Chronic Obstructive Pulmonary Diseases:
Journal of the COPD Foundation®

Original Research

The Association Between Systemic Arterial Hypertension and Chronic Obstructive Pulmonary Disease. Results from the U.S. National Health and Nutrition Examination Survey 1999-2018: A Cross-sectional Study

Xiaopeng Liang, MD[1] Oscar Hou In Chou, MSc[1] Bernard MY Cheung, PhD[1,2,3]

Abstract

Background: Systemic arterial hypertension (HTN) is one of the common comorbidities among patients with chronic obstructive pulmonary disease (COPD). This study aimed to investigate the association between HTN and COPD.

Methods: A total of 46,804 eligible non-pregnant participants aged ≥20 years examined in the Mobile Examination Center of the National Health and Nutrition Examination Survey (NHANES) 1999–2018 were included in this cross-sectional study. Participants with invalid data on covariates, HTN, and COPD were excluded. The association between HTN and COPD was studied using logistic regression upon adjusting the potential covariates.

Results: Among the participants, 46.1% (95% confidence interval [CI], 45.3–46.9) had HTN, and 6.8% (95% CI, 6.4–7.2) had self-reported COPD. COPD was associated with HTN (OR [odds ratio]=1.18, 95% CI [1.05–1.31], $P<0.01$) after adjusting for demographics, socioeconomic factors, smoking, diabetes, body mass index, and medication use, including inhaled corticosteroids and methylxanthines. The association between HTN and COPD was significant among adults younger than 60 years ($P<0.01$). Stratified by smoking status, there was a significant association between HTN and COPD in current heavy smokers (1.25, 95% CI [1.01–1.58]; $P=0.04$).

Conclusion: In this nationwide survey, COPD was associated with HTN. The association was more robust among adults younger than 60 years and current heavy smokers. Future prospective studies are needed to examine the relationship between HTN and COPD.

1. Division of Clinical Pharmacology and Therapeutics, Department of Medicine, School of Clinical Medicine, The University of Hong Kong, Hong Kong, China
2. State Key Laboratory of Pharmaceutical Biotechnology, The University of Hong Kong, Pokfulam, Hong Kong, China
3. Institute of Cardiovascular Science and Medicine, The University of Hong Kong, Pokfulam, Hong Kong, China

Abbreviations:

BMI=body mass index; **CI**=confidence interval; **COPD**=chronic obstructive pulmonary disease; **CVD**=cardiovascular disease; **ECM**=extracellular matrix; **HTN**=hypertension; **IQR**=interquartile range; **NHANES**=National Health and Nutrition Examination Survey

Funding Support:

No specific funding was received from the public, commercial, or not-for-profit sectors to carry out the work described in this article.

Citation:

Liang X, Chou OHI, Cheung BMY. The association between systemic arterial hypertension and chronic obstructive pulmonary disease. Results from the U.S. National Health and Nutrition Examination Survey 1999-2018: a cross-sectional study. *Chronic Obstr Pulm Dis.* 2023;10(2):190-198. doi: https://doi.org/10.15326/jcopdf.2022.0306

Publication Dates:

Date of Acceptance: March 19, 2023
Published Online Date: March 27, 2023

Address correspondence to:

Bernard M.Y. Cheung, PhD
Department of Medicine
School of Clinical Medicine
Queen Mary Hospital
102 Pokfulam Road
Hong Kong
Email: mycheung@hku.hk
Phone: +852 22554347
Fax: +852 28186474

Keywords:

systemic arterial hypertension, hypertension, COPD, smoking, NHANES

Note: This article has an online supplement

Introduction

Cardiovascular diseases (CVD) and chronic obstructive pulmonary disease (COPD) are 2 leading causes of death

in the world.[1,2] Systemic arterial hypertension (HTN) is an important modifiable risk factor for CVD, including coronary heart disease, stroke, and heart failure.[3,4] It contributes to 54% of strokes and 47% of ischemic heart diseases.[2] Antihypertensive treatment helps reduce cardiovascular mortality and morbidity,[5] such that effective blood pressure control reduces the risks of coronary heart disease by 25%, stroke by 35%, and heart failure by 50%.

