Original Article

Association of Pulmonary Symptoms and Co-Morbidity Diseases with Lung Function in Adult Smokers

Abstract

Background: This study aims to evaluate the relationship of pulmonary symptoms and co-morbidity diseases with lung function in adult smokers. **Methods:** Three hundred and fifty men adults over the age of 20 were involved. Spirometry tests were performed for measuring FVC, FEV1, and FEV1% FVC. COPD was categorized into four stages (I–IV) by the (GOLD) criteria of post-bronchodilator FEV1/FVC <0.70. For comparing the mean of pulmonary functions regarding the following variables, pulmonary symptoms, and co-morbidity diseases, t-test was used. Spearman's correlation analysis was performed to get association between stages of COPD and study variables. Further analysis using multiple regressions was conducted to confirm the predictors of the pulmonary functions. The level of significance is taken as $P < 0.05$. **Results:** The mean age of participants was 54.7543 ± 13.44. A total of 43 (19.5%) participants were COPD; 7% of them were Stage I, 23.3% were Stage II, 39.5% were Stage III, and 30.2% were Stage IV. The mean of FEV1 in participants with shortness of breath (P < 0.001), cough (P = 0.001), wheezing (P = 0.023), as well as cardiovascular disease (P = 0.038) was significantly less in compared to those without these symptoms and disease. Also the mean of FVC in participants with shortness of breath (P < 0.001) and cough (P = 0.029) was significantly less in compared to others. Finally, the mean of FEV1/FVC in participants with shortness of breath (P < 0.001), cough (P = 0.001), and wheezing (P = 0.01) was less. The relationship between stages of COPD and other variables indicated a significant association between stages of COPD and diabetes mellitus (β = -.342P = 0.030). According to linear regression model, shortness of breath was the only influential variable on FEV1 (B = -.383CI: -23.729, -12.155 $P < 0.001$), FVC (B = -.296CI: -.365CI: -15.336, -6.082 $P < 0.001$), and FEV1/FVC (B = -.365, CI: -18.362, -9.029 $P < 0.001$). **Conclusions:** Pulmonary symptoms including shortness of breath, cough, and wheezing influenced the lung function in adult smokers. Additionally, shortness of breath was associated with FEV1, FVC, and FEV1/FVC. Cardiovascular disease decreased FEV1 in smokers, whereas diabetes mellitus was associated with milder COPD stages.

Keywords: *Co-morbidity, respiratory function tests, smoking cessation, symptoms*

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Introduction

Obstructive airway disease usually occurs with respiratory symptoms such as wheezing, shortness of breath, cough, and sputum.[1,2] Moreover, several co-morbid conditions such as cardiovascular disease and diabetes mellitus in association with COPD increased the rate of mortality.[3,4] Studies have shown that decreased lung function is a marker of premature mortality, especially in cardiovascular disease.[5,6] Respiratory symptoms[7,8] and decreased lung function[7,8] are both[9,10] individually related to higher mortality rates. Poor control of symptoms is one of the most common reasons why adults with obstructive airway disease go to the emergency room and see a doctor.[11] In addition, the decline in lung function, expressed in forced expiratory volume in one second (FEV1), is accelerated in adults with asthma than in adults without asthma.[12] The association between respiratory symptoms and impaired lung function has already been investigated in individuals with asthma, and cough is especially important.[13,14] However, the relationship between respiratory symptoms and lung function in adult smokers is unclear. Therefore, our aim was to clarify the relationship between pulmonary symptoms as well as underlying diseases with lung function.

Methods

Design and population

This cross-sectional study was conducted from November 2019 to April 2020 at

How to cite this article: Sadeghi S, Ghiasi F, Toghyani A. Association of pulmonary symptoms and co-morbidity diseases with lung function in adult smokers. Int J Prev Med 2025;16:52.

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Access this article online

Website: www.ijpvmjournal.net/www.ijpm.ir

DOI: 10.4103/ijpvm.ijpvm_544_21

Quick Response Code:

AL-Zahra Hospital, Isfahan Medical University. This study was approved and funded by Isfahan Medical University in Code of Ethics (IR.MUI.MED.REC.1398.710). The inclusion criteria for the patients were being at the age of over 18 years having smoking, and in this study, the women did not meet the eligible criteria.

