Predictors of chronic obstructive pulmonary disease in women who have never smoked: a cohort study

Roger M. Engel [1], Katie de Luca[1], Petra L. Graham [2], Masoumeh Kaboli Farshchi[1,3], Subramanyam Vemulpad[1,4] and Julie Byles[5]

[1]Dept of Chiropractic, Faculty of Medicine, Health and Human Sciences, Macquarie University, Sydney, Australia. [2]School of Mathematical and Physical Sciences, Macquarie University, Sydney, Australia. [3]School of Persian and Complementary Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. [4]Dept of Molecular Sciences, Faculty of Science and Engineering, Macquarie University, Sydney, Australia. [5]School of Medicine and Public Health, University of Newcastle, Callaghan, Australia.

Corresponding author: Roger M. Engel (roger.engel@mq.edu.au)

Shareable abstract (@ERSpublications)
A history of breathing difficulties, asthma, allergies, hay fever and sinusitis are associated with an increased risk of developing COPD later in life in women who have never smoked. Lung function testing should be considered for these women. https://bit.ly/3jDX9Mp

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Abstract

COPD is responsible for an increasing number of deaths worldwide. Smoking is the most reliable predictor for developing COPD later in life. However, women make up the majority of patients with COPD who have never smoked. There is therefore a need to identify other factors that can predict COPD in women. The aim of this study is to identify factors associated with increasing the risk of developing COPD later in life in women who have never smoked.

Data from the Australian Longitudinal Study on Women's Health (ALSWH) cohort born between 1946 and 1951 were used to investigate potential predictors of COPD. Retrospective analyses were performed on data from two of the ALSWH surveys: wave 1 (1996) and wave 9 (2019).

There were 3584 women who self-reported as being never-smokers (at waves 1 and 9) and did not have COPD at baseline, of which 109 had developed COPD at wave 9. Logistic regression showed a significant relationship between COPD at wave 9 and baseline breathing difficulties ($p<0.001$), asthma ($p<0.001$) and allergies ($p=0.026$), though significance of asthma and allergies disappeared when included together in a single model, implying that women with these symptoms earlier in life were more likely to be diagnosed with COPD later in life compared to women without these symptoms.

Our study supports the inclusion of lung function testing in primary care settings for women over the age of 45 years who have never smoked and have a history of breathing difficulties, asthma or allergies.

Introduction

The term chronic respiratory disease (CRD) refers to diseases of the airways and other structures of the lung, with asthma and COPD the most common [1]. However, asthma and COPD differ substantially with respect to worldwide mortality. Recent estimates put the number of deaths from asthma at 461 000 [2] whereas for COPD, ranked as the third leading cause of death, the number of deaths reached 3.23 million in 2019 [1]. Identifying predictors of COPD therefore has a greater potential to impact morbidity and mortality.

Clinically, COPD presents as chronic bronchitis or emphysema and includes symptoms such as breathlessness, cough and sputum production, chest tightness and chest pain [3, 4]. The disease affects both men and women and is characterised by progressive airflow limitation, decreasing exercise capacity and deteriorating quality of life [5]. However, a recent review highlighted that the prevalence of COPD is increasing more rapidly in women than in men, mainly due to personal susceptibility and environmental risk factors [6].

People with COPD have lower levels of physical activity compared to people without COPD [7]. Lower levels of physical activity lead to decreased exercise capacity, a prognostic indicator for COPD [8]. Many people with early-stage COPD are unaware they have the condition or are reluctant to consult a doctor, dismissing the onset of symptoms as being part of "normal" ageing. This often results in a delay in diagnosis until the disease has become more advanced [9, 10], a situation which can affect long-term health as early diagnosis facilitates earlier intervention and a more favourable prognosis [11].

To date, smoking has been identified as the most important risk factor associated with developing COPD later in life [12, 13]. However, up to 45% of people with COPD are nonsmokers [14]. Identifying risk factors other than smoking for developing COPD later in life may be of particular relevance to women given that they make up the majority of patients with COPD who have never smoked [14].