COPD is a group of progressive lung conditions that causes incomplete reversible airflow due to airway or alveolar abnormalities.[6] It is the third leading cause of death worldwide.[1] COPD patients have over a 2-fold increase in CVD hospitalization and mortality compared to those without COPD.[7,8] COPD is strongly associated with CVD, including ischemic heart diseases, stroke, and atrial fibrillation.[9,10] Several potential mechanisms, such as aging,[11] systemic inflammation,[12] arterial stiffness,[13] and autonomic nerve dysfunction[14] were proposed to explain the association. Previous studies examined the relationship between CVD and COPD.[7-9] They focused on different targeted populations. One of the prospective studies included people aged 40 years or older,[8] while another study included men around 55 years old.[9]

Recently, the Eighth Joint National Committee highlighted the importance of managing both HTN and COPD to help reduce the burdens of the comorbidities.[15] Few have investigated the association between systemic arterial HTN and COPD in the general population. A Korean study revealed that COPD is independently associated with HTN in men aged 40 years and above.[16] Another study demonstrated that HTN is more prevalent among severe COPD patients aged 45 years or above but not below.[17] Further investigations are needed to investigate the association between COPD and HTN in the general population.

This study aimed to assess the association between HTN and COPD using the data from the U.S. National Health and Nutrition Examination Survey[18] (NHANES) 1999–2018.

Methods

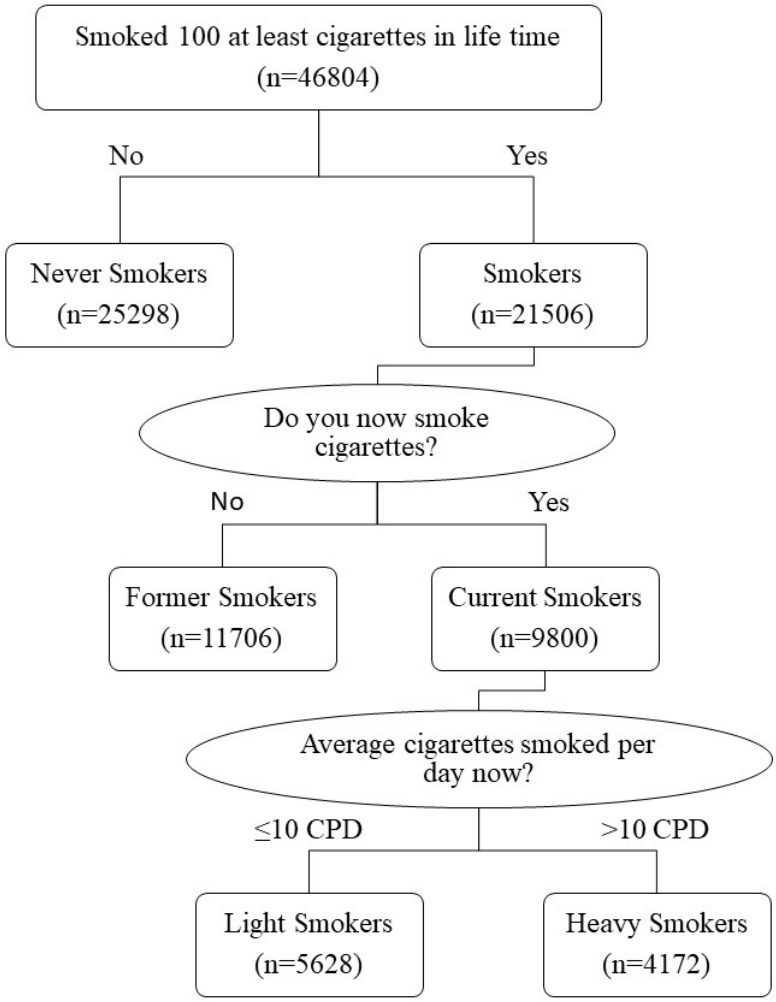
Study Population

NHANES was conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention. A complex, multistage, probability sampling design was used to select participants representative of the civilian non-institutionalized U.S. population. Informed consent was obtained from all adult participants, and the study was approved by the National Center for Health Statistics' Ethics Review Board. A total of 52,398 individuals aged 20 years and over participated in the Mobile Examination Center of NHANES 1999-2018. A total of 3725 participants with missing, unreliable, or uncertain important covariables, including socioeconomic factors (education level, family income level, occupation, and health insurance), body mass index, diabetes, smoking records, or asthma, were excluded (Supplementary Figure 1 in the online supplement). We also excluded incomplete, unreliable, or uncertain data for HTN (n=11) and COPD (n=162). Participants who were pregnant or lactating (n=1696) were also excluded. The demographics, examination results (blood pressure, body measures), medical condition questionnaire, laboratory data (glycated hemoglobin, plasma fasting glucose), and prescription medication information (theophylline and inhaled corticosteroids) were retrieved[18] from NHANES 1999–2018.

