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COPD in Never-Smokers: BOLD Australia Study

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Purpose: Tobacco smoking is the major risk factor for COPD, and it is common for other risk factors in never-smokers to be overlooked. We examined the prevalence of COPD among never-smokers in Australia and identified associated risk factors.

Methods: We used data from the Australia Burden of Obstructive Lung Disease (BOLD) study, a cross-section of people aged ≥40 years from six sites. Participants completed interviews and post-bronchodilator spirometry. COPD was primarily defined as an FEV_1 /FVC ratio <0.70 and secondarily as the ratio less than the lower limit of normal (LLN).

Results: The prevalence of COPD in the 1656 never-smokers who completed the study was 10.5% (95% CI: 9.1–12.1%) [ratio<LLN 4.6%]. The likelihood of having COPD increased with advancing age [odds ratio (OR) 4.11 in those 60–69 years and OR 8.73 in those 70 years and older], having attained up to 12 years of education (OR 1.75) compared to those with more than 12 years, having a history of asthma (OR 2.30), childhood hospitalization due to breathing problems before age 10 years (OR 2.50), or having a family history of respiratory diseases (OR 2.70). Being overweight or obese was associated with reduced prevalence of COPD compared with being normal weight. In males and females, advanced age, a history of asthma, and childhood breathing problems before age 10 were factors that elevated the likelihood of COPD. However, in males, additional factors such as a higher body mass index and a family history of respiratory diseases also contributed to increased odds of COPD.

Conclusion: COPD was prevalent in this population of never-smokers aged 40 years and over. This finding highlights the significance of risk factors other than smoking in the development of COPD.

Keywords: non-smokers, prevalence, spirometry, lower limit of normal, LLN, burden of obstructive lung disease, BOLD

Introduction

Ranked third among all causes of death globally, chronic obstructive pulmonary disease (COPD) remains one of the seven non-communicable diseases in the top 10 causes of death.[1] In Australia, COPD is the fifth leading cause of mortality with 14.5% of the general population aged 40 years and over found to have COPD in a recent survey.[2,3] Like other high-income countries, Australia has an ageing population with approximately 16% of the population aged 65 years and older.[4] Tobacco smoking is the most recognisable risk factor. However, with declining rates of smoking and increasing aging of the population, it is important to recognize other important causes of COPD.

Often considered a disease that predominantly affects men, studies have shown that COPD prevalence is increasing in women.[5] The convergence of risk factors, especially smoking and occupational exposures, are likely reasons for narrowing of the prevalence gap.[5] As women have higher rates of survival, hospital visits and medication use, the role

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of gender in both COPD and asthma becomes important for health systems particularly for efficient resource utilization and clinical and public health interventions.[6]

All international guidelines, including the Australian COPD-X plan, highlight smoking and other risk factors as being important for COPD.[7] As in other high-income countries, in Australia there has been a significant decline in smoking through a range of public health policies, such as increased taxation, plain packaging with graphic warnings, advertising restrictions and smoking bans. However, there has been limited focus on prevention of COPD among never-smokers through identification of non-smoking risk factors that may inform such prevention. Epidemiological studies have reported that the prevalence of COPD among persons who did not smoke, or were not exposed to smoking (although likely includes second-hand smoking), could range from 3% to 8% or even higher.[8–13] Some risk factors identified in these studies include older age, being male, body mass index, asthma, and comorbidities.

It is important to understand the characteristics of never-smokers in an ageing population. The objective of this analysis was to assess, among never-smokers, the prevalence and risk factors for abnormal lung function consistent with COPD, by sex.

Materials and Methods

Study Design and Population

This analysis used data from BOLD-Australia, a multi-site, cross-sectional study of non-institutionalized adults aged 40 years or older.[14] Six study centers, representing the sociodemographic and geographical composition of the population, were selected for sampling. Electoral rolls were used to obtain a sex-stratified random sample of participants, in all but one center which used a household census.[14] A total of 3522 adults participated in the study providing complete questionnaire data and high-quality post-bronchodilator spirometry measurements. This sub-group analysis focuses on 1656 (47.0%) who self-reported as never-smokers of cigarettes (tobacco). Further details of the Australian BOLD study methodology have been outlined elsewhere.[14,15]

The BOLD-Australia Study was approved by the Human Research Ethics Committee of the University of Sydney (ref. no. 12-2006/9724) in accordance with the ethical standards of these local committees on human experimentation and with the revised Helsinki Declaration 2000. All participants provided written informed consent.

Measures

Questionnaire

The BOLD study core questionnaire collected information such as sex, age, education, respiratory symptoms (cough, phlegm, wheeze, breathlessness), history of comorbid conditions (heart disease, hypertension, diabetes), family history of respiratory diseases, hospitalization for breathing problems prior to age 10, exposures to second-hand smoke in the home, working in dusty jobs for ≥1 year and occupational exposures.

Anthropometric and Lung Function Measurements

Measurements of weight (kg) and height (cm) were recorded, and body mass index (BMI) calculated. Pre- and post-bronchodilator spirometry was performed according to the joint ATS/ERS guidelines to obtain measurements of the forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and the FEV_1/FVC ratio and its associated lower limit of normal (LLN) was calculated using The Global Lung Initiative (version 1.3.4 build 4).[16,17]

Definitions

- Never-smokers: participants who responded "No" to the question "Have you ever smoked cigarettes?"
- Asthma: participant reported being informed by a doctor or other healthcare provider that they had "asthma, asthmatic bronchitis or allergic bronchitis".
- SOB on moderate exertion: shortness of breath when hurrying on the level or walking up a slight hill.
- Family history: first-degree relative with a diagnosis of emphysema, chronic bronchitis, or COPD
- BMI: categorised as Low <20, Normal 20≤ BMI <25, or Overweight/Obese ≥25 kg/m^2.