Each participant signed a consent form to take part in the study. The exclusion criteria for this study are: (a) presence of acute respiratory infections, (b) lung disease counting lung cancer, interstitial lung disease, tuberculosis, neuromuscular disorders, and pneumothorax, and (c) failing to perform technically acceptable respiratory function tests.

A total of 350 patients had inclusion criteria during the study period, but 129 participants were excluded according to the exclusion criteria for this study. Therefore, there were 221 participants evaluated in this study. An adult who has smoked 100 cigarettes in his or her lifetime and who currently smokes cigarettes defined "current smoker."[15] All participants, with or without symptoms, asked to fill out a checklist requesting information on age, smoking habit including age of the onset smoking, duration of smoking (year), number of cigarette packs consumed daily; pulmonary symptoms including shortness of breath, cough, sputum, and wheezing; underlying disorders including diabetes mellitus,[16] hypertension,[17] cardiovascular diseases (myocardial infarction, stroke, heart failure, angina or transient ischemic attacks),[18-20] and gastric reflux disease[21] And then they were tested for their lung function.

Pulmonary function assessment

Spirometry was performed before and 15 minutes after the administration of 400 micrograms of salbutamol by trained technicians according to the standards of the American Thoracic Society (ATS) and the European Respiratory Society (ERS).[22] While seated, the participants were asked to make a forced exhalation followed by a forced inhalation. Forced vital capacity (FVC), forced expiratory volume in one second (FEV1), and FEV1 percent in relation to the maximal FVC (FEV1%FVC) were recorded. FVC was characterized as the biggest acceptable curve of either forced expiratory or forced inspiratory vital capacity. Reported FEV1 is considered a good biological marker for the risk of obstructive pulmonary disease. If the quality of the spirometry was not satisfactory, the procedure was repeated until the best quality was achieved. The highest FVC and highest FEV1 values were selected from measurements that met the reproducibility criteria. A pulmonologist reviewed the quality of all the tests. Bronchodilator responsiveness (BDR) was calculated more than 12% changes of the baseline forced expiratory volume in one second (FEV1) if this also exceeds 200 mL according to ATS guidelines.[23] COPD was identified by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria of post-bronchodilator FEV1/FVC <0.70. FEV1/FVC <70%, in combination with FEV1 ≥80% (Stage I), or 50%≤FEV1 <80% (Stage II), or 30% ≤ FEV1 < 50% (Stage III), or FEV1 ≤30% (Stage IV). ATS guidelines were used to assess bronchodilator response (BDR) (post FEV1 12% more than pre FEV1).[24]

Variable definition

Age was self-reported. Detailed assessments of smoking history were recorded as reported by the participants at the time of enrollment including age at which participants started smoking (year), duration of smoking (calculated as the difference between the age at time of quitting or time of enrollment and the age at smoking initiation), and the average number of cigarette packs consumed daily.[25] Pulmonary symptoms include shortness of breath which assessed by asking the question, "Do you have to walk slower than people of your age on the level because of breathlessness?"; and "Are you too breathless to leave the house or breathless on dressing or undressing?", cough which assessed by asking the question, "Do you usually have a cough?", sputum production assessed by question the patients "Do you usually bring up phlegm from your chest?", wheezing assessed by asking the question "Does your chest ever sound wheezy or whistling apart from colds?",[26] and gastric reflux disease assessed by asking "Do you have heartburn and an unpleasant taste in the back of the mouth?".[21]

Subjects were classified as having diabetes if they reported either a diagnosis of diabetes at baseline or had impaired fasting or post-glucose load glucose levels (.140 mg/dL) upon examination. Subjects reporting a diagnosis of a previous myocardial infarction, stroke, heart failure, angina or transient ischemic attacks were classified as having cardiovascular disease at the baseline examination. Subjects were classified as having hypertension if they reported physician diagnosis of hypertension, were receiving treatment for hypertension, or had evidence of hypertension upon examination (diastolic blood pressure o90 mmHg or a systolic blood pressure o140 mmHg, based on three measurements).[27]

Study outcomes include pre/post FVC, pre/post FEV1, and pre/post FEV1/FVC measured by spirometry. COPD was defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria of post-bronchodilator FEV1/FVC <0.70 (22). Bronchodilator response (BDR) was calculated with (post FEV1 – preFEV1/preFEV1 ×100 is more than 12%).[24]

Statistical analysis

Data are presented as mean (SD) or frequency (percent). For comparing the mean of pulmonary functions in categories of variables, independent t-test was used. Pearson's Chi-square test was done to get association between severity of COPD and the variables of study. Further analysis using multiple regressions was conducted to confirm the predictors of the pulmonary functions. The level of significance is taken as

$P < 0.05$. Statistical analysis was conducted by the SPSS software version 16 (SPSS Inc., Chicago).