Definition

According to the self-reported demographics questionnaire, race/ethnicity was classified into 4 groups, namely non-Hispanic Whites, non-Hispanic Blacks, Mexican Americans, and others (including other Hispanic and multi-racial). Education levels were divided into 3 groups: high school or below, college, and college graduates or above. Household income was classified as below 130%, 131%– 338%, and above 339% based on the ratio of income to poverty. The participants were also categorized as employed or unemployed. Health insurance was categorized into private health insurance, public health insurance only, and no health insurance. Participants were categorized by age into 3 groups, 20–39 years old, 40–59 years old, and ≥60 years old. The "never smoker" status was defined as smoked less than 100 cigarettes in their lifetime. The "former smoker status" was defined as used to smoke 100 cigarettes or more in their lifetime but is no longer smoking now. "Current light smokers" was classified as smoking less than 10 cigarettes per day now, and "current heavy smokers" were people who smoke over 10 cigarettes per day (Figure 1). Diabetes was defined either as a self-reported physician diagnosis of diabetes or prescribed medicine for diabetes or elevated levels of fasting glucose (≥7.0mmol/L [≥126mg/dL]) or HbA1c (≥6.5%). Participants were defined as hypertensive if they have self-reported HTN, are taking prescribed antihypertension medications, or their measurement of blood pressure is ≥130/80mmHg according to the American Heart Association/American College of Cardiology 2017 guidelines.[3] COPD was defined according to the answers to the clinical questions "Has a doctor ever said you had COPD" or "Have you ever been told you had chronic bronchitis" or "Have you ever been told you had emphysema" in the medical conditions questionnaire as validated in a previous study.[19] Different methods of defining COPD were used in NHANES 2007–2012 as sensitivity analysis, including questionnaire-based and spirometry-based definitions. Theophylline and inhaled corticosteroids were defined using the unique generic drug code in NHANES.

Figure 1. The Flow Chart of the Number of Participants Stratified by the Definition of the Smoking Status



CPD=cigarettes per day

Statistical Analysis

Complex sample weights were adopted due to unequal probabilities of selection, nonresponse bias, and oversampling of non-Hispanic Blacks by using primary sampling units and strata. The characteristics of the participants were further stratified by hypertension status and COPD status. The independent *t*-test was used to compare continuous variables and the Chi-square test was used to compare categorical variables. Multiple logistic regression was used to assess the association between COPD and HTN. The demographics (age, gender, race/ethnicity), socioeconomic factors (education level, family income level, occupation, and health insurance), smoking, diabetes, body mass index, and medication use (inhaled corticosteroids and methylxanthines) were adjusted in the multiple logistic regression. The association between COPD and HTN was further stratified by gender, age, and smoking status. A mediation analysis of medication (theophylline and inhaled corticosteroids) between COPD and hypertension was conducted. Odds ratios (ORs) with corresponding 95% confidence intervals (CIs) and *P* values were reported. All significance tests were 2-tailed and considered significant if *P* values were less than 0.05. Statistical analysis was performed using STATA (version 15.1).

Results

Characteristics of Study Participants

In our study, a total of 46,804 eligible participants (interquartile range [IQR]=26 years; 48.8% [95% CI, 48.3–49.2] male) were included in this analysis. This sample represented 198,587,043 civilian non-institutionalized adults in the United States. The characteristics of the participants stratified by COPD status are shown in Table 1. Compared to the individuals without COPD, participants with COPD were older (mean age 53.74 versus 46.90, $P<0.01$). HTN was more prevalent among COPD participants than in participants without COPD (58.5% [95% CI, 56.4–60.6] versus 45.2 [95% CI, 44.4–46.0]). The characteristics of participants with or without HTN are shown in Supplementary Table

1 in the online supplement. The prevalence of COPD was much higher among hypertensive individuals than those without HTN (8.6% [95% CI, 8.1–9.2] versus 5.2% [95% CI, 4.8–5.7], *P*<0.01).

