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ORIGINAL RESEARCH

Obstructive Airway Disease is Associated with Increased Cardiovascular Disease Risk Independent of Phenotype: Evidence from Two Nationwide Population-Based Studies

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Background: Cardiovascular disease (CVD), as the most common comorbidity of chronic obstructive pulmonary disease (COPD), has received much attention. However, robust evidence of the relationship between other obstructive airway disease (OAD) phenotypes, such as asthma, asthma-COPD overlap (ACO), and CVD risk is limited. We aimed to compare the magnitude of CVD risk across different OAD phenotypes using two nationwide population-based studies.

Methods: We analyzed cross-sectional data from the National Health and Nutrition Examination Survey 1999–2018 (N=44,972, representing 183,508,900 adults). Survey-weighted descriptive analysis and logistic regression were used to investigate the prevalence of CVD (including heart failure, coronary heart disease, angina pectoris, and myocardial infarction) across OAD phenotypes and calculate odds ratios (ORs) with 95% confidence intervals (CIs). Additionally, longitudinal data from the China Health and Retirement Longitudinal Study (CHARLS) (N=13,533) were analyzed to validate these findings and calculate hazard ratios (HRs) with 95% CIs for new-onset CVD using Cox proportional hazards models.

Results: The weighted prevalence of at least one CVD in asthma, COPD, and ACO was 6.21%, 16.82%, and 20.75%, respectively. Individuals with asthma, COPD, and ACO had a significantly higher prevalence of CVD than those without OAD, with ORs of 1.55 (95% CI: 1.34–1.78), 1.76 (95% CI: 1.50–2.07), and 2.99 (95% CI: 2.47–3.61), respectively. During the 9-year follow-up, 2,444 (18.1%) individuals developed CVD in CHARLS. The incidence of CVD was significantly higher in individuals with asthma (HR=1.67, 95% CI: 1.26–2.21), COPD (HR=1.71, 95% CI: 1.48–1.97), and ACO (HR=2.67, 95% CI: 2.21–3.24) than those without OAD.

Conclusion: Individuals with OAD have a higher prevalence of comorbid CVD and an increased risk of developing CVD independent of phenotype, especially in those with ACO. These findings emphasize the need for awareness and appropriate cardiovascular screening in OAD.

Keywords: obstructive airway disease, asthma, COPD, asthma-COPD overlap, cardiovascular disease

Introduction

Chronic obstructive pulmonary disease (COPD) and asthma are two of the most prevalent obstructive airway diseases (OAD), affecting approximately 212.3 million and 262 million people respectively in 2019.[1,2] Concomitant cardiovascular disease (CVD) is common in COPD, likely due to shared risk factors (eg, aging, smoking, and persistent systemic inflammation), and contributing to the overall morbidity and mortality of patients with COPD.[3,4] Despite these associations, the diagnosis and appropriate management of CVD in COPD are often neglected.[5,6] The existing research on the

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link between asthma and CVD is equivocal. Several studies have linked asthma to an increased risk of CVD,[7–9] while others suggest that the increased risk of CVD conferred by asthma is only restricted to certain groups, such as smokers[9,10] and women.[11,12] However, several studies have found no significant link between asthma and CVD,[13,14] and a few have even proposed that asthma may offer a protective effect against CVD.[15] Up to now, there is no recommendation for early screening of CVD in asthma patients within the most recent Global Initiative for Asthma (GINA) guideline.[16]

Although COPD and asthma are distinct conditions with unique characteristics, they could coexist in the same individual, with overlap observed in 2.0% of the general population, 29.6% of those with COPD, and 26.5% of asthma patients.[17] This condition, termed asthma-COPD overlap (ACO), was jointly defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) and GINA in 2014.[18,19] Patients with ACO typically experience more severe symptoms, more frequent or severe respiratory exacerbations, and a lower quality of life compared to either condition present alone, leading to increased healthcare utilization and higher associated costs.[20–22] However, research on cardiovascular comorbidities in ACO remains limited, with most studies being cross-sectional,[23–25] involving small sample sizes,[24] or retrospective,[26] leading to inconsistent results.[23,25]

Considering the substantial impact and underdiagnosis of CVD comorbidities in OAD, as well as the clinical differences among OAD phenotypes, understanding the role of phenotype on CVD risk is essential for CVD screening and management. Existing research is limited by inconsistent results and a lack of geographic diversity in the population, with few studies comparing the magnitude of CVD risk across different OAD phenotypes within the same research. This study aimed to investigate the differences in CVD prevalence among patients with different OAD phenotypes using nationally representative cross-sectional data from the US and to validate these findings with longitudinal data from China.

Methods

Study Population

National Health and Nutrition Examination Survey (NHANES) is a cross-sectional survey conducted in the US that gathers health and nutrition data from a nationally representative population. The NHANES datasets are publicly accessible under the National Center for Health Statistics (NCHS) data use policy, which permits unrestricted analysis of de-identified health survey data. Since 1999, NHANES has been performed in 2-year cycles, gathering information through in-home interviews and visits to mobile examination centers (MECs). For our analysis, we included adults aged 20 years and older from 10 continuous NHANES cycles (1999–2018), with complete data on self-reported physician-diagnosed OAD, cardiovascular conditions (heart failure, coronary heart disease [CHD], angina pectoris, and myocardial infarction), and other relevant covariates (Figure 1A). Following the published analytic guidelines,[27] we calculated 20-year sampling weights using the MEC sampling weight. Further details about NHANES are available at https://wwwn.cdc.gov/nchs/nhanes/Default.aspx.