Results

Two hundred and twenty-one men participated in the study. The information about the measured variables is seen as frequency (percentage) or mean (SD) in Table 1. According to table, the mean age of participants was 54.75 ± 13.44. A total of 43 (19.5%) of them were COPD; 7% of them were Stage I, 23.3% were Stage II, 39.5% were Stage III, and 30.2% were Stage IV. For evaluation of bronchodilator response (BDR), we used ATS guidelines (post FEV1 – preFEV1/pre FEV1 × 100 more than 12%) and in 59 (26.7%) of participation, this criterion was positive.

The mean of FEV1, FVC, and FEV1/FVC after use of bronchodilator with respect to different categorizations has been shown in Table 2. According to independent t-test, the mean of FEV1 in participants with shortness of breath ($P < 0.001$), cough ($P = 0.001$), wheezing ($P = 0.023$), as well as cardiovascular disease ($P = 0.038$) was significantly less in compared to those without the symptoms and diseases. Also the mean of FVC in participants with shortness of breath ($P < 0.001$) and cough ($P = 0.029$) was significantly less in comparison to others. Finally, the mean of FEV1/FVC in participants with shortness of breath ($P < 0.001$), cough ($P = 0.001$), and wheezing ($P = 0.01$) was less.

The relationship between stages of COPD and other variables was shown in Table 3. According to this table, there was a significant association between stages of COPD and diabetes mellitus ($x^2 = 8.59$, $P = 0.035$).

We used a linear regression model for evaluating the effect of study variables on FEV1, FVC, and FEV1/FVC. FEV1, FVC, and FEV1/FVC were dependent variables. At first, we entered all variables in each model. Then we used Fagerland *et al.* (2013) method to select significant variables.[31] The information of the final three models is shown in Table 4. Shortness of breath was the influential variable on FEV1 (B = -.383 95%CI: -23.729, -12.155 $P < 0.001$). With regard to beta coefficients when shortness of breath increases, it results in decreasing the level of FEV1. Also shortness of breath was the influential variable on FVC (B = -.296 95%CI: -15.336, -6.082 $P < 0.001$) and FEV1/FVC (B = -.365 95% CI: -18.362, -9.029 $P < 0.001$). Beta coefficients indicated that there was a reversed relationship between shortness of breath and FVC as well as FEV1/FVC.

Table 1: Demographic and baseline information (*n*=221)

Variables	Categories	Count (%)/ Mean (SD)
Age	-	54.75±13.44
Age of the onset smoking (year)	-	20.97±7.06
Duration of smoking (year)	-	30.84±14.22
Number of cigarette packs consumed daily	-	1.44±3.90
Shortness of breath	No	106 (48)
	Yes	115 (52)
Cough	No	131 (59.3)
	Yes	90 (40.7)
Phlegm	No	82 (37.1)
	Yes	139 (62.9)
Wheezing	No	92 (41.6)
	Yes	129 (58.4)
Diabetes mellitus	No	201 (91)
	Yes	20 (9)
High blood pressure	No	183 (82.8)
	Yes	38 (17.2)
Cardiovascular disease	No	186 (84.2)
	Yes	35 (15.8)
Stomach reflex	No	149 (67.4)
	Yes	72 (32.6)
COPD*	No	176 (80.4)
	Yes	43 (19.5)
Severity (GOLD)	Stage I	3 (7)
	Stage II	10 (23.3)
	Stage III	17 (39.5)
	Stage IV	13 (30.2)
Bronchodilator response (BDR)	No	162 (73.3)
	Yes	59 (26.7)
Pre FEV1 (%)§	-	70.55±24.41
Pre FVC (%)‖	-	76.98±19.90
Pre FEV1/FVC (%)¶	-	88.73±17.77
Post FEV1 (%)**	-	75.36±23.44
Post FVC (%)††	-	80.73±18.12
Post FEV1/FVC (%)‡‡	-	91.23±18.76