The Association Between Hypertension and COPD

The multiple logistic regression analysis of COPD and HTN before and after adjustments for the covariates is displayed in Table 2. COPD was significantly associated with HTN before adjustments (unadjusted OR=1.71 [95% CI, 1.56–1.88]). After adjustments, the association remained significant (OR=1.18 [95% CI, 1.05–1.31], *P*<0.01). The association between HTN and COPD was significant among adults aged less than 60 years (*P*<0.01), and presence of COPD was associated with a decreased odds of HTN in adults > age 60 (OR=0.81, 95% CI [0.66–0.99], *P*=0.05) (Table 3). Stratified by gender, the association between HTN and COPD was found among women after adjustments (OR=1.14 [95% CI, 1.02–1.22], *P*<0.01) (Supplementary

Table 1. Baseline Characteristics of the COPD Group Versus the Non-COPD Group

Characteristics	COPD (n=3121)		Non-COPD (n=43683)		*P* value
	Unweighted N	Weighted % (95% CI)	Unweighted N	Weighted % (95% CI)	
Age (mean)[a]					
20–39 years	571	21.5(19.7–23.4)	14579	37.4(36.4–38.4)	<0.01
40–59 years	1056	39.2(37–41.5)	14373	38.3(37.6–39.1)	0.06
≥60 years	1494	39.3(37–41.6)	14731	24.3(23.5–25.1)	<0.01
Gender					
Men	1185	34.8(32.7–36.9)	21954	49.8(49.3–50.3)	<0.01
Women	1936	65.2(63.1–67.3)	21729	50.2(49.7–50.7)	<0.01
Race/Ethnicity					
Non-Hispanic White	1837	77.4(75.2–79.5)	18834	68(65.9–70)	<0.01
Non-Hispanic Black	604	9.4(8.1–10.8)	9061	10.9(9.8–12)	<0.01
Mexican Americans	482	7.3(6.2–8.7)	11610	14.3(12.8–15.9)	<0.01
Others	198	5.9(4.9–7.1)	4178	6.9(6.3–7.6)	<0.01
Education Level					
High School and Below	1689	49.1(46.5–51.8)	21903	41.1(39.8–42.4)	<0.01
Some College	996	33.4(31.3–35.6)	12139	30.3(29.6–31.1)	<0.01
College Graduate or Above	436	17.5(15.4–19.8)	9641	28.6(27.2–30.1)	<0.01
Poverty to Income Ratio					
≤130%	1194	29.8(27.1–32.7)	12220	19.6(18.6–20.6)	<0.01
131%–338%	1292	41.3(38.9–43.7)	18145	38(37.1–39)	<0.01
≥339%	635	28.9(26.2–31.7)	13318	42.4(41–43.8)	<0.01
Health Insurance Status					
No	477	15.2(13.5–17)	9415	17.9(17.1–18.8)	<0.01
Public	1279	33.7(31.5–36)	10954	18.4(17.7–19.1)	<0.01
Private	1365	51.1(48.5–53.7)	23314	63.7(62.5–64.9)	<0.01
Under Employment	1118	43.7(41–46.4)	25177	66.1(65.2–67)	<0.01
Smoking Status					
Never Smokers	1037	33.6(31.3–36)	24261	55.1(54.2–56)	<0.01
Former Smokers	1020	31.2(29–33.5)	10686	24.5(23.8–25.2)	<0.01
Current Smokers	1064	35.2(32.7–37.7)	8736	20.4(19.7–21.1)	<0.01
Among Current Smokers					
Light Smokers	496	41.4(37.8–45.2)	3604	52.1(50.3–53.8)	<0.01
Heavy Smokers	568	58.6(54.8–62.2)	3604	47.9(46.2–49.7)	<0.01
Other					
Overweight/Obesity	2356	75.1(73–77)	30616	68.5(67.7–69.4)	<0.01
Diabetes	831	21.5(19.8–23.3)	7205	11.8(11.3–12.3)	<0.01
Hypertension	1965	58.5(56.4–60.6)	21927	45.2(44.4–46)	<0.01
Medications					
Theophylline	2	0	0	0	0.98
Inhaled Corticosteroids	100	1.6(1.1–2.3)	51	0.3(0.2–0.4)	<0.01

[a]Mean age for COPD=53.74 and mean age for non-COPD=46.90. *P*-value<0.01.