- Urbanicity: classified as rural, urban and remote according to participants' reported postcodes and the Australian Bureau of Statistics (ABS) Statistical Area Level 4 classification.[18]
- Working in a dusty job: classified as working for more than one year in a dusty job.
- Vapours, Gases and Fumes: classified as working in occupations, 3 months or more, including chemical or plastics manufacturing, firefighting, or welding.
- COPD: defined according to the Global Initiative for Obstructive Lung Disease (GOLD) criteria of a fixed post-bronchodilator ratio of FEV_1/FVC <0.70. This was further categorised according to FEV_1 as a proportion of the predicted value into severity levels GOLD 1+ (FEV_1/FVC <0.70 and any FEV_1%predicted) and GOLD 2+ (FEV_1/FVC <0.70 and any FEV_1%predicted <80%).[19] This paper focuses on COPD as non-reversible airway obstruction, GOLD 1+.
- LLN: calculated as below the 5th percentile or lower boundary of the expected ratio of FEV_1/FVC. Global Lung Function Initiative data were used to calculate the LLN.

Statistical Analysis

Descriptive statistics for the never-smokers were calculated for demographic, health characteristics and the occupational exposures of participants and to obtain prevalence estimates for the outcomes COPD and ratio<LLN. Sex differences in demographics (age, ethnicity, education, BMI, and geographical location) and health characteristics (respiratory symptoms, history of respiratory conditions, comorbidities, and lung function) and occupational exposures (working in a dusty job for one year or more and vapors, gases, and fumes) were examined using chi-square and *t*-tests. Associations with COPD were assessed using chi-square tests and odds ratios (OR).

A directed acyclic graph (DAG) was constructed, using the DAGitty.v3.2 software,[20] to examine the relationship between the covariates and COPD inclusive of unmeasured exposures of genetics and air pollution (Figure 1). DAGs are diagrams used to help understand the relationships and influences between variables.[21] In this analysis, each covariate shown in the DAG, was selected one-at-a-time, and treated as an exposure to generate the minimum adjustment sets necessary for estimating the direct causal effects of risk factors for COPD. Logistic regression was then used to obtain odds ratios (aOR) adjusted for this minimum adjustment set of covariates. Potential covariates included: sex, age, education, BMI, Asthma, childhood breathing problems before age 10, family history of respiratory disease, presence of second-hand smoke in the home, vapors gases and fumes (>3 months exposure) and having worked a year or more in a dusty job. The DAG identified covariates for adjustment (example shown in Figure 2) and the results are presented Table 1 and Supplemental Table S1. This analysis was conducted separately for men and for women (Table 2).

The Global Lung Initiative equations (version 1.3.4 build 4) were used to calculate the LLN for FEV_1/FVC ratio.[17] Level of statistical significance was set at $\alpha<0.05$, and SPSS (ver25, IBM, Armonk, NY) was used to conduct the analysis on unweighted data.

Results

Demographic Characteristics of Never Smokers

The demographic characteristics of the never-smokers, classified by sex, are shown in Table 3. Most of the participants were Caucasian (90.9%) and had 12 years or less of education (70.5%). Females predominated (57.1%) and were significantly older than males (60 years vs 58 years, $p=0.011$). The mean BMI was 27.8 [SD=5.0] kg/m^2. Over two-thirds (68.3%) of the participants were overweight/obese and significantly more males than females (73.7% vs 64.3%, p<0.001), while more females were underweight (3.5% vs 1.4%, $p<0.001$). There were significantly more males than females residing in urban areas (45.9% vs 40.6%) and more females in rural areas (45.8% vs 39.8%) (p=0.046). Less than 1 in 7 lived in remote areas.

Health and Occupational Exposure Characteristics of Never Smokers

The most prevalent respiratory symptoms were cough (21.4%), shortness of breath (SOB) (23.4%) and wheeze (21.6%) (Table 3). There were no sex differences for wheeze, but more females than males reported usually having a cough