*Chronic Obstructive Lung Disease, §pre-bronchodilator forced expiratory volume in 1s, ‖pre-bronchodilator forced vital capacity, ¶pre-bronchodilator forced expiratory volume in 1s percent in relation to the maximal forced vital capacity, **post-bronchodilator forced expiratory volume in 1s, ††post-bronchodilator forced vital capacity, ‡‡post-bronchodilator forced expiratory volume in 1s percent in relation to the maximal forced vital capacity

Discussion

This study explored the association of pulmonary symptoms and underlying diseases with spirometry data in smoker adults and in COPD patients. The mean of FEV1 in participants with pulmonary symptoms of shortness of breath, cough, and wheezing was significantly less than participants without symptoms. The mean of FVC in participants with pulmonary symptoms of shortness of breath and cough was significantly less than participants without symptoms. The mean of FEV1/FVC in participants with pulmonary symptoms of shortness of breath, cough, and wheezing was significantly less than participants without symptoms. The shortness of breath was consistently associated with FEV1, FVC, and FEV1/FVC. Whittaker *et al.*[28] investigated characteristics associated with accelerated decline in a large population

Table 2: Independent samples *t*-test results of dependent and independent variables of the study

	Variables		*n*	Mean	SD	*P*
postFEV1**	Shortness of breath	No	105	84.7048	17.63897	*P*<0.001
		Yes	114	66.7632	24.86968	
PostFVC††	Shortness of breath	No	105	86.3143	14.03657	*P*<0.001
		Yes	114	75.6053	19.92758	
postFEV1FVC‡‡	Shortness of breath	No	105	98.3619	14.83118	*P*<0.001
		Yes	114	84.6667	19.64628	
postFEV1**	Cough	No	130	79.8769	22.69071	0.001
		Yes	89	68.7753	23.08913	
postFVC††	Cough	No	130	82.9462	17.02224	0.029
		Yes	89	77.5169	19.27558	
postFEV1FVC‡‡	Cough	No	130	94.7231	17.30753	0.001
		Yes	89	86.1348	19.71513	
postFEV1**	Phlegm	No	80	77.3000	22.69467	0.335
		Yes	139	74.2518	23.87804	
postFVC††	Phlegm	No	80	81.2625	16.61762	0.74
		Yes	139	80.4388	18.99318	
postFEV1FVC‡‡	Phlegm	No	80	93.5375	18.39231	0.16
		Yes	139	89.9065	18.91050	
postFEV1**	Wheezing	No	91	79.6154	22.36255	0.023
		Yes	128	72.3438	23.81406	
postFVC††	Wheezing	No	91	82.2967	16.28530	0.28
		Yes	128	79.6328	19.31621	
postFEV1FVC‡‡	Wheezing	No	91	95.0989	18.16165	0.01
		Yes	128	88.4844	18.76711	
postFEV1**	Diabetes Mellitus	No	199	75.4322	23.74005	0.89
		Yes	20	74.7000	20.82787	
postFVC††	Diabetes mellitus	No	199	80.6834	18.21658	0.88
		Yes	20	81.3000	17.65190	
postFEV1FVC‡‡	Diabetes mellitus	No	199	91.6683	18.86048	0.280
		Yes	20	86.9000	17.61847	
postFEV1**	High blood pressure	No	181	75.7845	23.71645	0.565
		Yes	38	73.3684	22.30916	
postFVC††	High blood pressure	No	181	81.0221	17.73037	0.616
		Yes	38	79.3947	20.10989	
postFEV1FVC‡‡	High blood pressure	No	181	91.6298	18.63930	0.496
		Yes	38	89.3421	19.48149	
postFEV1**	Cardiovascular disease	No	184	76.7935	22.96638	0.038
		Yes	35	67.8571	24.83492	
postFVC††	Cardiovascular disease	No	184	81.6087	17.45906	0.104
		Yes	35	76.1714	20.99087	
postFEV1FVC‡‡	Cardiovascular disease	No	184	91.9348	18.38198	0.205
		Yes	35	87.5429	20.53740	
postFEV1**	Stomach reflux	No	148	75.6149	23.36971	0.821
		Yes	71	74.8451	23.76411	
postFVC††	Stomach reflux	No	148	81.7905	17.98875	0.216
		Yes	71	78.5493	18.34572	
postFEV1FVC‡‡	Stomach reflux	No	148	90.6351	19.44402	0.497
		Yes	71	92.4789	17.32204	
		Yes	148	75.6149	23.36971	