COPD=chronic obstructive pulmonary disease; CI=confidence interval

Table 2 in the online supplement). Among current heavy smokers, COPD was positively correlated with HTN after adjustments (1.25, 95% CI [1.01–1.58], *P*=0.04). (Table 4). The mediation analysis demonstrated that the association between HTN and COPD was not mediated by theophylline and inhaled corticosteroids (Supplementary Figure 2 in the online supplement). The sensitivity analysis demonstrated that the association between HTN and COPD remained significant upon including pregnant or lactating women (Supplementary Table 3 in the online supplement). This association remained consistent with different COPD definitions, including questionnaire-based definitions and spirometry tests. (Supplementary Table 4 in the online supplement).

Discussion

This nationally representative survey of 46,804 participants suggested that HTN was associated with COPD in the general population after adjustments. The association was present in women, those aged less than 60 years, and current heavy smokers.

Systemic Arterial Hypertension Is Associated With COPD

Our findings demonstrated that COPD is associated with systemic arterial HTN. The results are consonant with the previous studies,[16,17,20] which reported the association in specific populations. HTN is among the most frequent comorbidities in COPD patients.[21] Multiple pathways have been proposed to explain the association.[22-24] Firstly, COPD-induced autonomic dysfunction may contribute to increased blood pressure. Due to airway obstruction and airway inflammation, COPD patients repeatedly suffer from hypoxemia, hypercapnia, and increased intrathoracic pressure, resulting in decreased baroreceptor sensitivity and excessive activation of sympathetic nerves.[14] Secondly, COPD patients have increased arterial stiffness, reducing wave reflection time and elevation of blood pressure.[25] Arterial stiffness is a consequence of the remodeling

Table 2. The Association Between Hypertension and COPD

Crude OR	Model 1	Model 2	Model 3
1.71(1.56–1.88)	1.32(1.18–1.48)	1.25(1.12–1.41)	1.18(1.05–1.31)

Model 1: Adjusted for age, gender, and race.
Model 2: Further adjusted for socioeconomic factors including health insurance coverage, education level, employment status, and poverty to income ratio.
Model 3: Further adjusted for smoking status (including former smokers and current smokers), BMI, diabetes, and medication (including theophylline and inhaled corticosteroids).

COPD=chronic obstructive pulmonary disease; OR=odds ratio; BMI=body mass index

Table 3. The Association Between Hypertension and COPD Stratified by Age

Age	Crude OR	Model 1	Model 2	Model 3
20–39 years	1.38(1.15–1.66)	1.60(1.32–1.95)	1.58(1.29–1.92)	1.34(1.08–1.67)
40–59 years	1.5(1.28–1.77)	1.61(1.36–1.89)	1.46(1.23–1.72)	1.25(1.05–1.49)
≥60 years	1.5(1.28–1.77)	0.96(0.79–1.16)	0.88(0.72–1.07)	0.81(0.66–0.99)

Model 1: Adjusted for gender and race.
Model 2: Further adjusted for socioeconomic factors including health insurance coverage, education level, employment status, and poverty to income ratio.
Model 3: Further adjusted for BMI, diabetes, and medication (including theophylline and inhaled corticosteroids).

COPD=chronic obstructive pulmonary disease; OR=odds ratio; BMI=body mass index

Table 4. The Association Between Hypertension and COPD Stratified by Smoking Status

	Crude OR		Model 1		Model 2		Model 3	
	OR	*P*	OR	*P*	OR	*P*	OR	*P*
Never Smokers	2.13(1.8–2.52)	<0.01	1.67(1.38–2.01)	<0.01	1.63(1.35–1.97)	<0.01	1.30(0.94–1.58)	0.07
Former Smokers	1.49(1.23–1.8)	<0.01	1.14(0.92–1.42)	0.27	1.09(0.88–1.34)	0.45	0.91(0.71–1.41)	0.42
Current Smokers	1.57(1.33–1.85)	<0.01	1.22(1.02–1.48)	0.03	1.18(0.97–1.44)	0.09	1.17(0.82–1.37)	0.58
Among Current Smokers								
Light Smokers	1.48(1.14–1.92)	<0.01	1.02(0.76–1.37)	0.83	1.00(0.74–1.36)	0.96	0.93(0.67–1.30)	0.68
Heavy Smokers	1.59(1.27–1.98)	<0.01	1.36(1.08–1.74)	<0.01	1.36(1.03–1.67)	0.03	1.25(1.01–1.58)	0.04

Model 1: Adjusted for gender and race.
Model 2: Further adjusted for socioeconomic factors including health insurance coverage, education level, employment status, and poverty to income ratio.
Model 3: Further adjusted for BMI, diabetes, and medication (including theophylline and inhaled corticosteroids).

