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Association of oxidative balance scores with cardiovascular and all cause mortality in patients with asthma

Wei Zhao[1,2], Yiyuan Sun[1,2] & Bohui Zhu[1]✉

Asthma poses significant societal costs, and a wholesome diet coupled with an energetic lifestyle might enhance postpartum results. Regrettably, empirical investigations into dietary and lifestyle aspects that amplify asthma risk remain scarce. The oxidative balance scores (OBS), quantifying oxidative stress from dietary elements and lifestyle parameters, lack a definitive link to overall and cardiovascular mortality among asthmatic individuals. Data sourced from NHANES (1999–2020) were utilized to investigate the correlation between the OBS index and all-cause and cardiovascular mortality among asthmatic patients. Rigor was maintained through the implementation of subgroup and sensitivity analyses to authenticate the findings. The study finally included 4,639 individuals with a mean age of 42.55 years and 43.46% males. Kaplan-Meier curves showed that asthmatics with lower OBS quartiles had a higher risk of all-cause and cardiovascular mortality. In the fully adjusted Model 2, the HR for all-cause mortality in the upper quartile of asthmatics in the OBS was 0.37 (95% CI: 0.26, 0.53), in contrast to the lower quartile of asthmatics. Cardiovascular disease mortality showed consistency (Q4, HR: 0.43, 95% CI: 0.19, 0.98). The association between the OBS index and both all-cause and cardiovascular mortality in asthma patients remained stable across different models and subgroup assessments. Restricted cubic spline curves showed that OBS was linearly associated with all-cause and cardiovascular mortality in asthmatics. A sensitivity analysis reinforced the negative correlation between the OBS index and mortality in asthma patients. The OBS index was negatively correlated with all-cause and cardiovascular mortality in patients with asthma, emphasizing the protective effect of an antioxidant diet and a healthy lifestyle in patients with asthma.

Keywords OBS, Asthma, NHANES, All-cause mortality, Cardiovascular mortality

Bronchial asthma (abbreviated as asthma) is a frequent chronic airway inflammatory disorder, marked by recurrent manifestations including wheezing, breathlessness, chest constriction, or coughing, alongside airway hyperreactivity and fluctuating expiratory airflow restriction[1,2]. The prevalence of asthma in adults within the United States amounts to roughly 7.7%. This respiratory ailment ranks as one of the most widespread chronic, non-transmissible afflictions globally, affecting numerous nations including the United States. Despite a notable decline in the overall asthma-related mortality rate from 15.1 per million in 2001 to 9.9 per million in 2017-this condition continues to exert a significant strain on both individual patients and broader societal structures[3,4]. In addition, patients with asthma tend to be at higher risk of having comorbidities, and multiple comorbidities may affect the same patient, including respiratory dysfunction, nasal polyposis, vocal cord dysfunction, chronic obstructive pulmonary disease (COPD), and others[5–7]. Given the persistently high morbidity and mortality rates, it is critical to enhance the management of patients with asthma. Although awareness of the risk of death in asthmatics has gradually increased over the past decades, there are still unknown factors that influence the risk of death in this group[8,9].

Oxidative stress refers to the situation where free radicals disrupt the balance of the body's oxidative and antioxidant systems, causing the body to tend toward an oxidative state, which has a negative impact on the body[10–12]. When harmful factors disrupt the body's equilibrium, causing excessive reactive oxygen (ROS) and reactive nitrogen production, under normal circumstances, a balanced level of ROS supports immunity, tissue repair, and defense against microorganisms[13,14]. At the same time, if ROS concentration surpasses the

[1]Department of Oncology, Gongli Hospital of Shanghai Pudong New Area, Shanghai 200135, China. [2]These authors contributed equally: Wei Zhao and Yiyuan Sun. ✉email: zxqh724@163.com

antioxidant defense threshold, direct assault on cellular components like nucleic acids, proteins, and lipids ensues, culminating in cell apoptosis and necrosis. Controversy surrounds the impact of antioxidant supplementation on asthmatic patients' outcomes, but partial research underscores the protective effect of dietary antioxidants, primarily sourced from vegetables and fruits, in asthma prevention and prognosis improvement[15]. The analysis of a single biomarker neglects complex systemic interactions between pro-oxidants and antioxidants, influenced by multiple factors, hindering precise impact evaluation on prognosis. Antioxidants' effects vary with dosage, introducing further complexity in single marker analysis[16,17]. The Oxidative Balance Score (OBS), accounting for combined dietary and lifestyle impacts on oxidative processes, offers a holistic assessment. By integrating synergistic and antagonistic interactions among oxidative/antioxidative system components, OBS surpasses previous limitations. Derived from dietary and lifestyle factor evaluations, the OBS quantifies an individual's oxidative and antioxidant equilibrium. Prior studies have highlighted OBS's predictive significance in conditions including cardiovascular disease, metabolic syndrome, and non-alcoholic fatty liver disease[18–20]. However, the prognostic significance of OBS in patients with asthma is unclear.