A**Post-bronchodilator forced expiratory volume in 1s, ††post-bronchodilator forced vital capacity, ‡‡post-bronchodilator forced expiratory volume in 1s percent in relation to the maximal forced vital capacity

of COPD patients over 13 years in a cohort study, which showed breathlessness, high mMRC dyspnea, and mild airflow obstruction were significantly associated with accelerated FEV1 decline. Also characteristics significantly

Table 3: Univariate associations between pulmonary symptoms, underling diseases, and stages of COPD. Pearson's Chi-square test was used

	Stage I	Stage II	Stage III	Stage IV	Pearson Chi-square	*P*
Shortness of breath						
No	1 (2.3)	2 (4.7)	4 (9.3)	1 (2.3)	1.74	0.629
Yes	2 (4.7)	8 (18.6)	13 (30.2)	12 (27.9)		
Cough						
No	0 (0)	5 (11.6)	8 (18.6)	6 (14.0)	2.59	0.459
Yes	3 (7)	5 (11.6)	9 (20.9)	7 (16.3)		
Phlegm						
No	0 (0)	3 (7)	7 (16.3)	4 (9.3)	2.07	0.558
Yes	3 (7)	7 (16.3)	10 (23.3)	9 (20.9)		
Wheezing						
No	0 (0)	3 (7)	6 (14)	3 (7)	1.79	0.616
Yes	3 (7)	7 (16.3)	11 (25.6)	10 (23.3)		
Diabetes mellitus						
No	1 (2.3)	8 (18.6)	16 (37.2)	12 (27.9)	8.59	0.035
Yes	2 (4.7)	2 (4.7)	1 (2.3)	1 (2.3)		
High blood pressure						
No	2 (4.7)	9 (20.9)	13 (30.2)	11 (25.6)	1.28	0.734
Yes	1 (2.3)	1 (2.3)	4 (9.3)	2 (4.7)		
Cardiovascular disease						
No	2 (4.7)	8 (18.6)	13 (30.2)	11 (25.6)	0.59	0.898
Yes	1 (2.3)	2 (4.7)	4 (9.3)	2 (4.7)		
Stomach reflux						
No	3 (7)	9 (20.9)	13 (30.2)	8 (18.6)	3.58	0.311
Yes	0 (0)	1 (2.3)	4 (9.3)	5 (11.6)		

Table 4: Regression analyses of shortness of breath and lung function indexes (FEV1, FVC, and FEV1/FVC)

Dependent variable	Independent variables	B	std	β	*P*	95,0% Confidence interval for B		R^2
						Lower Bound	Upper Bound	
FEV1:**	Shortness of breath	-17.942	2.936	-0.383	0.000	-23.729	-12.155	0.143
FVC:††	Shortness of breath	-10.709	2.348	-0.296	0.000	-15.336	-6.082	0.083
FEV1/FVC:‡‡	Shortness of breath	-13.695	2.368	-0.365	0.000	-18.362	-9.029	0.130

**Post bronchodilator forced expiratory volume in 1s, ††Post bronchodilator forced vital capacity, ‡‡Post bronchodilator forced expiratory volume in 1s percent in relation to the maximal forced vital capacity