COPD=chronic obstructive pulmonary disease; OR=odds ratio; BMI=body mass index

process, which involves elastin fragmentation and collagen replacement in the extracellular matrix (ECM). Arterial stiffness is aggravated among patients expressing the emphysema phenotype COPD; they are more susceptible to lung, skin, and arterial extracellular matrix remodelling.[26] COPD-related hypoxia may trigger systemic inflammation, accelerating the process of arterial stiffness. Last but not least, the administration of inhaled or systemic corticosteroids for treatment among COPD patients also contributes to the development of HTN.[27] There are also several overlapping mechanisms between the 2 conditions. One of which was the changes in the ECM. Altered expression of ECM proteins, such as elastin, collagen, and proteoglycans, contributes to the narrowing of airways and parenchyma.[28] The collagen and elastin expression are also altered by the vascular remodeling in hypertension. This resulted in the overproduction of collagen and scarcity in the amount of elastin, which reduces vascular compliance and increases blood pressure.[29]

Compared to the results in the Korean study,[16] which investigated the association in men, our results demonstrated COPD was not associated with hypertension among men after adjustments (Supplementary Table 2 in the online supplement). The discrepancies can be explained by the differences in the targeted population and the disease definition. In the Korean study,[16] COPD was defined by the combination of spirometry and smoking history. Participants aged less than 40 years, mild COPD patients, and non-smokers were excluded.

Similarly, a study revealed that severe respiratory dysfunction is associated with a higher risk of comorbid HTN among patients aged over 45 years. Individuals with Global initiative for chronic Obstructive Lung Disease (GOLD)[6] stage 3 or 4 COPD had a higher prevalence of HTN upon adjustments (OR=1.6, [95% CI 1.3–1.9]).[17] However, individuals "at-risk" of COPD (GOLD stage 0), with respiratory symptoms and risk factors but normal lung function, are also at risk of HTN (OR=1.2, [95% CI 1.1–1.3]). However, adults aged less than 45 years old were not included in this study; other risk factors that would attenuate the association, such as socioeconomic factors and medication use, were also not well addressed in this study.

A robust association between HTN and COPD was found among adults younger than 60, highlighting the need for smoking cessation starting early. Smoking is a well-established risk factor for HTN and COPD. Recently, there has been a substantial increase in the proportion of smokers who started smoking cigarettes in early adulthood (age≥18 years) and developed habitual cigarette smoking.[30]

We also found an association between HTN and COPD among current heavy smokers. This suggests the need for tobacco restriction among hypertensive patients. Smoking increases systemic arterial stiffness and has detrimental effects on endothelial functioning.[31,32] This subsequently inflicts vascular wall damage and hypertrophy.[31] The above pathway results in organ damage, especially in the lungs.[26] Recently, endothelial dysfunction was proposed to be correlated with pulmonary lesions in COPD due to vascular inflammation and anti-oxidant suppression.[33] However, the endothelial damage introduced by smoking could potentially be reversible as current smokers have worse endothelial function than former smokers.[34]

This study has some limitations that should be appreciated. Firstly, the NHANES is a cross-sectional survey, such that it does not provide longitudinal follow-up data. Given its retrospective nature, the results only demonstrate correlation but not causation. Future studies are needed to demonstrate the causal relationship. Secondly, NHANES uses a recall questionnaire for some variables, which are prone to recall and response bias. The diagnosis of COPD relies on the questionnaire survey without including standard investigations such as spirometry, as spirometry was only performed in selected years (2007–2012) in NHANES. However, we conducted a sensitivity analysis using different definitions of COPD; the association between HTN and COPD remained significant across the various definitions of COPD. As a previous study[35] suggested that questionnaire-based definitions demonstrated an overall accuracy of 89%–90%, the diagnosis of COPD using questionnaire-based definitions may still be a viable alternative. Lastly, due to the lack of forced expiratory volume in 1 data, further risk classification analysis of COPD patients was not available.

Conclusions

In conclusion, our results from this cross-sectional study demonstrated a significant association between hypertension and COPD, especially among adults aged less than 60 years and current heavy smokers. Future prospective studies are needed to examine the relationship between HTN and COPD.

Acknowledgements

Author Contributions: XL is responsible for conceptualization, methodology, data analysis, and drafting of the manuscript. OHIC is responsible for conceptualization and revision of the manuscript. BMC is responsible for methodology, supervision, and revision of the manuscript. All authors have read and approved the submission of the manuscript.