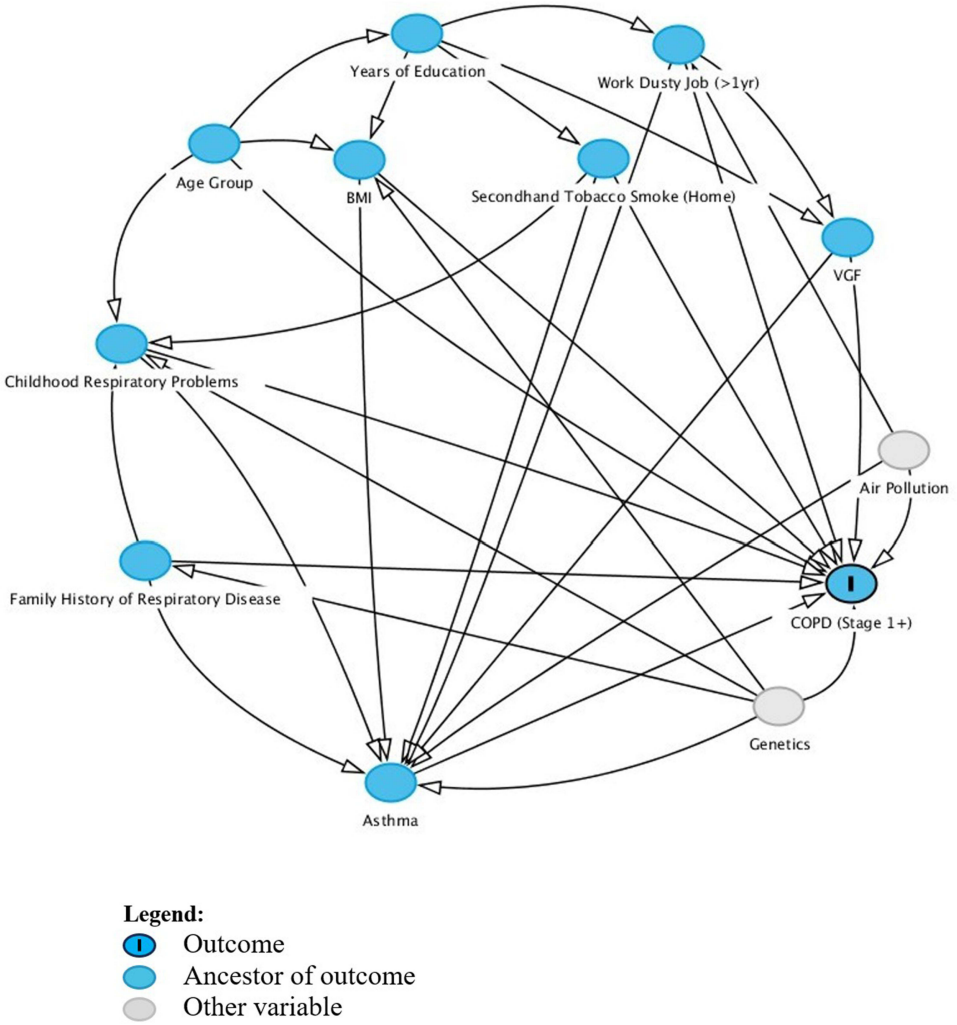

Figure 1 Directed Acyclic Graph (DAG) Showing Relationship between Proposed Exposure Variables and COPD among Never Smokers, BOLD Australia.
Abbreviations: BMI, Body Mass Index; BOLD, Burden of Obstructive Lung Disease; COPD, Chronic Obstructive Pulmonary Disease; VGF, Vapors, Gases and Fumes.

(30.8% vs 22.8%, $p<0.001$) and being SOB on moderate exertion (30.9% vs 13.6%, $p<0.001$), while more males reported phlegm (16% vs 12.3%, $p=0.029$).

Twenty-three percent of never-smokers reported a history of some respiratory condition, more commonly among females than males ($p<0.001$) (Table 3). Asthma (21.5%) and a reported family history of COPD (18.1%) were most frequently reported and significantly more by females than males (p<0.001). No significant differences by sex were observed for those who reported hospitalization due to breathing problems before the age of 10 years.

The most frequently reported occupational exposure was working in a dusty job for one year or more (27.8%), more commonly in males (p<0.001), with similar findings for inorganic dust, organic dust or vapors, gases, and fumes ($p<0.001$). No sex differences were seen for exposure to second-hand smoke within the home.

The prevalence of COPD was 10.5% (95% CI: 9.1–12.1%) when defined as FEV_1/FVC ratio <0.70 and 4.6% (3.7–5.8%) when defined as the ratio < LLN. There were no significant sex differences observed for either definition (Table 3). Doctor diagnosed COPD was reported by 4.1% of participants and significantly more females than males reported a diagnosis (5.5% vs 2.3%, p<0.001). Out of 212 pairs (13%) where people had different COPD diagnoses (spirometry vs self-reported doctor diagnoses), 75% with FEV_1/FVC ratio < 0.70 did not report a doctor's diagnosis of COPD while 25% with FEV_1/FVC ratio > 0.70 (ie with spirometric evidence of no COPD) did report doctor diagnosed COPD (McNemar's test, p=0.002).

