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Childhood asthma was associated with the presence of cardio-cerebrovascular diseases in US middle-aged and elderly

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ABSTRACT

Background: Asthma and cardio-cerebrovascular diseases (CVDs) share a common etiology of chronic systemic inflammation. Our manuscript was to investigate the association between childhood asthma and CVDs in middle-aged and elderly.
Methods: A total of 12,070 US middle-aged and elder were enrolled in the National Health and Nutrition Examination Survey. Childhood asthma was defined as a previous diagnosis of asthma at <18 years of age. Associations between childhood asthma and overall and cause-specific CVDs were evaluated using multivariable logistic regression models and subgroup analyses, including coronary artery disease (CAD), angina, and stroke.
Results: The prevalence of CVDs, including CAD ($p = 0.031$) and angina ($p < 0.001$), was significantly higher in patients with asthma ($p = 0.008$). Asthma was independently associated with a higher risk of CVDs (odds ratio [OR]:1.50, 95 % confidence interval [CI]: 1.22–1.84, $p < 0.001$), CAD (OR: 1.55, 95 %CI: 1.17–2.02, $p = 0.002$), and angina (OR: 1.93, 95 %CI: 1.42–2.58, $p < 0.001$) while not related to stroke ($p = 0.233$). Subgroup analysis suggested that the association was consistent across sex, race, and the presence of obesity, chronic obstructive pulmonary disease, and diabetes.
Conclusions: Childhood asthma was significantly associated with the presence of cardiocerebrovascular diseases, including CAD and angina in middle-aged and elderly. These findings underscore the importance of addressing childhood asthma as a potential risk factor for cardiovascular morbidity in middle-aged and elderly populations.

1. Introduction

Asthma is a global health problem characterized by reversible airflow obstruction, which has been identified as an important contributor to disease burden (Moorman et al., 2012). With the aging of the global population, cardio-cerebrovascular diseases (CVD) are the leading cause of morbidity and mortality worldwide (Nieuwenhuijsen, 2018). Asthma and CVDs share a common etiology of chronic systemic inflammation (Tattersall et al., 2015; Gurgone et al., 2020).

Epidemiological studies have reported conflicting results regarding the association between asthma and CVDs. Cepelis et al. reported that patients with asthma have a higher risk of atrial fibrillation (Cepelis et al., 2018). Several *meta*-analyses have reported an association between asthma, coronary artery disease (CAD) (Wang et al., 2017) and stroke (Wen et al., 2016). Other studies only confirmed this relationship in specific subgroups, such as smokers (Colak et al., 2015) and women (Onufrak et al., 2008). In addition, several studies found no correlation between two diseases (Schanen et al., 2005). Due to the comorbidity of these two diseases, it is difficult to speculate causality in the above-mentioned observational studies. In this study, we aimed to explore the association between childhood asthma and cardio-cerebrovascular diseases in middle-aged and older populations.

2. Methods

2.1. Study population

Participants were selected from the National Health and Nutrition Examination Survey (NHANES) cycle of 1999–2014. Individuals with missing records on asthma (n = 421) and on cardiovascular diseases (n

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= 866) were excluded from the middle age and elderly. A total of 12,070 participants aged ≥45 years were enrolled in the study. The study was approved by the Institutional Review Board of the National Center for Health Statistics, and all participants provided written informed consent (Protocol ##98-12).

2.2. Exposure and variables

The NHANES collects information on asthma using a self-administered questionnaire. Childhood asthma was defined as a positive response to the question, "Has a doctor or other health professional ever told you that you have asthma?" years, and the mean age at diagnosis was < 18 years.

We used questionnaires and examinations to obtain the baseline characteristics of the participants, including sex, age, race, education, physical activity, smoking status, chronic obstructive pulmonary disease (COPD), and diabetes. Total cholesterol and glycerides levels were measured using an automatic biochemical analyzer.

CVDs was ascertained by a definite response to the question "Has a doctor or other health professional ever told you that you have coronary heart disease, angina pectoris or stroke?".

2.3. Statistical analysis

Comparisons between numeric parameters were performed using Student's t tests, and categorical variables were analyzed using the chi-square test. The complex, weighted survey analysis was taken into account. Logistic regression models were used to explore the relationship between childhood asthma and the prevalence of CVDs, including CAD, angina, and stroke. Model 1 was not adjusted. Model 2 was adjusted for age, sex, race, education, physical activity, and smoking status. Model 3 was additionally adjusted for body mass index (BMI), COPD, diabetes, cholesterol, and triglyceride levels. Subgroup analysis was performed using similar statistical modeling stratified by sex, obesity, race, COPD, and diabetes. All statistical analyses were performed using IBM SPSS 25.0. Statistical significance was set at p value < 0.05.