Several studies have investigated other potential predictors of COPD [15–17]. Bui *et al.* [15] used the trajectories of forced expiratory volume in 1 s (FEV_1) to identify modifiable early-life exposures that might minimise COPD risk later in life. They included maternal smoking and immunisation. Other studies identified chronic systemic inflammation as being associated with increasing the risk of developing COPD later in life [18]. While there have been studies on the factors associated with developing COPD in women who have a history of smoking, there is a gap in the literature around the identity of these factors in women who have never smoked.

The aim of this study is to identify factors associated with increasing the risk of developing COPD later in life in women who have never personally smoked.

Methods

The Australian Longitudinal Study on Women's Health (ALSWH) is a population-based survey that explores the factors that contribute to the health and wellbeing of Australian women [18]. It collects data from four cohorts of women based on their year of birth: those born between 1921 and 1926; 1946 and 1951; 1973 and 1978; and 1989 and 1995. Data are collected across a range of health-related fields including arthritis, back pain, osteoporosis, diabetes, cardiac, respiratory, reproductive and mental health, cancer, ageing, tobacco, alcohol and other drug use, and exercise capacity [19]. In the field of respiratory health, the surveys include specific questions about chronic bronchitis, emphysema and COPD. The baseline survey (wave 1) was conducted in April 1996. Participants are surveyed every 3 years with the most recent survey conducted in 2019 (wave 9). Data being reported here were from the 1946 to 1951 cohort with analyses performed on the results from waves 1 and 9.

The 1946 to 1951 cohort of women were between 45 and 50 years of age at wave 1 and between 65 and 70 years at the time of completing wave 9. The factors of interest in the ALSWH surveys relating to respiratory health and wellbeing were physician-based diagnosis of COPD (the ALSWH survey question relating to COPD groups chronic bronchitis, emphysema, lung disease and COPD together), asthma, presence of allergies, hay fever and/or sinusitis, difficulty breathing, the presence of chest and/or back pain, limitations in walking various distances, and overall physical and mental health. Presence and/or treatment for COPD in the previous 3 years was used as the primary outcome for analysis. Potential predictors of COPD at wave 9 included the baseline (wave 1) variables "presence and frequency of allergies, hay fever and/or sinusitis", "breathing difficulty", "chest pain" and "back pain" in the last 12 months for which the following ordinal responses were provided: Never/Rarely/Sometimes/Often; presence and/or treatment for "asthma" in the past 3 years; "limitations in walking" 1 km, ½ km and 100 m for which the following ordinal responses were provided for each distance: Not limited/Limited a little/Limited a lot; and 36-item Short-Form Health Survey (SF-36) summary scores, *i.e.* the physical component summary (PCS) and mental component summary (MCS), for which higher scores indicate better health.

Statistical analysis

Demographic and other variables considered for analysis were summarised using means and standard deviations for continuous variables and count with percentage for categorical/ordinal variables. Differences between the COPD and no COPD groups by baseline predictor were compared using two-sample t-tests for the continuous variables, Fisher's exact tests for the binary categorical variables and Kruskal–Wallis tests for ordinal variables. Logistic regression models were used to determine the odds of having COPD in wave 9 for each of the baseline predictor variables described, after adjusting for body mass index (BMI) as a measure of obesity, education level (less than high school, high school/trade/diploma, university or higher) and a measure of socioeconomic status of the area in which the participants live called the Socioeconomic Indexes for Areas (SEIFA) index of relative socioeconomic disadvantage (IRSD). The SEIFA IRSD is an

index developed by the Australian Bureau of Statistics that summarises measures of economic and social resources in an area including percentage of households with low income, low education, high unemployment and unskilled occupations [20]. In the SEIFA IRSD, lower scores mean more disadvantage. Predictor variables with small group sizes for some categories were collapsed into the previous category for logistic modelling. All variables significant at the 10% level in the initial analysis were included in a multivariable model which used backwards elimination to arrive at the most parsimonious final model. Only participants with observations at both baseline (wave 1) and wave 9 were included in the analyses. Participants with bronchitis/emphysema present at baseline were excluded from the analysis. Results are presented as odds ratios with 95% confidence intervals. Intervals excluding 1 imply significantly different odds compared to the reference level. p-values <0.05 were deemed significant. All analyses were completed using R version 4.1.0 statistical software [21].