The China Health and Retirement Longitudinal Study (CHARLS) is an ongoing nationwide cohort using the multistage stratified cluster sampling procedure on middle-aged and older individuals in China.[28] The study started in 2011 with a baseline survey of 17,708 participants (Wave 1) from 28 provinces. Follow-up surveys have been conducted every 2–3 years using face-to-face interviews, with Wave 2 in 2013, Wave 3 in 2015, Wave 4 in 2018, and Wave 5 in 2020. Further information about the CHARLS data is available at http://charls.pku.edu.cn/en. All published datasets were accessible after registration was approved. In our study, we included participants who met the following criteria: (1) complete baseline data on OAD status, (2) no history of CVD at baseline, and (3) at least one follow-up (Figure 1B).

Definitions of COPD, Asthma and ACO

During household visits, NHANES participants were interviewed by trained staff using the Computer Assisted Personal Interviewing-CAPI (interviewer administered) system about various health conditions. Participants with an affirmative answer to the question, "Has a doctor or other health professional ever told you that you had chronic bronchitis and/or emphysema?" were classified as having COPD. Similarly, those with an affirmative answer to the question, "Has a doctor or other health professional ever told you that you had asthma?" were classified as having asthma. In the CHARLS, the definitions of COPD and asthma were similar to those used in NHANES (Table S1). We classified participants into four

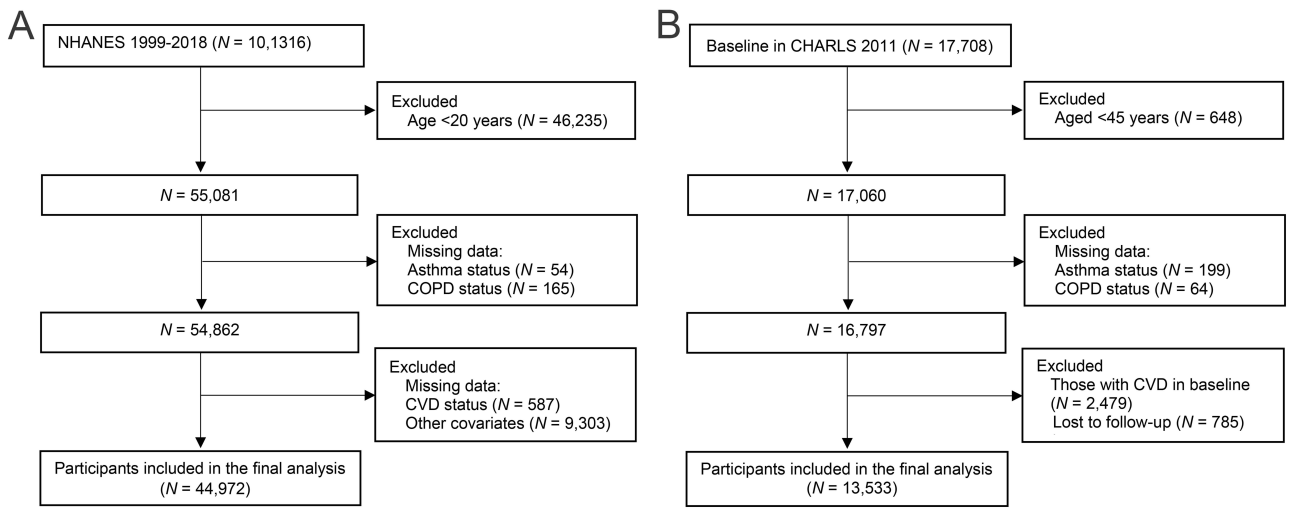

Figure 1 Selection of the analytical sample in NHANES 1999–2018 (**A**) and CHARLS (**B**).
Abbreviations: COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; NHANES, National Health and Nutrition Examination Survey; CHARLS, China Health and Retirement Longitudinal Study.

groups: (I) no OAD (neither asthma nor COPD), (II) asthma (only asthma, not COPD), (III) COPD (only COPD, not asthma), and (IV) ACO (both asthma and COPD).

Assessment of CVD

In NHANES, participants were considered to have CVD if they had any one of the following conditions: heart failure, CHD, myocardial infarction, or angina pectoris in response to the question "Have you ever been told by a doctor or other health professional that you had__" (Table S1). In CHARLS, the incidence of CVD was defined as new-onset events between Wave 2 and Wave 5. These events were based on self-reported physician diagnoses, as indicated by the question, "Have you been diagnosed with heart attack, coronary heart disease, angina, congestive heart failure, or other heart problems by a doctor?" The endpoint of follow-up was at the first occurrence of CVD, death, or the censoring date, whichever came first. The censoring date was the date of the last survey in which each participant attended. This definition follows the methodology used in previous CHARLS studies.[29,30]

Covariates Assessments

The study considered several covariates known to influence cardiovascular risk, including age, sex, race/ethnicity (NHANES only), place of residence (CHARLS only), marital status, education level, poverty income ratio (PIR) (NHANES only), body mass index (BMI), smoking status, hypertension, and diabetes. Education level was recorded as a categorical variable, with three levels in NHANES (less than high school, high school or equivalent, and college or above) and four levels in CHARLS (no completion of primary school, sishu/home school/elementary school, middle school, and high school and above). PIR was categorized into: <1.3, 1.3–3.5, and >3.5. BMI was classified into <18.5, 18.5-<25, 25-<30, and ≥30 kg/m². Smoking status was categorized into three groups: never smoker, former smoker, and current smoker, based on whether ever smoked ≥100 cigarettes and if yes, further asked whether the participant is smoking currently. Hypertension and diabetes were identified based on the self-reported physician-diagnosed status.