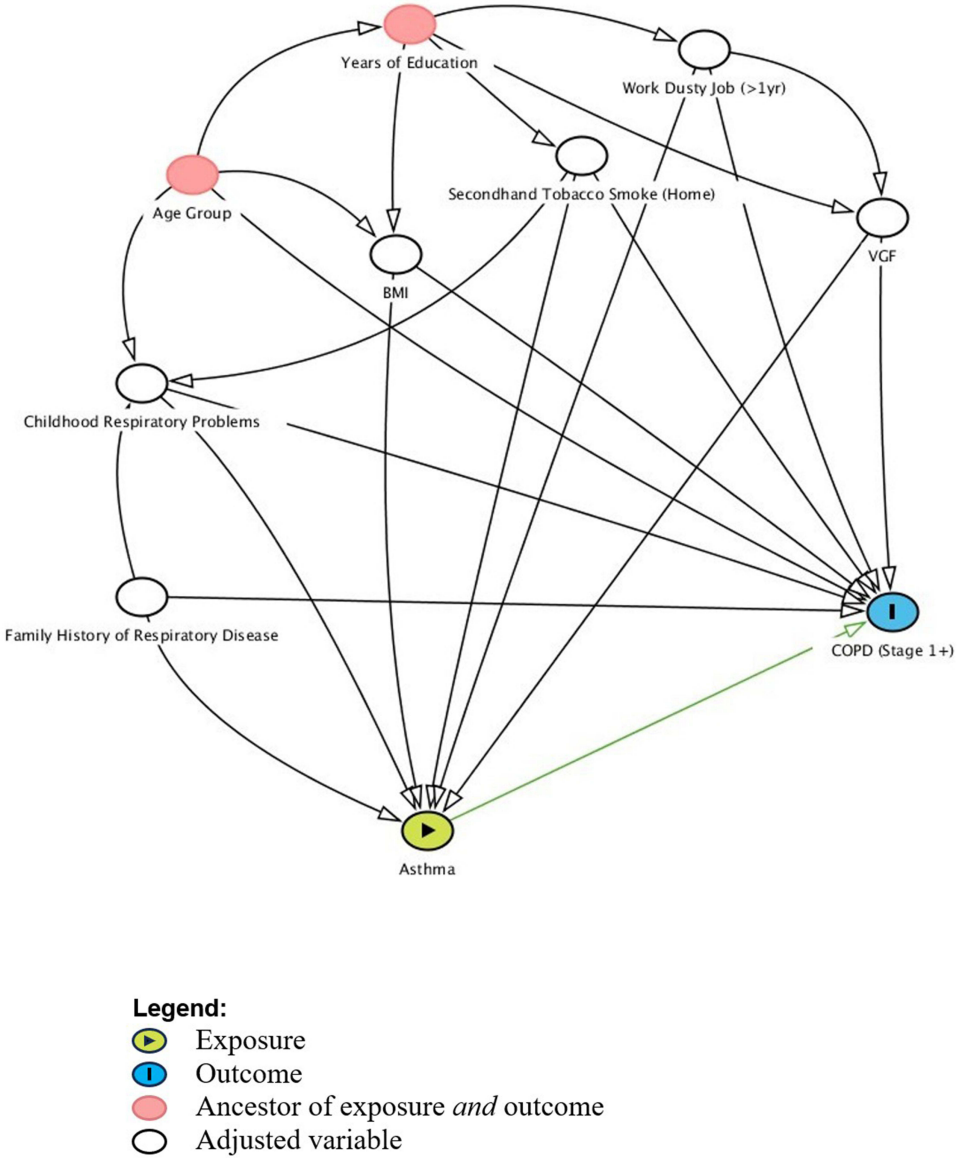

Figure 2 Directed Acyclic Graph (DAG) Illustrating the Relationship between Asthma and COPD among Never Smokers, BOLD Australia.
Notes: Minimum adjustment to estimate the direct effect of asthma on COPD: Secondhand tobacco smoke (home), Body mass index (BMI), breathing problems before age 10 years, family history of respiratory disease, work dusty job (>1yr) and vapors gases and fumes (VGF).
Abbreviations: BMI, Body Mass Index; BOLD, Burden of Obstructive Lung Disease; COPD, Chronic Obstructive Pulmonary Disease; VGF, Vapors, Gases and Fumes.

Lung Function Profiles

Overall Profile – All Persons

Never-smokers with COPD defined as FEV_1/FVC ratio <0.70 were significantly older than those without COPD [mean age 68 (SD 11) vs mean age 58 (11 years), p<0.001].

In Table 1, we examined exposure variables to identify significant uOR and aORs overall and by sex. As age increased the odds of COPD increased 4-fold among those 60–69 and nearly 9-fold for those 70 and older compared to those aged 40–49 years, after controlling for covariates listed in Table 1 (aOR=4.11 and 8.73, respectively) (Table 1). Those with a family history of respiratory disease (aOR = 1.51) and who experienced hospitalization due to breathing problems before the age of 10 years (aOR=2.70) were at increased risk of COPD, compared to those without. Controlling for the covariates did not substantially alter (<10% increase) the odds (Table 1).

Table 1 Characteristics of Never-Smokers and Adjusted Odds Ratios for Selected Exposure Variables by COPD (GOLD 1+), BOLD Australia

Characteristics	COPD (n=174)		No COPD (n=1482)		Unadjusted OR (95% CI)	Adjusted OR (95% CI)
	n	%	n	%		
Demographic Characteristics [T]						
Sex						
Male	85	48.9%	626	42.2%	1.31 (0.95, 1.79)	
Age Group						
40–49 years	16	9.2%	403	27.2%	1	1
50–59 years	25	14.4%	468	31.6%	1.34 (0.71, 2.55)	1.29 (0.66, 2.49)
60–69 years	52	29.9%	339	22.9%	**3.86 (2.17, 6.89)**	**4.11 (2.24, 7.55)**
70+ years	81	46.6%	272	18.4%	**7.50 (4.29, 13.10)**	**8.73 (2.83, 15.78)**
	Adjusted covariates: Secondhand Tobacco Smoke (Home), BMI, Breathing Problems before Age 10 years, Years of Education, Family History of Respiratory Disease, Asthma, Work in Dusty Job (>1yr)					
Ethnicity						
Caucasian	164	94.3%	1340	90.5%	1.75 (0.92, 3.53)	
Years of Education						
(> 12 years)	35	20.1%	454	30.6%	**0.57 (0.39, 0.84)**	0.83 (0.54, 1.28)
	Adjusted covariates: Secondhand Tobacco Smoke (Home), Age Group, BMI, VGF, Work Dusty Job (>1yr), Asthma, Breathing Problems before Age 10 years, Family History of Respiratory Disease					
Body Mass Index						
Normal	58	34.1%	414	28.5%	1	1
Low	5	2.9%	37	2.5%	0.96 (0.36, 2.55)	0.82 (0.29, 2.34)
Overweight/Obese	107	62.9%	1002	69.0%	0.76 (0.54, 1.07)	**0.64 (0.45, 0.93)**
	Adjusted covariates: Secondhand Tobacco Smoke (Home), Age Group, Asthma, Breathing Problems before Age 10 years, Family History of Respiratory Disease, VGF, Work Dusty Job (>1yr)					
Urbanicity						
Urban	79	45.4%	631	42.6%	1	
Rural	78	44.8%	638	43.0%	0.98 (0.70, 1.36)	
Remote	17	9.8%	213	14.4%	0.64 (0.37, 1.10)	
Health Characteristics, Occupational and Environmental Exposures [T]						
Symptoms						
Cough	58	33.3%	395	26.7%	1.38 (0.98, 1.92)	
Phlegm	32	18.4%	198	13.4%	1.46 (0.97, 2.21)	
Wheeze (last 12 months)	73	42.0%	285	19.2%	**3.03 (2.19, 4.21)**	
Shortness of Breath (n=1587) [†]	53	32.3%	319	22.4%	**1.65 (1.16, 2.34)**	
History of Respiratory Conditions						
Chronic Bronchitis	12	6.9%	40	2.7%	**2.67 (1.37, 5.19)**	
Doctor Diagnosed COPD	15	8.6%	53	3.6%	**2.54 (1.40, 4.62)**	
Any Respiratory Condition	68	39.1%	319	21.5%	**2.34 (1.68, 3.25)**	

(*Continued*)

Table 1 (Continued).