TABLE 1 Summary statistics for baseline demographics and predictor variables

Baseline variable	COPD in wave 9		p-value	Overall
	No	Yes		
Subjects n	3475	109		3584
Age years	47.6±1.5	47.7±1.4	0.205#	47.6±1.5
BMI kg·m^{-2}	25.4±4.7	26.5±5.5	0.059#	25.5±4.7
SF-36 PCS	51.9±7.8	49.9±9.3	0.035#	51.9±7.9
SF-36 MCS	49.5±10.0	46.4±11.1	0.004#	49.5±10.1
SEIFA IRSD	1011±86	1000±77	0.160#	1010±85
Education level			0.009¶	
Less than high school	1748 (42.8)	61 (56.0)		1539 (43.2)
High school/trade/diploma	1328 (38.5)	33 (30.3)		1361 (38.2)
University/postgraduate	645 (18.7)	15 (13.8)		660 (18.5)
Presence of back pain			0.077¶	
Never	901 (26.0)	20 (18.3)		921 (25.8)
Rarely	932 (26.9)	31 (28.4)		963 (27.0)
Sometimes	1100 (31.8)	37 (33.9)		1137 (31.8)
Often	529 (15.3)	21 (19.3)		550 (15.4)
Presence of chest pain			0.204¶	
Never	2769 (80.4)	82 (75.2)		2851 (80.2)
Rarely	419 (12.2)	18 (16.5)		437 (12.3)
Sometimes/often	256 (7.4)	9 (8.3)		265 (7.5)
Breathing difficulties			<0.001¶	
Never	2723 (78.9)	62 (57.4)		2785 (78.3)
Rarely	367 (10.6)	23 (21.3)		390 (11.0)
Sometimes/often	361 (10.5)	23 (21.3)		384 (10.8)
Asthma			<0.001+	
No	3104 (89.4)	82 (75.2)		3186 (89.0)
Yes	368 (10.6)	27 (24.8)		395 (11.0)
Presence of allergies, hay fever, sinusitis			0.002¶	
Never	1478 (42.8)	31 (28.7)		1509 (42.4)
Rarely	613 (17.7)	22 (20.4)		635 (17.8)
Sometimes	911 (26.4)	33 (30.6)		944 (26.5)
Often	453 (13.1)	22 (20.4)		475 (13.3)
Walking 100 m			0.113+	
Not limited	3317 (96.5)	101 (93.5)		3418 (96.4)
Limited (a little or a lot)	122 (3.5)	7 (6.5)		129 (3.6)
Walking ½ km			0.049+	
Not limited	3204 (93.3)	95 (88.0)		3299 (93.2)
Limited (a little or a lot)	229 (6.7)	13 (12.0)		242 (6.8)
Walking 1 km			0.024+	
Not limited	2951 (85.9)	84 (77.8)		3035 (85.7)
Limited (a little or a lot)	483 (14.1)	24 (22.2)		507 (14.3)

Data presented as n (%) or mean±SD unless otherwise indicated. BMI: body mass index; SF-36 PCS: physical component summary; SF-36 MCS: mental component summary; SEIFA IRSD: Socioeconomic Indexes for Areas index of relative socioeconomic disadvantage. p-values are from: #: two-sample t-test; ¶: Kruskal–Wallis test; +: Fisher's exact test.

The ALSWH project received ethics approval from the University of Newcastle Human Research Ethics Committee (approval number H 076 0795) with approval for this study given by the ALSWH Steering Committee (project number A754).

