatment for this population in a way that addresses both socioeconomic and geographical barriers.

There are several limitations to this study that warrant mention. First, the study population consisted of women recruited through a larger randomized controlled trial, which may impact the generalizability of our study findings. In addition, we were unable to ascertain asthma incidence date, as health administrative databases were only

Table 2. Subdistribution hazard model for incident chronic obstructive pulmonary disease (i.e., asthma and chronic obstructive pulmonary disease overlap syndrome) among women with prevalent asthma, with death as a competing risk ($N = 4,051$)

Parameter	SHR	95% CI	*P* Value
10-$\mu g/m^3$ increase in $PM_{2.5}$ exposure 1998–2006	1.11	0.88–1.40	0.38
Age at entry into CNBSS, yr (ref: age 40–44 yr)			
45–49	1.18	1.03–1.36	0.019
50–54	1.77	1.55–2.02	<0.0001
55-59	2.02	1.74–2.35	<0.0001
Marital status (ref: married)			
Never married	0.99	0.79–1.25	0.94
Divorced/separated/widowed	1.09	0.95–1.25	0.23
Highest level of educational attainment (ref: university)			
Less than HS	1.39	1.18–1.63	<0.0001
HS/trade/vocation school	1.26	1.08–1.48	0.004
College or business school	1.20	1.04–1.38	0.013
Occupation (ref: homemaker or unemployed)			
Employed	0.86	0.77–0.96	0.006
Unknown	0.88	0.65–1.19	0.40
BMI group (ref: <25)			
⩾25 to <30	1.09	0.97–1.23	0.13
⩾30	1.22	1.06–1.41	0.007
Unknown	1.14	0.80–1.63	0.47
Cigarette smoking (ref: never)			
<5 pack-years	1.05	0.89–1.24	0.54
5 to <15 pack-years	1.33	1.14–1.55	0.0004
15 to <25 pack-years	1.98	1.70–2.31	<0.0001
⩾25 pack-years	2.51	2.17–2.89	<0.0001
Unknown pack-years	1.22	0.94–1.59	0.14
Unknown smoking status	1.11	0.51–2.41	0.80
Mean income	1.00	1.00–1.01	0.34
Rural (ref: no)			
Yes	1.22	1.04–1.43	0.013
Missing	0.52	0.31–0.87	0.014

Definition of abbreviations: BMI = body mass index; CI = confidence interval; CNBSS = Canadian National Breast Screening Study; HS = high school; $PM_{2.5}$ = particulate matter with an aerodynamic diameter ⩽2.5 μm; SHR = subhazard ratio.
Also adjusted for history of the following health conditions: congestive heart failure, hypertension, non-lung cancer, lung cancer, diabetes, acute myocardial infarction, angina, stroke, and ischemic heart disease.

available from 1992 onward. Similarly, we were unable to measure the cohort's air pollution exposure history dating earlier than 2003 because of data unavailability; thus, estimates may not accurately represent lifelong exposure to air pollutants. We were also unable to obtain information about secondhand smoke, which could be an important contributor to ACOS. Our study is also limited by the accuracy of our health administrative definitions of asthma and COPD. Furthermore, although we have identified that women with asthma are particularly vulnerable to developing ACOS, we were unable to compare ACOS incidence in men because of our use of the CNBSS cohort, which may have limited our perspective.

On the other hand, our study was strengthened by the availability of detailed participant-level risk factor data, a large sample size, and a long follow-up period, allowing for adequate time to observe ACOS development. Other studies on ACOS development have not been able to observe participants well into their seventies. Moreover, our statistical approach adjusted for death as a competing risk, which is important when studying an aging population. Our study is one of few looking prospectively at COPD incidence in people with asthma and the first to focus on women, who have been identified as both a high-risk and a high-burden group.

In conclusion, this study identified important modifiable risk factors associated with COPD incidence in women with asthma, including high BMI, history of cigarette smoking, and lower educational attainment, which may help to explain a recent increase in ACOS observed in women. This study also identified a concerning high incidence of ACOS in this population, as more than one-third of women with prevalent asthma developed COPD during follow-up. Future research should aim to better understand how long-term asthma management and/or severity impacts the progression from asthma to a fixed airway obstruction (ACOS). A better understanding of the origins of ACOS will help to inform the design of prevention initiatives intended to decrease risk of loss of lung function resulting in ACOS. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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