3. Results

A sum of 12,070 participants were enrolled in the study. Compared with individuals without asthma, participants with asthma tended to be younger and non-Hispanic. As shown in Table 1, the prevalence of CVDs, including CAD (p = 0.031) and angina (p < 0.001), was significantly higher in patients with asthma (p = 0.008). Although stroke was more common in the asthma group, the difference was not significant.

As shown in Table 2, childhood asthma was related to an increased prevalence of CVDs in the unadjusted Model 1 (odds ratio [OR] 1.30, 95 % confidence interval [CI] 1.07 to 1.57; p = 0.007), the partly-adjusted Model 2 (OR 1.49, 95 % CI 1.22 to 1.81; p < 0.001), and fully adjusted Model 3 (OR 1.50, 95 % CI 1.22 to 1.84; p < 0.001), respectively. Specially, asthma was significantly associated with CAD (OR: 1.55, 95 % CI: 1.17–2.02, p = 0.002) and angina (OR: 1.93, 95 %CI: 1.42–2.58, p < 0.001) but not related to stroke (p = 0.233).

Subgroup analysis (Table 3) suggested that the association between childhood asthma and CVDs was consistent across sex (p = 0.337), race (p = 0.651), presence of obesity (p = 0.253), COPD (p = 0.457), and diabetes (p = 0.095).

Table 1
Characteristics of US middle-aged and elderly according to the presence of childhood asthma from NHANES 1999–2014.

Variable	Overall	Without asthma	With asthma	P value
Male (%)	6115 (50.7)	5868 (50.9)	247 (46.4)	0.051
Age, years	70.9 ± 7.5	71.0 ± 7.5	69.1 ± 7.2	<0.001
Race (%)				<0.001
Non-Hispanic white	6671 (55.3)	6370 (55.2)	301 (56.6)	
Non-Hispanic black	2173 (18.0)	2054 (17.8)	119 (22.4)	
Mexican American	1882 (15.6)	1841 (16.0)	41 (7.7)	
Others	1344 (11.1)	1273 (11.0)	71 (13.3)	
Education				<0.001
Less than high school	4379 (36.3)	4232 (36.7)	147 (27.6)	
High school	2883 (23.9)	2745 (23.8)	138 (25.9)	
More than high school	4808 (39.8)	4561 (39.5)	247 (46.4)	
Activity (%)				0.103
Vigorous	2302 (19.1)	2210 (19.2)	92 (17.3)	
Moderate	6884 (57.0)	6591 (57.1)	293 (55.1)	
Inactive	2884 (23.9)	2737 (23.7)	147 (27.6)	
Smoker, %				0.009
Current	341 (2.8)	322 (2.8)	19 (3.6)	
Past	2212 (18.3)	2099 (18.2)	113 (21.2)	
Never	9517 (78.8)	9117 (79.0)	400 (75.2)	
BMI, kg/m^2	28.5 ± 5.7	28.5 ± 5.7	29.4 ± 6.4	<0.001
COPD (%)	4754 (39.4)	4531 (39.3)	223 (41.9)	0.239
Diabetes (%)	3345 (27.7)	3191 (27.7)	154 (28.9)	0.548
Cholesterol, mg/dl	198.3 ± 43.9	198.3 ± 43.9	199.2 ± 43.3	0.65
Triglycerides, mg/dl	155.5 ± 108.7	155.3 ± 107.8	159.2 ± 126.7	0.419
CAD (%)	1222 (10.1)	1153 (10.0)	69 (13.0)	0.031
Angina (%)	774 (6.4)	719 (6.2)	55 (10.3)	<0.001
Stroke (%)	989 (8.2)	942 (8.2)	47 (8.8)	0.638
CVD (%)	2925 (24.2)	2770 (24.0)	155 (29.1)	0.008

Data are presented as the mean (SD) or n (%). BMI, body mass index; CAD, coronary artery disease; CVD, cardiovascular disease.

Table 2
Association of childhood asthma with overall and cause-specific CVDs of US middle-aged and elderly from NHANES 1999–2014.