associated with accelerated FVC decline included cough, sputum production, severe airflow obstruction, and history of heart failure. It was recommended that breathlessness should also be considered in assessing lung function progression. Yamane *et al*.[29] investigated whether the presence of productive cough is a risk factor for the development of COPD during the mean follow-up period of 33.6 20.4 months. The finding showed statistically significant declines in FEV1, %FEV1, and FEV1% during the study period. These findings were supported our result in the present study. Shin *et al*.[30] examined the relationship between respiratory symptoms and FEV1 in 7518 individuals aged 40–69 years without airflow obstruction based on spirometric testing and in the absence of a medical history of pulmonary disease. The findings suggested that respiratory symptoms included shortness of breath and wheezing are associated with a lower FEV1 in men and nonsmoking women with normal lung function. We found that there was a significant difference between the mean of FEV1 in participants with cardiovascular disease in comparison to those without cardiovascular disease. Silvestre *et al*.[32] evaluated whether decline in lung function is associated with heart failure, coronary heart disease, and stroke. Among 10,351 participants at about 17 years of follow-up, the result documented that the rapid decline in lung function is associated with a higher incidence of subsequent cardiovascular disease. The other findings of our study were the presence of diabetes mellitus had an inverse association with GOLD COPD severity. In the study of Watz *et al*.,[33] the frequencies of the metabolic syndrome and consequence hyperglycemia in patients with GOLD stages II, III, and IV were 53, 37, and 44%, respectively. In addition in the study of Quajer *et al*.,[34] the frequency decreases to about 10% at GOLD stages III and IV. The weight loss that frequently occurs in patients who are in the more severe stages of COPD may be the cause

of our observations that association with GOLD COPD severity was inverse.

Conclusion

In conclusion, among pulmonary symptoms, shortness of breath, cough, and wheezing influenced lung function strongly in adult smokers. Moreover, according to the linear regression model, shortness of breath was associated with FEV1, FVC, and FEV1/FVC. Cardiovascular disease could decrease the level of FEV1, whereas diabetic mellitus was associated with milder GOLD COPD severity.

Acknowledgments

The authors thank the staff and participants of this study for their important contributions.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Received: 30 Dec 21 **Accepted:** 27 Oct 22
Published: 26 Aug 25