Statistical Analysis

In NHANES, weights are applied to each participant to reflect the number of people they represent in the general population. Detailed information on the weighting methodology can be found elsewhere.[31] We calculated the weighted population prevalence estimates for different OAD phenotypes using the MEC sample weights. Descriptive statistics were grouped by OAD phenotype. Continuous variable with non-normal distribution was presented as the median (25th, 75th) and compared using the Kruskal–Wallis *H*-test for complex survey samples.

Categorical variables were reported as unweighted counts (N) and weighted percentages (%) and compared through the Rao–Scott chi-square test. The prevalence of different forms of CVD across OAD phenotypes was assessed and reported as both unweighted and weighted counts, along with weighted percentages and 95% confidence intervals (CI). For each CVD outcome, three logistic regression models were used. Model 1 included only OAD phenotype, while model 2 adjusted for sociodemographic covariates: age, sex, race/ethnicity, marital status, education level, and the PIR. Model 3 additionally accounted for health-related variables, including BMI category, smoking status, hypertension, and diabetes.

In CHARLS, continuous variables were analyzed using one-way ANOVA, while categorical variables were assessed using the chi-square test. Kaplan-Meier curve and Cox proportional hazard models were performed to evaluate the new-onset CVD risk across OAD phenotypes. Model 1 included only OAD phenotypes. Model 2 adjusted for age, sex, living place, marital status, and education level. Model 3 was further adjusted for BMI category, smoking status, hypertension, and diabetes. Missing data for covariates were handled using multiple imputations with the *mice* package in R. Subgroup analyses were performed to explore the relationship of OAD phenotypes with CVD risk in model 3 by age, sex, living place, BMI category, smoking status, hypertension, and diabetes. Sensitivity analyses were performed by reanalyzing the complete dataset without multiple imputations and excluding individuals who developed CVD in Wave 2.

Statistical significance was defined as a two-sided *P*-value <0.05. All analyses were conducted using R software version 4.3.3.

Exemption from Ethical Statements

The NHANES was approved by the NCHS Ethics Review Board, and the CHARLS study was approved by the Institutional Review Board at Peking University (IRB00001052-11,015). All participants in both surveys provided written informed consent. This study was exempted from approval according to national legal guidelines (item 1 and 2 of Article 32 of the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects dated February 18, 2023, China).

Results

Population Characteristics

The final NHANES sample included 44,972 individuals aged ≥20 years with complete data (weighted N=183,508,900) (Figure 1A). Of these, 7830 individuals (weighted N=32,936,489) were identified as having OAD, representing 17.9% of US adults. The details of the prevalence of different OAD phenotypes by sex, age, race/ethnicity, smoking status, BMI, and education level were described in Table S2 and Figure S1. Among these individuals, asthma, COPD, and ACO account for 61.5%, 21.6%, and 16.9% of the total OAD population, respectively. Table 1 summarizes the sociodemographic and health-related characteristics of the included population. Among the OAD phenotypes, individuals with COPD had the highest median age and smoking rates but the lowest education levels. Additionally, those with ACO were more likely to have comorbid conditions such as obesity, hypertension, and diabetes.

Table 1 Descriptive Characteristics of Adults Aged ≥20 with and Without OAD in the US Population, 1999–2018

Characteristics	Total	No OAD	OAD			*P*-value *	*P*-value †
			Asthma	COPD	ACO		
Unweighted N	44,972	37,142	4703	1754	1373		
Weighted N	183,508,900	150,572,411	20,257,972	7,126,044	5,552,472		
Weighted population % ‡	-	82.1 (81.5–82.6)	11.0 (10.6–11.5)	3.9 (3.6–4.2)	3.0 (2.8–3.3)		
Weighted % §	-	-	61.5 (59.8–63.2)	21.6 (20.3–23.0)	16.9 (15.7–18.0)		
Age, years	48 (34, 64)	48 (34, 63)	42 (29, 59)	61 (45, 72)	56 (42.5, 67)	<0.001	<0.001

(*Continued*)

Table 1 (Continued).