Results

There were 13 714 women in the 1946–1951 cohort who completed wave 1 in 1996 (baseline) and 7956 women who completed wave 9 in 2019. Of these, 3584 self-reported as personally being never-smokers (at both waves 1 and 9; note that information on passive smoking was not available) and did not have bronchitis or emphysema at wave 1. At wave 9, 109 women had been diagnosed or treated for COPD in the previous 3 years while 3475 women had not. Summary statistics for included participants are shown in table 1. Women with COPD in wave 9 were not significantly different in age or BMI from women who did not have COPD ($p>0.05$). Women with COPD at wave 9 were more likely to have breathing difficulties ($p<0.001$), asthma ($p<0.001$), allergies, hay fever and sinusitis ($p=0.002$), and limitations in walking ½ km ($p=0.049$) and 1 km ($p=0.024$) at baseline compared to women who did not have bronchitis or emphysema at wave 9. There were no differences in the proportion of those with baseline back and chest pain, or limitation in walking 100 m for women with *versus* without COPD at wave 9.

After adjusting for BMI, education level and socioeconomic status (*via* the SEIFA IRSD), logistic regression analysis of each predictor separately (table S1) showed a significant relationship between COPD and baseline breathing difficulties (*versus* never; Rarely: OR 2.74, 95% CI 1.64–4.43; Sometimes/often: OR 2.62, 95% CI 1.55–4.27; $p<0.001$), baseline presence of asthma (OR 2.73, 95% CI 1.70–4.27; $p<0.001$), and allergies, hay fever or sinusitis at baseline (*versus* never; Often: OR 2.29, 95% CI 1.30–3.98; $p=0.027$), implying women with these symptoms earlier in life were more likely to be diagnosed with COPD later in life compared to women without these symptoms. Women with higher (better) baseline SF-36 summary scores for both PCS and MCS had significantly lower odds of being diagnosed with COPD at wave 9 than women with lower baseline summary scores (OR 0.79, 95% CI 0.64–0.99; $p=0.041$ and OR 0.76, 95% CI 0.65–0.91; $p=0.002$, respectively) per 10-point change in those scores. There were no significant differences in odds of COPD at wave 9 by limitations in walking ½ km and 1 km at wave 1 though odds of COPD for both variables, which were significant in table 1 (OR 1.91, 95% CI 1.01–3.35 for ½ km; and OR 1.75, 95% CI 1.08–2.73 for 1 km), combined with the small change in odds, suggests a potential lack of power rather than a lack of association.

Backwards elimination of all variables significant at the 10% level in the initial modelling included in a subsequent analysis resulted in a final model containing breathing difficulties, presence of asthma, SF-36 MCS and SF-36 PCS as well as BMI, education level and SEIFA index of relative disadvantage (see table 2). Odds ratios were similar to those observed in the initial modelling except that asthma and PCS were no longer significant after adjusting for the other variables.

TABLE 2 Odds of having COPD in wave 9 in never-smokers with 95% confidence interval, multivariable model

Predictor variable	OR (95% CI)	p-value
BMI	1.01 (0.97–1.05)	0.736
Education level		0.042
Less than high school	Reference	
High school/trade/diploma	0.63 (0.40–0.98)	
University/postgraduate	0.58 (0.30–1.03)	
SEIFA (per 100 units)	0.95 (0.76–1.21)	0.692
Breathing difficulties		<0.001
Never	Reference	
Rarely	2.31 (1.34–3.86)	
Sometimes/often	1.68 (0.89–3.08)	
Presence of asthma		0.083
No	Reference	
Yes	1.65 (0.92–2.89)	
SF-36 PCS (per 10 units)	0.84 (0.67–1.05)	0.115
SF-36 MCS (per 10 units)	0.78 (0.66–0.94)	0.008

BMI: body mass index; SEIFA: Socioeconomic Indexes for Areas; SF-36 PCS: physical component summary; SF-36 MCS: mental component summary.