Data Sharing: The data that support the findings of this study are available in NHANES 1999–2018. These data were derived from the following sources available in the public domain https://www.cdc.gov/nchs/nhanes/index.htm.

Declaration of Interest

All authors declare no conflicts of interest.

References

1. 1. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet.* 2012;380(9859):2095-2128. https://doi.org/10.1016/S0140-6736(12)61728-0

2. Lawes CM, Vander Hoorn S, Rodgers A. Global burden of blood-pressure-related disease, 2001. *Lancet.* 2008;371(9623):1513-1518. https://doi.org/10.1016/S0140-6736(08)60655-8

3. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/ APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension.* 2018;71(6):e13-e115. https://doi.org/10.1161/HYP.0000000000000065

4. Rapsomaniki E, Timmis A, George J, et al. Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1·25 million people. *Lancet.* 2014;383(9932):1899-1911. https://doi.org/10.1016/S0140-6736(14)60685-1

5. Antonakoudis G, Poulimenos L, Kifnidis K, Zouras C, Antonakoudis H. Blood pressure control and cardiovascular risk reduction. *Hippokratia.* 2007;11(3):114-119.

6. Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. GOLD Executive Summary. *Am J Respir Crit Care Med.* 2017;195(5):557-582. https://doi.org/10.1164/rccm.201701-0218PP

7. Morgan AD, Zakeri R, Quint JK. Defining the relationship between COPD and CVD: what are the implications for clinical practice? *Ther Adv Respir Dis.* 2018;12:1-16. https://doi.org/10.1177/1753465817750524

8. Sidney S, Sorel M, Quesenberry CP, Jr., DeLuise C, Lanes S, Eisner MD. COPD and incident cardiovascular disease hospitalizations and mortality: Kaiser Permanente Medical Care Program. *Chest.* 2005;128(4):2068-2075. https://doi.org/10.1378/chest.128.4.2068

9. Engström G, Hedblad B, Valind S, Janzon L. Increased incidence of myocardial infarction and stroke in hypertensive men with reduced lung function. *J Hypertens.* 2001;19(2):295-301. https://doi.org/10.1097/00004872-200102000-00017

10. Buch P, Friberg J, Scharling H, Lange P, Prescott E. Reduced lung function and risk of atrial fibrillation in the Copenhagen City Heart Study. *Eur Respir J.* 2003;21(6):1012-1016. https://doi.org/10.1183/09031936.03.00051502

11. MacNee W. Accelerated lung aging: a novel pathogenic mechanism of chronic obstructive pulmonary disease (COPD). *Biochem Soc Trans.* 2009;37(Pt 4):819-823. https://doi.org/10.1042/BST0370819

12. de Torres JP, Cordoba-Lanus E, López-Aguilar C, et al. C-reactive protein levels and clinically important predictive outcomes in stable COPD patients. *Eur Respir J.* 2006;27(5):902-907. https://doi.org/10.1183/09031936.06.00109605

13. Willum-Hansen T, Staessen JA, Torp-Pedersen C, et al. Prognostic value of aortic pulse wave velocity as index of arterial stiffness in the general population. *Circulation.* 2006;113(5):664-670. https://doi.org/10.1161/CIRCULATIONAHA.105.579342

14. Bartels MN, Gonzalez JM, Kim W, De Meersman RE. Oxygen supplementation and cardiac-autonomic modulation in COPD. *Chest.* 2000;118(3):691-696. https://doi.org/10.1378/chest.118.3.691

15. James PA, Oparil S, Carter BL, et al. 2014 Evidence-based guideline for the management of high blood pressure in adults. Report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA.* 2014;311(5):507-520. https://doi.org/10.1001/jama.2013.284427

16. Kim SH, Park JH, Lee JK, Heo EY, Kim DK, Chung HS. Chronic obstructive pulmonary disease is independently associated with hypertension in men: a survey design analysis using nationwide survey data. *Medicine (Baltimore).* 2017;96(19):e6826. https://doi.org/10.1097/MD.0000000000006826

17. Mannino DM, Thorn D, Swensen A, Holguin F. Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. *Eur Respir J.* 2008;32(4):962-969. https://doi.org/10.1183/09031936.00012408

18. Centers for Disease Control and Prevention (CDC). National Health and Nutrition Examination Survey Questionnaire. Continuous NHANES. CDC website. Published 1999. Accessed August 30, 2021. https://wwwn.cdc.gov/nchs/nhanes/ContinuousNhanes/Default.aspx?BeginYear=1999(1999)

19. Feinstein L, Wilkerson J, Salo PM, et al. Validation of questionnaire-based case definitions for chronic obstructive pulmonary cisease. *Epidemiology.* 2020;31(3):459-466. https://doi.org/10.1097/EDE.0000000000001176

20. Dhungel S, Paudel B, Shah S. Study of prevalence of hypertension in chronic obstructive pulmonary disease patients admitted at Nepal Medical College and Teaching Hospital. *Nepal Med Coll J.* 2005;7(2):90-92.