Characteristics	COPD (n=174)		No COPD (n=1482)		Unadjusted OR (95% CI)	Adjusted OR (95% CI)
	n	%	n	%		
Asthma	63	36.2%	293	19.8%	**2.30 (1.65, 3.22)**	**2.06 (1.45, 2.94)**
	Adjusted covariates: Secondhand Tobacco Smoke (Home), BMI, Breathing Problems before Age 10 years, Family History of Respiratory Disease, VGF, Work Dusty Job (>1yr)					
Breathing Problems Before Age 10	23	13.4%	85	5.8%	**2.50 (1.53, 4.08)**	**2.70 (1.55, 4.73)**
	Adjusted covariates: Secondhand Tobacco Smoke (Home), Age Group, Asthma, BMI, Family History of Respiratory Disease, VGF, Work Dusty Job (>1yr)					
Family History Respiratory Problems	42	24.1%	258	17.4%	**1.51 (1.04, 2.19)**	**1.51 (1.01, 2.26)**
	Adjusted covariates: Secondhand Tobacco Smoke (Home), Age Group, Asthma, BMI, Breathing Problems before Age 10 years, VGF, Work Dusty Job (>1yr), Educational Level Attained					
Co-Morbid Conditions						
Heart Disease	27	15.5%	100	6.7%	**2.54 (1.61, 4.01)**	
Hypertension	75	43.1%	492	33.2%	**1.52 (1.11, 2.10)**	
Diabetes	17	9.8%	131	8.8%	1.12 (0.66, 1.90)	
Occupational Exposures						
Secondhand Smoke (home)	11	6.3%	95	6.4%	0.98 (0.52, 1.88)	1.15 (0.54, 2.45)
	Adjusted covariates: Age Group, Asthma, BMI, Breathing Problems before Age 10 years, Family History of Respiratory Disease, VGF, Work Dusty Job (>1yr)					
Worked in Dusty Job (>1 year)	59	33.9%	401	27.1%	1.38 (0.99, 1.93)	1.26 (0.88, 1.82)
	Adjusted covariates: Secondhand Tobacco Smoke (Home), Years of Education, Asthma, BMI, Breathing Problems before Age 10 years, Family History of Respiratory Disease, VGF					
Vapors Gas and Fumes	17	9.8%	119	8.0%	1.24 (0.73, 2.12)	1.17 (0.66, 2.07)
	Adjusted covariates: Secondhand Tobacco Smoke (Home), Years of Education, Asthma, BMI, Breathing Problems before Age 10 years, Family History of Respiratory Disease, Work Dusty Job (>1yr)					

Notes: GOLD 1+ is defined as the ratio of the forced expiratory volume(FEV_1) in the first one second to the forced vital capacity (FVC) <0.70 and any FEV1%predicted. BMI: Low (<20 kg/m^2), Normal (20–25 kg/m^2), Overweight/Obese (>25 kg/m^2). Each covariate was run as an individual exposure variable. Adjusted covariates are shown. Statistics in bold are significant at α<0.05. A direct effects model was used. [¶]Unexposed numbers not shown for dichotomous variables. [†]Shortness of breath on moderate exercise.

Abbreviations: BMI, Body Mass Index; BOLD, Burden of Obstructive Lung Disease; CI, Confidence Interval; COPD, Chronic Obstructive Pulmonary Disease; OR, Odds Ratio; VGF, Vapors, Gases and Fumes; Yr, Year.

Among never-smokers with more than 12 years of education, the odds of COPD were 43% lower (uOR = 0.57) than for those with less education, but the aOR was not significant after adjusting for the covariates (Table 1). The odds of COPD among overweight/obese never-smokers were 36% lower (aOR=0.64) compared to those with normal weight, after adjusting for the relevant covariates (see Table 1). No associations were observed for second-hand smoke in the home, nor for occupational exposures.

COPD- Profiles for Males and Females

When the data were examined by sex (Table 2), males who never smoked had a near 6-fold increase in odds of COPD among those aged 60–69 years and an 11-fold increase among those aged 70 years and older (aOR=5.88 and 11.05, respectively) compared to the 40–49-year age group, after controlling for covariates. Among male never-smokers, after controlling for covariates, the odds of COPD also increased among those with asthma (aOR=2.45), a family history of

Table 2 Adjusted and Unadjusted Odds Ratios by Sex for Selected Exposure Variables and COPD Among Never Smokers, BOLD Australia