Discussion

In Australian women aged 45–50 years and who have never smoked, the presence of breathing difficulties, asthma and/or allergies, hay fever and sinusitis at baseline were statistically significant predictors of developing COPD >20 years later. Moreover, the odds of developing COPD were more than twice the rate for women who rarely have breathing difficulties, any asthma, or allergies, hay fever and sinusitis often, compared to women who do not have these symptoms. Women who smoke are more susceptible to developing COPD than men because they have smaller airway size and therefore receive a greater dose of toxin for the same amount of inhaled smoke [22, 23]. While the prevalence of COPD among women who are never-smokers is lower than for men, the proportion of never-smokers with COPD is much higher for women than it is for men [24]. This has led to speculation that as women age, the high proportion of never-smokers with COPD may be the result of the effect changing hormonal levels have on lung function during menopause [25]. When considered in conjunction with our findings, measuring lung function using spirometry in women over the age of 45 years who have never smoked and have a history of breathing difficulties, asthma, allergies, hay fever or sinusitis would facilitate earlier detection of a CRD such as COPD. In the presence of a history of childhood asthma, measuring lung function in these women would be even more pertinent given the link between asthma and an increase in risk of developing COPD later in life [26, 27].

As early diagnosis facilitates earlier intervention and a more favourable prognosis [11], this approach would suit primary care settings where the respiratory history of a patient is known. Complicating this scenario is a level of uncertainty surrounding the diagnosis of COPD where patients considered to have the disease may not meet the threshold for airflow obstruction or simply be misdiagnosed. In an audit of >1000 patients in primary care, approximately one-third were found to not meet the guideline-specified FEV_1/forced vital capacity (FVC) criteria for airflow obstruction [28]. Furthermore, in patients presenting with chronic cough, failure to recognise the syndrome of chronic cough can result in a misdiagnosis of exacerbation of COPD [29].

Given the uncertainty surrounding the diagnosis of COPD in primary care, additional steps may need to be taken to confirm the diagnosis before applying intervention. One suggestion in the presence of a normal examination and a chest radiograph is to use FEV_1 % predicted instead of FEV_1/FVC as the diagnostic threshold [28].

Our results showing that asthma, allergies, hay fever and sinusitis are predictors of developing a CRD such as COPD later in life are supported by the literature [30, 31]. However, our results showing that back pain was not a predictor of COPD in women who have never smoked appear at odds with the literature showing that patients with COPD experience more low back pain generally compared to those without COPD [32–34]. This disagreement can be explained by two reasons. First, that men with COPD experience more low back pain than women with COPD [32–34]. As the ALSWH study only collected data from women, our analyses were unable to account for the differences in pain distribution across sexes. Second, as the incidence of low back pain increases after the onset of COPD [34], any pre-diagnosis predictive ability would be limited.

Strengths and limitations

The strengths of this study include the longitudinal design of the ALSWH, allowing for data to be regularly collected over a 23-year period, and the relevance of the research question about identifying factors associated with the risk of developing COPD later in life in women who have never smoked. There are several limitations associated with the study. The collection of only women's data may limit generalisability to the broader population. However, population studies support the view that men may be similarly affected by COPD as women [35–37]. While our study used data from a single country, Australia, the rates of COPD in many developed countries are similar [38]. There is therefore no basis for assuming our results would not be applicable to other developed countries. The ALSWH study relies on self-reporting of physician-diagnosed COPD in the past 3 years. While this method increases the level of confidence regarding diagnosis, self-reporting of symptoms has been shown to include a degree of inaccuracy in studies related to other chronic diseases such as arthritis [39]. Furthermore, given the level of uncertainty surrounding the diagnosis of COPD in primary care and the risk of misdiagnosis in patients with chronic cough syndrome, we acknowledge the potential that our data and therefore analyses could contain a degree of error.

Conclusion

Identifying predictors of COPD is important for improving the implementation of strategies designed to manage CRD. The results from our study provide support for the inclusion of lung function testing in

primary care settings for women over the age of 45 years who have never smoked and have a history of breathing difficulties, asthma, allergies, hay fever and/or sinusitis, albeit with additional confirmation required in some settings. This approach has the potential to reduce the burden of disease by facilitating early identification of women at risk of developing CRD and allowing for the earlier introduction of measures designed to slow or prevent disease progression.

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Author contributions: R.M. Engel, K. de Luca, M. Kaboli Farshchi and S. Vemulpad were involved in the study design, interpreting the results and drafting the manuscript. P.L. Graham conducted the statistical analyses, and helped draft the methods and results section of the manuscript. R.M. Engel and J. Byles supervised the study. All authors read, revised and approved the final manuscript.

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