21. Barr RG, Celli BR, Mannino DM, et al. Comorbidities, patient knowledge, and disease management in a national sample of patients with COPD. *Am J Med.* 2009;122(4):348-355. https://doi.org/10.1016/j.amjmed.2008.09.042

22. Gan WQ, Man SF, Senthilselvan A, Sin DD. Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. *Thorax.* 2004;59(7):574-580. https://doi.org/10.1136/thx.2003.019588

23. Mahmud A, Feely J. Arterial stiffness is related to systemic inflammation in essential hypertension. *Hypertension.* 2005;46(5):1118-1122. https://doi.org/10.1161/01.HYP.0000185463.27209.b0

24. Chae CU, Lee RT, Rifai N, Ridker PM. Blood pressure and inflammation in apparently healthy men. *Hypertension*. 2001;38(3):399-403. https://doi.org/10.1161/01.HYP.38.3.399

25. Mills NL, Miller JJ, Anand A, et al. Increased arterial stiffness in patients with chronic obstructive pulmonary disease: a mechanism for increased cardiovascular risk. *Thorax*. 2008;63(4):306-311. https://doi.org/10.1136/thx.2007.083493

26. Maclay JD, McAllister DA, Rabinovich R, et al. Systemic elastin degradation in chronic obstructive pulmonary disease. *Thorax*. 2012;67(7):606-612. https://doi.org/10.1136/thoraxjnl-2011-200949

27. Barr RG, Celli BR, Martinez FJ, et al. Physician and patient perceptions in COPD: the COPD Resource Network Needs Assessment Survey. *Am J Med*. 2005;118(12):1415. https://doi.org/10.1016/j.amjmed.2005.07.059

28. Bidan CM, Veldsink AC, Meurs H, Gosens R. Airway and extracellular matrix mechanics in COPD. *Front Physiol*. 2015;6:346. https://doi.org/10.3389/fphys.2015.00346

29. Lemarié CA, Tharaux PL, Lehoux S. Extracellular matrix alterations in hypertensive vascular remodeling. *J Mol Cell Cardiol*. 2010;48(3):433-439. https://doi.org/10.1016/j.yjmcc.2009.09.018

30. Barrington-Trimis JL, Braymiller JL, Unger JB, et al. Trends in the age of cigarette smoking initiation among young adults in the US from 2002 to 2018. *JAMA Netw Open*. 2020;3(10):e2019022. https://doi.org/10.1001/jamanetworkopen.2020.19022

31. Doonan RJ, Hausvater A, Scallan C, Mikhailidis DP, Pilote L, Daskalopoulou SS. The effect of smoking on arterial stiffness. *Hypertens Res*. 2010;33(5):398-410. https://doi.org/10.1038/hr.2010.25

32. Karatzi K, Papamichael C, Karatzis E, et al. Acute smoke-induced endothelial dysfunction is more prolonged in smokers than in non-smokers. *Int J Cardiol*. 2007;120(3):404-406. https://doi.org/10.1016/j.ijcard.2006.07.200

33. Polverino F, Celli BR, Owen CA. COPD as an endothelial disorder: endothelial injury linking lesions in the lungs and other organs? (2017 Grover Conference Series). *Pulm Circ*. 2018;8(1):1-18. https://doi.org/10.1177/2045894018758528

34. Celermajer DS, Sorensen KE, Georgakopoulos D, et al. Cigarette smoking is associated with dose-related and potentially reversible impairment of endothelium-dependent dilation in healthy young adults. *Circulation*. 1993;88(5 Pt 1):2149-2155. https://doi.org/10.1161/01.CIR.88.5.2149

35. Feinstein L, Wilkerson J, Salo PM, et al. Validation of questionnaire-based case definitions for chronic obstructive pulmonary disease. *Epidemiology*. 2020;31(3):459-466. https://doi.org/10.1097/EDE.0000000000001176