Characteristics	Total	No OAD	OAD			*P*-value *	*P*-value †
			Asthma	COPD	ACO		
Sex, %						<0.001	<0.001
Male	21625 (48.0)	18,362 (49.6)	2015 (43.4)	766 (41.1)	482 (30.7)		
Female	23347 (52.0)	18,780 (50.4)	2688 (56.6)	988 (58.9)	891 (69.3)		
Race/ethnicity, %						<0.001	<0.001
Mexican American	7536 (7.8)	6783 (8.6)	504 (5.3)	160 (3.3)	89 (2.3)		
Non-Hispanic White	20,376 (69.2)	16,302 (68.5)	2166 (69.2)	1119 (80.1)	789 (75.7)		
Non-Hispanic Black	9424 (11.0)	7639 (10.9)	1207 (13.4)	290 (8.4)	288 (10.5)		
Other	7636 (11.9)	6418 (12.1)	826 (12.1)	185 (8.2)	207 (11.4)		
Education level,						<0.001	<0.001
Less than high school	11,542 (16.3)	9619 (16.1)	999 (13.9)	543 (23.7)	381 (19.9)		
High school or equivalent	10,402 (23.8)	8602 (23.8)	1022 (21.8)	470 (29.7)	308 (22.9)		
College or above	23,028 (59.9)	18,921 (60.0)	2682 (64.4)	741 (46.6)	684 (57.1)		
Marital status						<0.001	0.406
Married	24,064 (57.1)	20,427 (58.5)	2209 (51.5)	811 (49.6)	617 (50.9)		
Other	20,908 (42.9)	16,715 (1.5)	2494 (48.5)	943 (50.4)	756 (49.1)		
Family PIR, %						<0.001	<0.001
<1.3	13,508 (20.7)	10,741 (19.6)	1551 (23.3)	625 (26.7)	591 (34.1)		
1.3–3.5	17,317 (36.1)	14,402 (36.0)	1656 (33.6)	757 (44.2)	502 (37.7)		
>3.5	14,147 (43.2)	11,999 (44.5)	1496 (43.1)	372 (29.2)	280 (28.3)		
Smoking status, %						<0.001	<0.001
Never smoker	24,504 (54.0)	20,946 (55.9)	2571 (53.6)	532 (29.7)	455 (36.4)		
Former smoker	12,839 (28.3)	10,338 (27.6)	1308 (29.0)	684 (36.6)	509 (33.1)		
Current smoker	7629 (17.7)	5858 (16.5)	824 (17.4)	538 (33.7)	409 (30.5)		
BMI category						<0.001	<0.001
<18.5kg/m^2	706 (1.6)	552 (1.5)	71 (1.7)	51 (3.2)	32 (2.3)		
18.5-<25kg/m^2	12,664 (29.4)	10,749 (30.1)	1184 (28.3)	452 (25.1)	279 (20.5)		
25-<30kg/m^2	15,103 (33.2)	12,834 (34.2)	1388 (28.8)	514 (28.0)	367 (27.9)		
≥30kg/m^2	16,499 (35.8)	13,007 (34.2)	2060 (41.1)	737 (43.7)	695 (49.2)		
Hypertension						<0.001	<0.001
No	29,548 (69.9)	25,034 (71.4)	3013 (69.4)	878 (54.7)	623 (51.2)		
Yes	15,424 (30.1)	12,108 (28.6)	1690 (30.6)	876 (45.3)	750 (48.8)		
Diabetes						<0.001	<0.001
No	39,712 (91.5)	33,083 (92.0)	4139 (91.9)	1439 (84.8)	1051 (82.3)		
Yes	5260 (8.5)	4509 (8.0)	564 (8.1)	315 (15.2)	322 (17.7)	<0.001	<0.001

Notes: The descriptive statistics were calculated after accounting for the complex sampling design. Continuous variables are expressed as the median (25th, 75th), and categorical variables are expressed as unweighted frequency (weighted percent).* *P*-value is for the between-group differences estimated from the Kruskal–Wallis *H*-test for a continuous variable and the Rao-Scott chi-square test for categorical variables, including no OAD, asthma, COPD, and ACO groups.† *P*-value is for the between-group differences estimated from the Kruskal–Wallis *H*-test for a continuous variable and the Rao-Scott chi-square test for categorical variables, including asthma, COPD, and ACO groups. ‡ Weighted population % indicates the prevalence estimates among US adults aged ≥20 years old. § Weighted % indicates the prevalence estimates within US adults aged ≥20 years old with OAD.

Abbreviations: OAD, obstructive airway disease; COPD, chronic obstructive pulmonary disease; ACO, asthma-COPD overlap; PIR, poverty income ratio; BMI, body mass index.

Prevalence of CVD Risk by OAD Phenotype

The prevalence of CVD among different OAD phenotypes is presented in Table 2 and Figure S2. Adults without OAD had the lowest prevalence of CVD (5.44%). Of these individuals with OAD, the reported prevalence of CVD in asthma, COPD, and ACO was 6.21%, 16.82%, and 20.75%, respectively (P <0.001). In agreement with these findings, the reported prevalence of CHD, heart failure, myocardial infarction, and angina was consistently higher in individuals with COPD and ACO when compared to asthma and those without OAD.

Table 2 Prevalence of Cardiovascular Disease in Adults Aged 20 with and Without OAD in the US Population, 1999–2018

	Total	No OAD	OAD			*P*-value *	*P*-value †
			Asthma	COPD	ACO		
Unweighted N	44,972	37,142	4703	1754	1373		
Weighted N	183,508,900	150,572,411	20,257,972	7,126,044	5,552,472		
Cardiovascular disease						<0.001	<0.001
Unweighted N	3701	2616	400	361	324		
Weighted N	11,800,789	8,192,666	1,257,398	1,198,416	1,152,308		
Weighted %	6.43 (6.09–6.77)	5.44 (5.05–5.832)	6.21 (5.32–7.09)	16.82 (14.72–18.92)	20.75 (17.42–24.08)		
Heart failure						<0.001	<0.001
Unweighted N	1361	877	152	163	169		
Weighted N	3,927,146	2,416,943	469,189	490,794	550,220		
Weighted %	2.14 (1.97–2.31)	1.61 (1.46–1.75)	2.32 (1.86–2.78)	6.89 (5.51–8.26)	9.91 (8.24–11.58)		
Coronary heart disease						<0.001	<0.001
Unweighted N	1785	1310	156	181	138		
Weighted N	5,974,473	4,327,173	507,182	615,401	524,718		
Weighted %	3.26 (3.00–3.51)	2.87 (2.63–3.12)	2.50 (1.96–3.05)	8.64 (6.78–10.49)	9.45 (7.36–11.54)		
Angina pectoris						<0.001	<0.001
Unweighted N	1247	805	150	163	129		
Weighted N	4,271,811	2,720,391	467,064	565,734	518,621		
Weighted %	2.33 (2.11–2.54)	1.81 (1.61–2.00)	2.31 (1.80–2.81)	7.94 (6.49–9.39)	9.34 (7.10–11.58)		
Myocardial infarction						<0.001	<0.001
Unweighted N	1828	1294	195	181	158		
Weighted N	5,779,592	4,068,713	580,844	577,269	552,766		
Weighted %	3.15 (2.92–3.38)	2.70 (2.48–2.92)	2.87 (2.41–3.32)	8.10 (6.59–9.61)	9.96 (8.26–11.65)		

Notes: Weighted N was estimated after accounting for the complex sampling of the survey according to the published NHANES analytic guidelines.* *P*-value is for the between-group differences estimated from the Rao-Scott chi-square test, including no OAD, asthma, COPD, and ACO groups.† *P*-value is for the between-group differences estimated from the Rao-Scott chi-square test, including asthma, COPD, and ACO groups.