References

1. GBD 2015 Chronic Respiratory Disease Collaborators. Global, regional, and national deaths, prevalence, disability-adjusted life years, and years lived with disability for chronic obstructive pulmonary disease and asthma, 1990–2015: A systematic analysis for the Global Burden of Disease Study 2015. Lancet Respir Med 2017;5:691-706.
2. Jakeways N, McKeever T, Lewis SA, Weiss ST, Britton J. Relationship between FEV1 reduction and respiratory symptoms in the general population. Eur Respir J 2003;21:658-63.
3. Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. Eur Respir J 2009;33:1165-85.
4. Agustí A. Systemic effects of chronic obstructive pulmonary disease: What we know and what we don't know (but should). Proc Am Thor Soc 2007;4:522-5.
5. Young RP, Hopkins R, Eaton TE. Forced expiratory volume in one second: Not just a lung function test but a marker of premature death from all causes. Eur Respir J 2007;30:616-22.
6. Burney PG, Hooper R. Forced vital capacity, airway obstruction and survival in a general population sample from the USA. Thorax 2011;66:49-54.
7. Gulsvik A, Bakke PS, Brøgger J, Nielsen R, Stavem K. Respiratory symptoms and mortality in four general population cohorts over 45 years. Respir Med 2020;170:106060.
8. Frostad A, Søyseth V, Andersen A, Gulsvik A. Respiratory symptoms as predictors of all-cause mortality in an urban community: A 30-year follow-up. J Intern Med 2006;259:520-9.
9. Ryan G, Knuiman MW, Divitini ML, James A, Musk AW, Bartholomew HC. Decline in lung function and mortality: The Busselton health study. J Epidemiol Community Health 1999;53:230-4.
10. Knuiman MW, James AL, Divitini ML, Ryan G, Bartholomew HC, Musk AW. Lung function, respiratory symptoms, and mortality: Results from the Busselton health study. Ann Epidemiol 1999;9:297-306.
11. Hamdan AJ, Ahmed A, Abdullah AH, Khan M, Baharoon S, Salih SB, *et al*. Improper inhaler technique is associated with poor asthma control and frequent emergency department visits. Allergy Asthma Clin Immunol 2013;9:8.
12. Lange P, Parner J, Vestbo J, Schnohr P, Jensen G. A 15-year follow-up study of ventilatory function in adults with asthma. N Engl J Med 1998;339:1194-200.
13. Krzyzanowski M, Camilli AE, Lebowitz MD. Relationships between pulmonary function and changes in chronic respiratory symptoms: Comparison of Tucson and Cracow longitudinal studies. Chest 1990;98:62-70.
14. Çolak Y, Afzal S, Lange P, Laursen LC, Nordestgaard BG, Dahl M. Role and impact of chronic cough in individuals with asthma from the general population. J Allergy Clin Immunol Pract 2019;7:1783-92.
15. Cornelius ME, Wang TW, Jamal A, Loretan CG, Neff LJ. Tobacco product use among adults—United States, 2019. MMWR Morb Mortal Wkly Rep 2020;69:1736.
16. Mellitus D. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2005;28:S5-10.
17. Cifu AS, Davis AM. Prevention, detection, evaluation, and management of high blood pressure in adults. JAMA 2017;318:2132-4.
18. Anderson JL, Morrow DA. Acute myocardial infarction. N Engl J Med 2017;376:2053-64.
19. LO EH, Dalkara T, Moskowitz MA. Mechanisms, challenges and opportunities in stroke. Nat Rev Neurosci 2003;4.5:399-414.
20. Braunwald E. Unstable angina: A classification. In: Unstable Angina. Berlin, Heidelberg, Springer; 1990. p. 103-11.
21. Holbrook WP, Furuholm J, Gudmundsson K, Theodors A, Meurman JH. Gastric reflux is a significant causative factor of tooth erosion. J Dent Res 2009;88:422-6.
22. Jian W, Zheng J, Hu Y, Li Y, Gao Y, An J. What is the difference between FEV1 change in percentage predicted value and change over baseline in the assessment of bronchodilator responsiveness in patients with COPD?. J Thorac Dis 2013;5:393-9.
23. Sterk PJ. Let's not forget: the GOLD criteria for COPD are based on post-bronchodilator FEV1. Eur Respir J 2004;23:497-8.
24. Minas M, Kostikas K, Papaioannou AI, Mystridou P, Karetsi E, Georgoulias P, *et al*. The association of metabolic syndrome with adipose tissue hormones and insulin resistance in patients with COPD without co-morbidities. COPD 2011;8:414-20.
25. Bhatt SP, Kim Y-I, Harrington KF, Hokanson JE, Lutz SM, Cho MH, *et al*. Smoking duration alone provides stronger risk estimates of chronic obstructive pulmonary disease than pack-years. Thorax 2018;73:414-21.
26. Hedlund U, Eriksson K, Ronmark E. Socio-economic status is related to incidence of asthma and respiratory symptoms in adults. Eur Respir J 2006;28:303-410.
27. Mannino DM, *et al*. Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. Eur Respir J 2008;32:962-9.
28. Whittaker HR, Pimenta JM, Jarvis D, Kiddle SJ, Quint JK. Characteristics associated with accelerated lung function decline in a primary care population with chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 2020;15:3079-91.
29. Yamane T, Hattori N, Kitahara Y, Haruta Y, Sasaki H, Yokoyama A, Kohno N. Productive cough is an independent risk factor for the development of COPD in former smokers. Respirology 2010;15:313-8.
30. Shin C, Lee S, Abbott RD, Kim JH, Lee SY, In KH, Kimm K. Relationships between respiratory symptoms and FEV 1 in men and women with normal lung function: The Korean health and

genome study. Lung 2005;183:301-9.
31. Fagerland MW, Hosmer DW. A goodness-of-fit test for the proportional odds regression model. Statistics in medicine 2013;32:2235-49.
32. Silvestre OM, Nadruz W, Querejeta Roca G, Claggett B, Solomon SD, Mirabelli MC, *et al*. Declining lung function and cardiovascular risk: The ARIC study. J Am Coll Cardiol 2018;72:1109-22.
33. Watz H, Waschki B, Kirsten A, Müller KC, Kretschmar G, Meyer T, *et al*. The metabolic syndrome in patients with chronic bronchitis and COPD: Frequency and associated consequences for systemic inflammation and physical inactivity. Chest 2009;136:1039-46.
34. Quajer PH, Tammeling GJ, Cotes JE, Pedersen OF, Perlin R, Yernault JC. Lung volumes and forced ventilatory flows. Report working party. Standardization of lung function test European Community for steel and oral official statement of the European respiratory society. Eur Respir J 1993;16:5-40.