Exposure Variables	Males		Females	
	Unadjusted OR (95% CI)	**Adjusted OR (95% CI)**	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)**
Age Group				
40–49 years	1	1	1	1
50–59 years	0.97 (0.38, 2.49)	0.90 (0.33, 2.48)	1.78 (0.72, 4.42)	1.69 (0.67, 4.25)
60–69 years	**4.86 (2.23, 10.6)**	**5.88 (2.48, 13.9)**	**3.27 (1.37, 7.78)**	**3.32 (1.35, 8.13)**
≥70 years	**7.69 (3.58, 16.5)**	**11.05 (4.69, 26.1)**	**7.77 (3.41, 17.7)**	**7.87 (3.32, 18.7)**
	Adjusted covariates: Secondhand Tobacco Smoke (Home), BMI, Breathing Problems before Age 10 years, Years of Education, Family History of Respiratory Disease, Asthma, Work in Dusty Job (>1yr)			
Body Mass Index				
Normal	1	1	1	1
Low	0.53 (0.06, 4.34)	0.34 (0.04, 3.10)	1.38 (0.45, 4.23)	1.19 (0.36, 3.93)
Overweight/Obese	**0.52 (0.322, 0.86)**	**0.52 (0.30, 0.90)**	1.01 (0.62, 1.62)	0.79 (0.47, 1.31)
	Adjusted covariates: Secondhand Tobacco Smoke (Home), Age Group, Asthma, Breathing Problems before Age 10 years, Family History of Respiratory Disease, Vapors, Gases and Fumes (VGF), Work Dusty Job (>1yr)			
Years of Education (>12 years)	0.59 (0.35, 1.01)	0.90 (0.48, 1.70)	0.53 (0.35, 1.01)	0.73 (0.39, 1.35)
	Adjusted covariates: Secondhand Tobacco Smoke (Home), Age Group, BMI, VGF, Work Dusty Job (>1yr). Asthma, Breathing Problems before Age 10 years, Family History of Respiratory Disease			
Asthma	**2.90 (1.76, 4.77)**	**2.45 (1.42, 4.23)**	**2.05 (1.30, 3.24)**	**1.85 (1.14, 2.99)**
	Adjusted covariates: Secondhand Tobacco Smoke (Home), BMI, Breathing Problems before Age 10 years, Family History of Respiratory Disease, VGF, Work Dusty Job (>1yr)			
Family History of Respiratory Disease	**1.93 (1.10, 3.39)**	**2.15 (1.11, 4.16)**	1.33 (0.81, 2.21)	1.33 (0.78, 2.25)
	Adjusted covariates: Secondhand Tobacco Smoke (Home), Age Group, Asthma, BMI, Breathing Problems before Age 10 years, VGF, Work Dusty Job (>1yr). Additional Adjustments: Educational Level Attained			
Breathing Problems before Age 10 years	**2.65 (1.32, 5.32)**	**2.67 (1.14, 6.25)**	**2.34 (1.17, 4.69)**	**2.49 (1.16, 5.37)**
	Adjusted covariates: Secondhand Tobacco Smoke (Home), Age Group, Asthma, BMI, Family History of Respiratory Disease, VGF, Work Dusty Job (>1yr)			
Secondhand Tobacco Smoke	1.35 (0.58, 3.12)	1.24 (0.42, 3.65)	0.67 (0.24, 1.90)	0.99 (0.32, 2.89)
	Adjusted covariates: Age Group, Asthma, BMI, Breathing Problems before Age 10 years, Family History of Respiratory Disease, VGF, Work Dusty Job (>1yr)			
Work in Dusty Job (>1year)	1.33 (0.84, 2.09)	1.28 (0.77, 2.14)	1.25 (0.71, 2.19)	1.07 (0.60, 1.93)
	Adjusted covariates: Secondhand Tobacco Smoke (Home), Years of Education, Asthma, BMI, Breathing Problems before Age 10 years, Family History of Respiratory Disease, VGF			
Occupational Exposure to Gases, Vapors, and Fumes	1.17 (0.66, 2.07)	1.08 (0.58, 2.01)	1.06 (0.05, 6.55)	–
	Adjusted covariates: Secondhand Tobacco Smoke (Home), Years of Education, Asthma, BMI, Breathing Problems before Age 10 years, Family History of Respiratory Disease, Work Dusty Job (>1yr)			

Notes: BMI: Low (<20 kg/m^2), Normal (20–25 kg/m^2), Overweight/Obese (>25 kg/m^2). Each covariate was run as a separate exposure variable. Adjusted covariates are shown. Statistics in bold are significant at α<0.05. Direct effects models were fitted.

Abbreviations: BMI, Body Mass Index; BOLD, Burden of Obstructive Lung Disease; CI, Confidence Interval; COPD, Chronic Obstructive Pulmonary Disease; OR, Odds Ratio; VGF, Vapors, Gases and Fumes; Yr, Year.