Abbreviations: OAD, obstructive airway disease; COPD, chronic obstructive pulmonary disease; ACO, asthma-COPD overlap.

Association Between OAD Phenotypes and the Prevalence of CVD

After full adjustment (model 3), multiple logistic regression models showed that individuals with asthma had higher odds of reporting CVD when compared to those without OAD (OR=1.55, 95% CI: 1.34–1.78). The odds were 1.76 times higher for COPD (95% CI: 1.50–2.07), and 2.99 times higher for ACO (95% CI: 2.47–3.61) (Figure 2 and Table S3). Consistently, all three OAD phenotypes had statistically greater odds of reporting heart failure, CHD (except for asthma, P=0.238), myocardial infarction, and angina pectoris than those without OAD in model 3. When restricting the analysis population to the age group of 20–44 years, we found that the association between asthma, ACO, and the risk of CVD was still significant and even more pronounced (Table S4).

We further compared the prevalence of CVD among OAD patients (Table 3). When using asthma as the reference, individuals with COPD had higher odds of reporting CVD and specific CVD in model 1 (ORs ranging from 2.84 to 3.68, all P <0.001) and model 2 (except for myocardial infarction, P=0.054). In model 3, the odds for angina pectoris remained significant in COPD compared to asthma (OR=1.77, 95% CI 1.25–2.50). In contrast, the ACO group had statistically greater odds of CVD and specific CVD than the asthma group in model 3 (ORs ranging from 1.74 to 2.35, all P <0.001). When using COPD as the reference, the ACO group had statistically greater odds of CVD, heart failure, and myocardial infarction (ORs ranging from 1.57 to 1.85, all P <0.05).

Validation Using the CHARLS Cohort

A total of 13,533 participants from the CHARLS cohort were included in the longitudinal analysis (Figure 1B). Compared to the NHANES population, individuals with ACO in CHARLS were older and more likely to be males. The sociodemographic and health-related characteristics are presented in Table S5. During the 9-year follow-up, 2,444 participants (18.1%) developed CVD. Figure 3 shows the incidence of CVD in different OAD phenotypes. After full

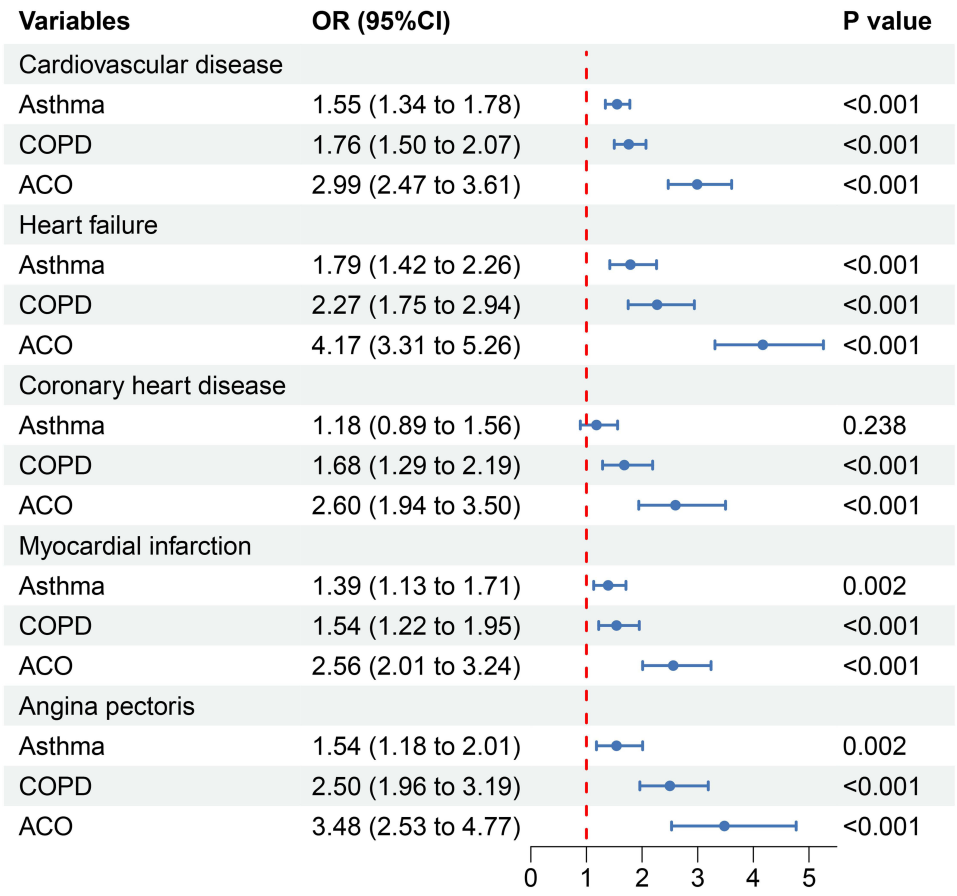

Figure 2 Association between OAD phenotypes and cardiovascular disease outcomes in the US population, 1999–2018.
Notes: Using survey-weighted multivariate logistic regression, odds ratios were calculated with the no OAD group as the reference. The model was adjusted for sociodemographic covariates (age, gender, race/ethnicity, education level, family poverty income ratio, and marital status) and health-related covariates (smoking status, BMI category, hypertension, and diabetes). Participants were classified into no OAD (neither asthma nor COPD), asthma (only asthma, not COPD), COPD (only COPD, not asthma), and ACO (both asthma and COPD).
Abbreviations: OR, odds ratios; 95% CI, 95% confidence interval; OAD, obstructive airway disease; COPD, chronic obstructive pulmonary disease; ACO, asthma-COPD overlap.