	Model 1		Model 2		Model 3	
	OR [95 % CI]	P	OR [95 % CI]	P	OR [95 % CI]	P
CVDs	1.30 [1.07, 1.57]	0.007	1.49 [1.22, 1.81]	<0.001	1.50 [1.22, 1.84]	<0.001
CAD	1.34 [1.03, 1.73]	<0.001	1.53 [1.16, 1.99]	0.002	1.55 [1.17, 2.02]	0.002
Angina	1.74 [1.29, 2.30]	<0.001	1.91 [1.41, 2.55]	<0.001	1.93 [1.42, 2.58]	<0.001
Stroke	1.09 [0.79, 1.47]	0.582	1.21 [0.88, 1.64]	0.226	1.21 [0.87, 1.64]	0.233

Model 1 was not adjusted.
Model 2 was adjusted for age, sex, race, education, activity, smoking status, and BMI.
Model 3 was adjusted for age, sex, race, education, activity, smoking status, BMI, COPD, diabetes, cholesterol, and triglyceride levels. OR, odds ratio; CI, confidence interval.

4. Discussion

In this cross-sectional study involving 12,070 middle-aged and older participants, we investigated the correlation between childhood asthma and the occurrence of CVDs in middle-aged and older populations. Our findings demonstrated that childhood asthma was associated with a higher risk of CVDs, including CAD and angina, but not stroke.

Data regarding the association between asthma and CVD are controversial in prospective and retrospective studies. The Atherosclerosis Risk in Communities study reported a null association between asthma and CAD (Schanen et al., 2005). Liu et al. found a significant relationship between asthma and CAD (Liu et al., 2017). A Framingham Offspring Cohort showed that asthma is a risk factor for myocardial infarction, angina, stroke, and heart failure, after controlling for

Table 3
Subgroup analysis of association of childhood asthma with CVDs of US middle-aged and elderly from NHANES 1999–2014.

Subgroup	OR [95 % CI]	P	P for interaction
Gender			0.337
Female	1.67 [1.25, 2.22]	<0.001	
Male	1.36 [1.01, 1.81]	0.037	
BMI			0.253
<30	1.69 [1.30, 2.19]	<0.001	
≥30	1.27 [0.91, 1.74]	0.151	
Race			0.651
Non-Hispanic white	1.54 [1.17, 2.01]	0.002	
Non-Hispanic black	1.33 [0.85, 2.03]	0.194	
Mexican American	2.32 [1.12, 4.60]	0.018	
Others	1.38 [0.72, 2.51]	0.307	
COPD			0.457
No	1.45 [1.10, 1.89]	0.002	
Yes	1.57 [1.15, 2.12]	0.194	
Diabetes			0.095
No	1.73 [1.35, 2.21]	<0.001	
Yes	1.10 [0.76, 1.56]	0.612	

established confounders (Pollevick et al., 2021). In line with these findings, our study confirmed a positive association between asthma and CVDs. Our study does not provide evidence of relationship between asthma and stroke, which is consistent with previous study that a Korean National Health Insurance Service Cohort found that asthma did not increase the risk of haemorrhagic or ischaemic stroke (Kim et al., 2019). Further large-scale clinical studies are warranted to elucidate this issue.

The pathophysiological mechanisms underlying this relationship are debated. First, chronic airway inflammation produces leukotrienes and 5-lipo-oxygenase, which contribute to accelerated atherosclerosis (Tattersall et al., 2015; Chen et al., 2021). Moreover, reduced lung function due to airway remodeling has been associated with elevated CVDs (Adrish and Hanania, 2023). Enhanced coagulation activation in asthma can lead to acute coronary events (de Boer and Majoor, 2012).

There are several limitations to this study. Firstly, childhood asthma was self-reported but not diagnosed using spirometry data due to the inaccuracy in spirometry testing involving children. Besides, there is also the possibility of confounding bias due to unmeasured factors, such as medications, diets and environmental exposure. Finally, subsequent remission history is missing in original dataset.

In conclusion, our study found that childhood asthma was associated with a higher risk of CVDs, including CAD and angina, but not stroke.

CRediT authorship contribution statement

Hedi Zhang: Formal analysis. **Licheng Shi:** Formal analysis. **Jiannan Liu:** Supervision. **Huifen Zheng:** Writing – review & editing. **Xiaofang Shi:** Investigation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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