Table 3 Characteristics of Never-Smokers by Sex, BOLD-Australia Study

Characteristics	All (N=1656)		Male (n=711)		Female (n=945)		*p-value*
	n	%	n	%	n	%	
Demographics Characteristics							
Age, mean (SD)	59.3	11.6	58.4	11.6	59.9	11.5	**0.011***
Age Group							0.080
40–49 years	419	25.3%	202	28.3%	217	22.9%	
50–59 years	493	29.8%	208	29.3%	285	30.1%	
60–69 years	391	23.6%	157	22.0%	234	24.8%	
70+ years	353	21.3%	144	20.3%	209	22.1%	
Ethnicity							0.998
Caucasian	1504	90.9%	646	90.9%	858	90.9%	
Indigenous	67	4.0%	29	4.1%	38	4.0%	
Other	84	5.1%	36	5.1%	48	5.1%	
Years of Education							**0.057**
≤12 years	1167	70.5%	483	67.9%	684	72.4%	
> 12 years	484	29.3%	225	31.8%	259	27.5%	
BMI (kg/m^2), mean (SD)	27.8	5.0	27.7	4.0	27.8	5.6	0.734*
BMI Category							**<0.0001**
Low	42	2.6%	10	1.4%	32	3.5%	
Normal	472	29.1%	173	24.8%	299	32.3%	
Overweight/Obese	1109	68.3%	514	73.7%	595	64.3%	
Urbanicity							**0.046**
Rural	716	43.2%	283	39.8%	433	45.8%	
Urban	710	42.9%	326	45.9%	384	40.6%	
Remote	230	13.9%	102	14.3%	128	13.5%	
Health Characteristics, Occupational and Environmental Exposures							
Symptoms							
Cough	453	27.4%	162	22.8%	291	30.8%	**<0.001**
Shortness of Breath (moderate exercise)	372	23.4%	93	13.6%	279	30.9%	**<0.001**
Wheeze (last 12 month)	358	21.6%	146	20.5%	212	22.5%	0.347
Phlegm	230	13.9%	114	16.0%	116	12.3%	**0.029**
History of Respiratory Conditions							
Any Respiratory Condition	387	23.4%	134	18.9%	253	26.8%	**<0.001**
Asthma	356	21.5%	124	17.4%	232	24.6%	**<0.001**
Family History	300	18.1%	100	14.1%	200	21.2%	**<0.001**
Breathing Problems Pre-Age 10	108	6.6%	49	7.0%	59	6.3%	0.592
Chronic Bronchitis	52	3.1%	8	1.1%	44	4.7%	**<0.001**
Co-morbidities							
Hypertension	567	34.2%	228	32.1%	339	35.9%	0.106
Heart Disease	127	7.7%	59	8.3%	68	7.2%	0.404
Diabetes	148	8.9%	54	7.6%	94	9.9%	0.097
Lung Function (Post-bronchodilator)							
Doctor Diagnosed COPD	68	4.1%	16	2.3%	52	5.5%	**0.001**
COPD GOLD 1+	174	10.5%	85	12.0%	89	9.4%	0.096
COPD GOLD 2+	71	4.3%	26	3.7%	45	4.8%	0.272
COPD LLN Stage 1+	77	4.6%	32	4.5%	45	4.8%	0.803
COPD LLN Stage 2+	50	3.0%	19	2.7%	31	3.3%	0.474

(*Continued*)

Table 3 (Continued).

Characteristics	All (N=1656)		Male (n=711)		Female (n=945)		*p-value*
	n	%	n	%	n	%	
Occupational & Environmental Exposures							
Work in Dusty Job (>1 year)	460	27.8%	307	43.2%	153	16.2%	**<0.001**
Organic Dust (≥3 months)	271	19.5%	166	23.3%	105	11.1%	**<0.001**
Vapors, Gases and Fumes (≥3 months)	136	8.2%	127	17.9%	9	1.0%	**<0.001**
Inorganic Dust (≥3 months)	131	7.9%	113	15.9%	18	1.9%	**<0.001**
Secondhand Tobacco Smoke (home)	106	6.4%	46	6.5%	61	6.3%	0.921

Notes: Percentages presented unless otherwise stated; *t-test statistic; Significant p-values are in bold; GOLD 1+ is defined as the ratio of the forced expiratory volume(FEV_1) in the first one second to the forced vital capacity (FVC) <0.70 and any FEV1%predicted; and GOLD 2+ is defined as FEV1/FVC <0.70 and any FEV1%predicted <80%; BMI: Low (<20 kg/m^2), Normal (20–25 kg/m^2), Overweight/Obese (>25 kg/m^2).

Abbreviations: BMI, Body Mass Index; BOLD, Burden of Obstructive Lung Disease; COPD, Chronic Obstructive Pulmonary Disease; GOLD, Global Burden of Obstructive Lung Disease; LLN, Lower Limit of Normal; SD, Standard Deviation.

respiratory disease (aOR=2.15), and a history of hospitalization due to breathing problems prior to age 10 years (aOR=2.67). There were no observed associations for BMI, years of education, exposure to second-hand smoke and working in a dusty job for more than a year.

For females who never smoked, the odds of COPD increased for those aged 60–69 years (aOR=3.32) and 70 years and over (aOR=7.87) compared with those aged 40–49 years There was no substantial change in the odds after controlling for the covariates in Table 2. The odds of COPD also increased among female never-smokers with asthma (aOR=1.85) and those with history of hospitalization due to breathing problems prior to age 10 (aOR=2.49), after controlling for covariates. There were no observed associations for BMI or a family history of respiratory disease.

Ratio FEV_1/FVC < LLN Profile

Odds ratios are presented in Supplemental Table S1 for selected independent variables of ratio <LLN1+, after controlling for the potential confounding effects identified by the DAGs. Compared to never-smokers aged 40–49 years, the risk of ratio <LLN1+ increased 2-fold among those aged ≥70 years, after adjusting for relevant covariates. Increased odds of COPD remained among those with asthma (aOR=5.00) and breathing problems before the age of 10 years (aOR=4.52) after adjusting for covariates. There were no observed associations for BMI, years of education, family history of respiratory disease, and exposure to second-hand smoke in the home, working in a dusty job, or vapors, gases, and fumes.

Discussion

In this study of Australian never-smokers aged 40 years and older, the prevalence of mild to very severe airflow limitation was observed to be 10.5%, as defined by COPD GOLD 1+, and 4.6% when based on the lower limit of normal. A substantial proportion of never-smokers were either misdiagnosed or underdiagnosed by their physicians for COPD. The analysis identified several independent predictors of COPD. These included older age, fewer years of education, a history of asthma, a family history of respiratory disease, and experiencing hospitalization due to breathing difficulties before the age of 10 years. Notably, the predictors common to both males and females were older age, asthma, and a history of hospitalization for breathing difficulties before age 10. Family history of respiratory disease was a further predictor of COPD in men but overweight/obesity in men presented as being protective.