adjustment (model 3), the incidence of CVD was significantly higher in those with asthma (HR=1.67, 95% CI: 1.26–2.21), COPD (HR=1.71, 95% CI: 1.48–1.97), and ACO (HR=2.67, 95% CI: 2.21–3.24) compared to those without OAD (Table 4). When asthma was used as the reference, the incidence of CVD in the COPD group was not statistically

Table 3 Association of Different OAD Phenotypes with Cardiovascular Disease Using Asthma and COPD as Reference in the US Population, 1999–2018

	Model 1			Model 2			Model 3		
	OR	**95% CI**	***P*-value**	**OR**	**95% CI**	***P*-value**	**OR**	**95% CI**	***P*-value**
Cardiovascular disease									
COPD (Asthma ref) *	2.84	(2.37–3.41)	<0.001	1.34	(1.09–1.65)	0.006	1.16	(0.93–1.45)	0.184
ACO (Asthma ref) *	3.66	(3.05–4.41)	<0.001	2.25	(1.82–2.79)	<0.001	1.84	(1.46–2.31)	<0.001
ACO (COPD ref) †	1.29	(1.05–1.59)	0.017	1.67	(1.32–2.11)	<0.001	1.59	(1.25–2.02)	<0.001
Heart failure									
COPD (Asthma ref) *	3.12	(2.35–4.15)	<0.01	1.43	(1.05–1.94)	0.022	1.3	(0.95–1.78)	0.096
ACO (Asthma ref) *	4.64	(3.51–6.14)	<0.001	2.75	(2.04–3.70)	<0.001	2.31	(1.70–3.15)	<0.001
ACO (COPD ref) †	1.49	(1.11–1.99)	0.008	1.96	(1.42–2.70)	<0.001	1.85	(1.33–2.55)	<0.001

(*Continued*)

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Table 3 (Continued).

	Model 1			Model 2			Model 3		
	OR	**95% CI**	***P*-value**	**OR**	**95% CI**	***P*-value**	**OR**	**95% CI**	***P*-value**
Coronary heart disease									
COPD (Asthma ref) *	3.68	(2.61–5.18)	<0.001	1.66	(1.13–2.45)	0.011	1.45	(0.96–2.18)	0.078
ACO (Asthma ref) *	4.06	(3.00–5.51)	<0.001	2.60	(1.87–3.62)	<0.001	2.15	(1.51–3.06)	<0.001
ACO (COPD ref) †	1.10	(0.77–1.59)	0.593	1.53	(1.03–2.27)	0.037	1.44	(0.96–2.17)	0.076
Myocardial infarction									
COPD (Asthma ref) *	2.99	(2.31–3.86)	<0.001	1.33	(1.00–1.79)	0.054	1.10	(0.82–1.48)	0.516
ACO (Asthma ref) *	3.75	(2.93–4.79)	<0.001	2.22	(1.68–2.94)	<0.001	1.74	(1.30–2.33)	<0.001
ACO (COPD ref) †	1.25	(0.96–1.64)	0.097	1.63	(1.22–2.17)	0.001	1.57	(1.17–2.11)	0.003
Angina pectoris									
COPD (Asthma ref) *	3.65	(2.65–5.04)	<0.001	1.87	(1.32–2.64)	<0.001	1.77	(1.25–2.50)	0.001
ACO (Asthma ref) *	4.37	(3.08–6.20)	<0.001	2.7	(1.86–3.93)	<0.001	2.35	(1.61–3.44)	<0.001
ACO (COPD ref) †	1.19	(0.88–1.63)	0.258	1.46	(1.05–2.03)	0.025	1.36	(0.97–1.89)	0.072

Notes: Using survey-weighted multivariate logistic regression, odds ratios were calculated with asthma and COPD as reference groups. Model 1 included OAD phenotype as the sole response variable. Model 2 further adjusted for the sociodemographic covariates age, gender, race/ethnicity, education level, family poverty income ratio, and marital status. Model 3 further adjusted for the health-related covariates BMI category, smoking status, hypertension, and diabetes based on model 2. * Asthma group was used as the reference. † COPD group was used as the reference.
Abbreviations: OR, odds ratio; 95% CI, 95% confidence interval; COPD, chronic obstructive pulmonary disease; ACO, asthma-COPD overlap.

significant (P >0.05). However, the ACO group showed a significantly higher risk of developing CVD than the asthma group (HR=1.59, 95% CI: 1.13–2.22). Furthermore, when COPD was used as the reference, the CVD risk remained significantly higher in the ACO group (HR=1.57, 95% CI: 1.25–1.98).