In the main BOLD-Australia study approximately one in every three of those with COPD (33%) had never smoked, and this finding was consistent with other studies, yet global estimates for COPD indicate 22–51% were never smokers.[22–24] In this sub-analysis, the 10.5% prevalence of mild to severe COPD (GOLD Stage 1+) observed among never-smokers was approximately half that of ever-smokers (21.1%). In contrast to never smokers, Toelle et al reported a 14.5% weighted prevalence of COPD (smokers and never ever smokers) among the general Australian population.[3] In general, the prevalence of COPD among never-smokers in our study was relatively consistent with a reported prevalence

of 12.2% for 14 BOLD country sites and within a wide range of 1.1% to 40% in other reports.[8,9,24–26] The variability observed across these studies may be explained by the different methods and definitions used for COPD, socioeconomic status, demographics, or tobacco control measures.

Although COPD is a leading cause of mortality and morbidity globally, it is often underdiagnosed.[27–29] This underdiagnosis varied from 10% to 95% across studies. A study that utilized data from four large population-based surveys, including BOLD-International, reported that 81.4% of spirometry-defined COPD cases were under-diagnosed.[30] Our study had similar findings, with a high rate of underdiagnosis in never-smokers; three in four spirometry-confirmed COPD patients. This could be related to the low use of spirometry by health providers, poor awareness of COPD symptoms among patients, or a low suspicion of the disease, as these were never-smokers. The greater number of females with physician-diagnosed COPD could be because they are more likely to seek medical attention than men, although the higher count of older women compared to men might indicate that women sought medical care when the disease was more advanced.[31]

Studies of respiratory symptoms in never-smokers have shown that they are less likely to have common COPD symptoms such as dyspnea and wheezing and a lower prevalence of cough and sputum than smokers.[8,24] In our analysis of only never-smokers, we found that the symptoms associated with COPD were wheezing in the previous 12 months and dyspnea. Similar to the Austrian BOLD study, never-smokers were mostly older females.[13] We found that respiratory conditions, such as chronic bronchitis and asthma, were more commonly reported by females and were also associated with COPD in never-smokers. Chronic bronchitis in the presence of exacerbations and asthma overlapping with COPD are considered clinical phenotypes of COPD in smokers.[32] However, this disease overlap was not as clear in never-smokers. Similar to other studies, we also report a few cases of chronic bronchitis among never-smokers.[22,24] Furthermore, more than one in three with COPD, post-bronchodilator, had self-reported asthma.

Salvi and Barnes showed that a low socioeconomic status (SES) was associated with COPD and proposed it as a risk factor.[23] The present analysis showed that people with less education, as a proxy for low SES, were more likely to have COPD. This association between low SES and disease is consistent with unhealthy lifestyle practices, higher environmental and occupational exposures, and biological risk factors, resulting in reduced lung function.[9,19] COPD is also known to develop over a long period of time, typically manifesting later in life at 40 years or older. Our study showed that COPD increased with age in both males and females, and age ≥60 years was a strong predictor of COPD. Disease manifestation is mainly due to the cumulative effect of airway injuries early in life and the natural decline in lung function due to aging. This indicates that the presence of COPD in never-smokers could also be linked to different lung function trajectories that could be observed at an early stage in life.[33]

Early lung damage or respiratory conditions during childhood contribute to the development of COPD in adulthood. In our study, early childhood breathing problems were associated with an increased risk of COPD in both sexes. Adverse events manifesting in childhood (eg, viral infections, pneumonia, bronchitis) could lead to the development of COPD later in life.[34] A further complication is the age-related decline in lung function. This highlights the importance of establishing baseline peak lung function, usually achieved in the early twenties, as a risk marker for COPD in the future. Our study also found that a family history of first-degree relatives with a diagnosis of emphysema, chronic bronchitis, or COPD was an independent predictor of COPD in never-smokers. Previous studies reporting family history yielded mixed results,[10,35] and the Tunisian BOLD study found no associations.[10,12,35] There was also a strong association between COPD and family history in men in our study, but none was detected in women. The association in men could have an epigenetic basis with family history being a proxy for the interaction between genetic predisposition and environmental exposures.[36] Since genetic factors are known to play a role in the development of COPD, it is likely that the predisposition for COPD could be more prominent or that the interaction with the environment is greater in men than in women.

An inherent characteristic of the sample was the BMI profile of the participants. In this study, overweight/obesity appeared to reduce the risk of COPD, particularly among men. However, obesity is recognized widely as a known risk factor for many other chronic conditions. Nonetheless, our findings align with other research studies, underscoring overweight/obesity can be protective although BMI is associated with lung function decline.[37,38] This paradox may require further research since the observed association could be due to the complex relationship

between BMI and lung vital capacity. Vital capacity is known to decrease with age which would further be compounded by the added weight from being overweight/obese, reducing lung compliance.

A strength of this study is the large sample size of never-smokers provided robust findings, and the use of quality-controlled spirometry served to objectively define COPD, aligning with the aim to establish comparable statistics with other studies. However, some limitations should be acknowledged. The cross-sectional design of the study limits our ability to infer causation. The significance of some associations might not have persisted following the analysis stratified by socioeconomic status due to insufficient statistical power. Most risk factors, like occupational exposures, relied on self-report, introducing potential recall bias. While we also presented COPD as defined by the lower limit of normal, it should be noted that some misclassification could be present, given the greater use of the GOLD criteria up to now. Notably, GOLD estimates might potentially overestimate COPD due to the inclusion of mild airflow limitation, particularly among older age groups.

Conclusion

The observed prevalence of COPD among never-smokers was greater than expected. These findings underscore the complex interplay of diverse factors in the development of COPD among never-smokers. Despite generally healthier status compared to smokers, never-smokers account for a notable proportion of COPD cases across a range of severity among older individuals. The study highlights that epigenetic effects are likely at work, particularly in cases of family history of respiratory disease and childhood respiratory issues, amplifying COPD risk. Further exploration of these aspects remains pivotal. Routine screening by establishing baseline lung function in early twenties, followed by periodic measurements for monitoring changes should be implemented. Such an approach would aid early detection and prevention strategies.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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