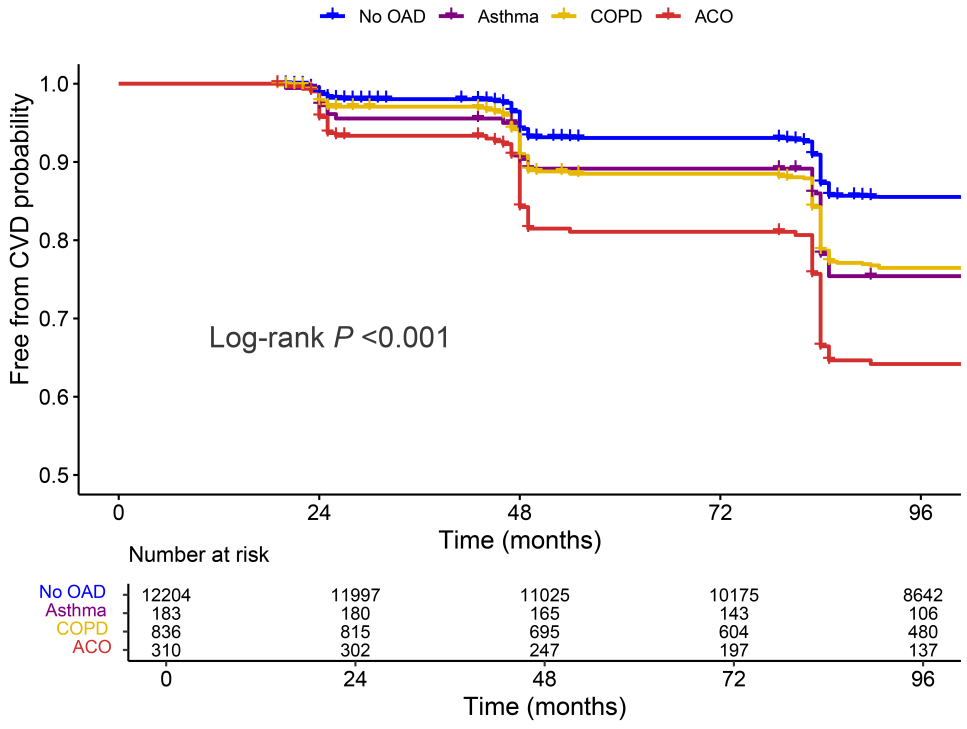

Figure 3 Kaplan–Meier curves for the incidence of cardiovascular disease by different OAD phenotypes. Participants were classified into no OAD (neither asthma nor COPD), asthma (only asthma, not COPD), COPD (only COPD, not asthma), and ACO (both asthma and COPD).
Abbreviations: OAD, obstructive airway disease; COPD, chronic obstructive pulmonary disease; ACO, asthma-COPD overlap.

Table 4 Associations of Different OAD Phenotypes with the New-Onset Cardiovascular Disease in the CHARLS

	Model 1			Model 2			Model 3		
	HR	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**
Asthma *	1.77	(1.34–2.34)	<0.001	1.75	(1.32–2.31)	<0.001	1.67	(1.26–2.21)	<0.001
COPD *	1.72	(1.49–1.98)	<0.001	1.70	(1.47–1.96)	<0.001	1.71	(1.48–1.97)	<0.001
ACO *	2.82	(2.34–3.41)	<0.001	2.79	(2.30–3.37)	<0.001	2.67	(2.21–3.24)	<0.001
COPD (Asthma ref) †	0.97	(0.72–1.32)	0.853	0.98	(0.72–1.33)	0.88	1.00	(0.73–1.36)	0.997
ACO (Asthma ref) †	1.60	(1.15–2.22)	0.006	1.59	(1.14–2.22)	0.006	1.59	(1.13–2.22)	0.007
ACO (COPD ref) ‡	1.64	(1.31–2.06)	<0.001	1.62	(1.29–2.04)	<0.001	1.57	(1.25–1.98)	<0.001

Notes: Model 1 included OAD phenotype as the sole response variable.Model 2 further adjusted for the sociodemographic covariates age, gender, living place, education level, and marital status.Model 3 further adjusted for the health-related covariates BMI category, smoking status, hypertension, and diabetes based on model 2.* No-OAD group was used as the reference.† Asthma group was used as the reference.‡ COPD group was used as the reference.

Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval; COPD, chronic obstructive pulmonary disease; ACO, asthma-COPD overlap.

In the subgroup analyses, significant associations between OAD phenotypes and the incidence of CVD were observed in almost all subgroups, and no significant interactions were observed across different subgroups except for hypertension (*P* for interaction=0.012) (Table S6). To enhance the robustness of our results, we performed sensitivity analyses by restricting the sample to participants with complete covariate data and excluding those who developed CVD in wave 2. These analyses consistently supported the primary results (Table S7 and Table S8).

Discussion

Our study is the first nationally representative analysis to examine the relationship between OAD phenotypes and various forms of CVD using NHANES data from 1999 to 2018. We confirmed that not only COPD but also asthma are independent risk factors for CVD. When asthma and COPD occur in the same individuals, the risk of CVD is significantly higher compared to either condition is present alone. We further validated these results using nationwide longitudinal data from China, which showed consistent findings. These results underscore the need for cardiovascular screening in individuals with OAD regardless of phenotype, especially in those with ACO.

Meta-analysis revealed that individuals with COPD had a 2.5-fold elevated CVD risk compared to those without COPD,[3] and when comorbid with CVD, the risk of mortality is notably increased.[32,33] Furthermore, several studies suggest that the burden of CVD in COPD may be underestimated,[34] with 21% to 29% of COPD patients having undiagnosed CVD.[5,35] Recent research has shown that COPD is associated with increased CVD risk regardless of phenotype (chronic bronchitis, emphysema).[36] However, other research has found this association between COPD and CVD existed only in those with GOLD stage ≥2,[37] and some reported no significant link after adjusting for traditional cardiovascular risk factors.[38] Our results observed a significant association between COPD and all forms of CVD, even after adjusting for common demographic and health-related risk factors. In addition, we observed a stronger association between COPD and CVD risk than asthma in NHANES; however, this association was not seen in the longitudinal analysis from China. Further longitudinal data are needed to compare the relative magnitude of CVD risk between asthma and COPD.

Limited studies have explored the link between asthma and CVD, often yielding conflicting results.[7,13,15] For example, cross-sectional data from National Health Interview Surveys (NHIS) found that individuals who reported ever having asthma were associated with an increased risk of angina pectoris, CHD, and heart attacks.[7] The Atherosclerosis Risk in Communities (ARIC) study, involving 13,501 middle-aged adults, found no independent association between a history of asthma and the incidence of CHD (HR=0.87, 95% CI 0.66–1.14).[13] Intriguingly, research from Italy showed that asthma exhibited protective impacts against acute or old myocardial infarction, with an odds ratio of 0.84 (95% CI 0.77–0.91).[15] Our results add to strong evidence that asthma is associated with an increased CVD risk in both cross-sectional and longitudinal analyses, even after detailed adjustment for CVD risk factors such as hypertension, diabetes, BMI, smoking, and socioeconomic status. The association between asthma and CVD was still significant and even more pronounced in

young adults (20–44 years). In addition, previous studies[10–12] showed that this association between asthma and CVD may be confined to certain groups. Data from the ARIC study[12] found that adult-onset asthma experienced a 2-fold increased risk of CHD in women instead of men. However, data from the Copenhagen General Population Study found that the risks for CVD were restricted to smokers with asthma.[10] Aligning with these studies,[11,12] we observed a stronger association between asthma and CVD in women. However, in contrast to the earlier studies by Pollevick et al[9] and Colak et al,[10] we found this association remained significant in never-smokers but not in ever-smokers. Additionally, our findings revealed that the association was no longer significant among individuals with hypertension, diabetes, or overweight. The exact mechanism behind asthma and CVD remains unclear. Investigators have suggested that shared systemic inflammatory, such as interleukin 6 (IL-6), C-reactive protein (CRP), fibrinogen, and d-dimer, are potential mediators of the association between asthma and CVD.[9,12] Additional research is warranted to clarify the pathways by which asthma is associated with CVD, which may lead to novel prevention strategies.

Consistent with previous studies,[23,25] patients with ACO in NHANES 1999–2018 were more likely to be females and less likely to smoke compared to those with COPD alone. However, the CHARLS showed that ACO was more frequent in males, similar trend was also observed in another study from China.[19] The increased prevalence of ACO in males could be seen as a reflection of higher exposure to tobacco in Chinese males than in females.[39] Cross-sectional results from Spain showed that IHD was less common in ACO patients than those with COPD alone after adjustment, with an odds ratio of 0.88 (95% CI, 0.79–0.98).[23] Conversely, a retrospective study has shown that ACO patients were associated with higher CVD risk compared with COPD alone.[26] Although some studies[20,24,40] have involved cardiovascular comorbidities in ACO patients, they often lacked adjustment for confounding variables, making it difficult to draw definitive conclusions. In addition, few studies have explored the risk of CVD in ACO patients using asthma as a reference. Our results expanded current knowledge by quantifying the magnitude of differences between asthma, COPD, and ACO, and found that individuals with ACO exhibited the strongest association with all forms of CVD among OAD phenotype. In addition, subgroup analyses confirmed that the association remained significant across all strata, underscoring the need for proactive CVD screening in all ACO patients.

Our study has several strengths. We analyzed 20 years of data from NHANES, representing approximately 183.5 million US adults, which provided robust, well-powered cross-sectional effect estimates. Considering the onset of CVD diagnosis in OAD patients was before, concomitant, or after the diagnosis of OAD. To improve the reliability of results, we therefore conducted longitudinal analyses in the CHARLS dataset, a nationwide longitudinal survey in China, which offered high-quality baseline data and comprehensive tracking of new-onset CVD over an extended follow-up period. The consistency of results from these two studies further strengthened the reliability of our findings. However, there are several limitations to consider. First, the self-reported nature of the data may have introduced measurement errors due to factors such as self-presentation, health literacy, and memory bias. Moreover, the absence of objective measures such as spirometry and imaging to confirm OAD severity or phenotype further complicates the interpretation of the results. Second, obtaining spirometry data for a more precise assessment would have been ideal. However, NHANES only included spirometry data in 3 of the 10 cycles used in this study. Previous studies have shown that even individuals with preserved ratio impaired spirometry (PRISm) face significantly increased CVD risk,[37,41] implying that the absence of spirometry could influence these associations. Third, the overlap of concepts between certain CVDs (eg, participants responded "Yes" to angina pectoris but "No" to CHD) could lead to less accurate prevalence estimates for specific conditions. Fourth, there are notable differences in the covariates collected between the CHARLS and NHANES study samples, such as ethnic composition and age ranges. Additionally, due to a high rate of missing family income data in the CHARLS (>40%), we thus excluded this variable in the longitudinal analysis. Furthermore, because of differences in educational levels between the two countries' populations, we applied distinct classification methods for education in each dataset.

Conclusion

In conclusion, the current study provided evidence that individuals with OAD are associated with increased CVD risk independent of phenotype in nationwide cross-sectional and longitudinal surveys. Among OAD patients, those with ACO exhibited the strongest association with CVD when compared with asthma or COPD. These findings underscore the importance

of awareness and appropriate cardiovascular screening in OAD. Future research should incorporate objective diagnostic tools, including spirometry and imaging, to validate OAD phenotypes and explore their mechanistic links to CVD risk.

Data Sharing Statement

The data analyzed in this study can be obtained by contacting the corresponding author with a reasonable request. The NHANES database used in this study is publicly available and can be accessed at https://wwwn.cdc.gov/nchs/nhanes/Default.aspx. The CHARLS data is available at http://charls.pku.edu.cn/en.

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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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Disclosure

The authors report no conflicts of interest in this work.

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