Utilizing the comprehensive dataset from the National Health and Nutrition Examination Survey (NHANES), this study sought to investigate the relationship between OBS and all-cause as well as cardiovascular mortality among asthmatics.

Method

Study description

The participants for this study were sourced from the NHANES database within the United States, established by the Centers for Disease Control and Prevention (CDC) and the National Center for Health Statistics (NCHS) to assess the health and nutrition of American adults and children. NHANES, an ongoing biennial health survey employing a multicenter stratified sampling technique, comprises four stages designed for a comprehensive nationwide health evaluation of non-institutionalized individuals. It combines questionnaires and physical exams. Questionnaires delve into demographics, socioeconomics, lifestyle, diet, medical history, and medications. Physical exams include standard measurements and lab tests. Ethical approval from the NCHS Ethics Committee was secured, with informed consent from all participants. Data for this analysis were derived from the 1999–2020 NHANES database.

Study target population

This study harnessed data from the NHANES 1999–2020 survey timeframe due to its provision of exhaustive details on asthma, OBS computation-related metrics, all-cause mortality, and cardiovascular demise, all crucial for our analysis. Originating with 116,876 participants, we meticulously applied exclusions to uphold the analysis' integrity: 95,200 subjects did not suffer from asthma, 2,332 subjects were omitted for lacking death records, and an additional 9,671 were excluded for incomplete OBS data. Following these criteria, we were left with 4,639 suitable participants for our investigation. Figure 1 graphically outlines the participant selection procedure.

Definition of OBS

This cross-sectional analysis comprises two sections: dietary OBS and lifestyle OBS. The OBS computation utilized sixteen nutrients and four lifestyle elements. Dietary OBS components encompassed dietary fiber (g/d), carotenoids (RE/d), riboflavin (mg/d), niacin (mg/d), vitamin B6 (mg/d), total folate (mcg/d), vitamin B12 (mcg/d), vitamin C (mg/d), vitamin E (ATE) (mg/d), calcium (mg/d), magnesium (mg/d), zinc (mg/d), copper (mg/d), selenium (mcg/d), total fat (g/d), and iron (mg/d). Moreover, lifestyle OBS took into account physical activity (MET-minutes/week), BMI (kg/m^2), alcohol intake (g/d), and cotinine (ng/mL). These twenty components were further classified into five pro-oxidants and fifteen antioxidants, which were then divided into three categories, with ratings ranging from 0 to 2. In contrast, pro-oxidants received ratings in reverse, with 0 being the highest and 2 the lowest. Consequently, the overall composite OBS was determined by assessing the ratings of antioxidant and pro-oxidant components. Comprehensive computations have been elaborately outlined in preceding research[11].

Definition of asthma

Data on asthma were gathered via standardized questionnaires administered by trained interviewers. The research employed self-reported questionnaire outcomes to ascertain asthma presence. Asthma was delineated based on participants' responses to the inquiry, "Has a healthcare provider ever informed you of having asthma?" A yes response was recorded. Absences, refusals, or uncertain answers were deemed as non-valid data points.

Outcome

Participant survival was assessed using mortality data from the CDC's National Death Index (NDI) as of December 31, 2019, for causes including all-cause and cardiovascular disease (CVD) deaths. The causes of death documented in these records follow the International Classification of Diseases, Tenth Revision (ICD-10). All-cause mortality encompasses fatalities resulting from any underlying cause, whereas deaths specifically due to cardiovascular conditions are classified according to ICD-10 codes I00-I09, I11, I13, and I20-I51.

Covariate selection

We selected the following covariates based on previous studies and clinical experience[21–23]: (1) Demographic data: age, sex (male/female), race (Mexican American/non-Hispanic black/non-Hispanic White/other Hispanic/other race), education (less than high school/high school/more than high school), marital status (married, never married/widowed), and poverty income ratio (PIR). (2) Biochemical data: white blood cells (WBC), lymphocytes, eosinophils, and neutrophils. (3) Lifestyle: smoking status (former/never/current), and drinking

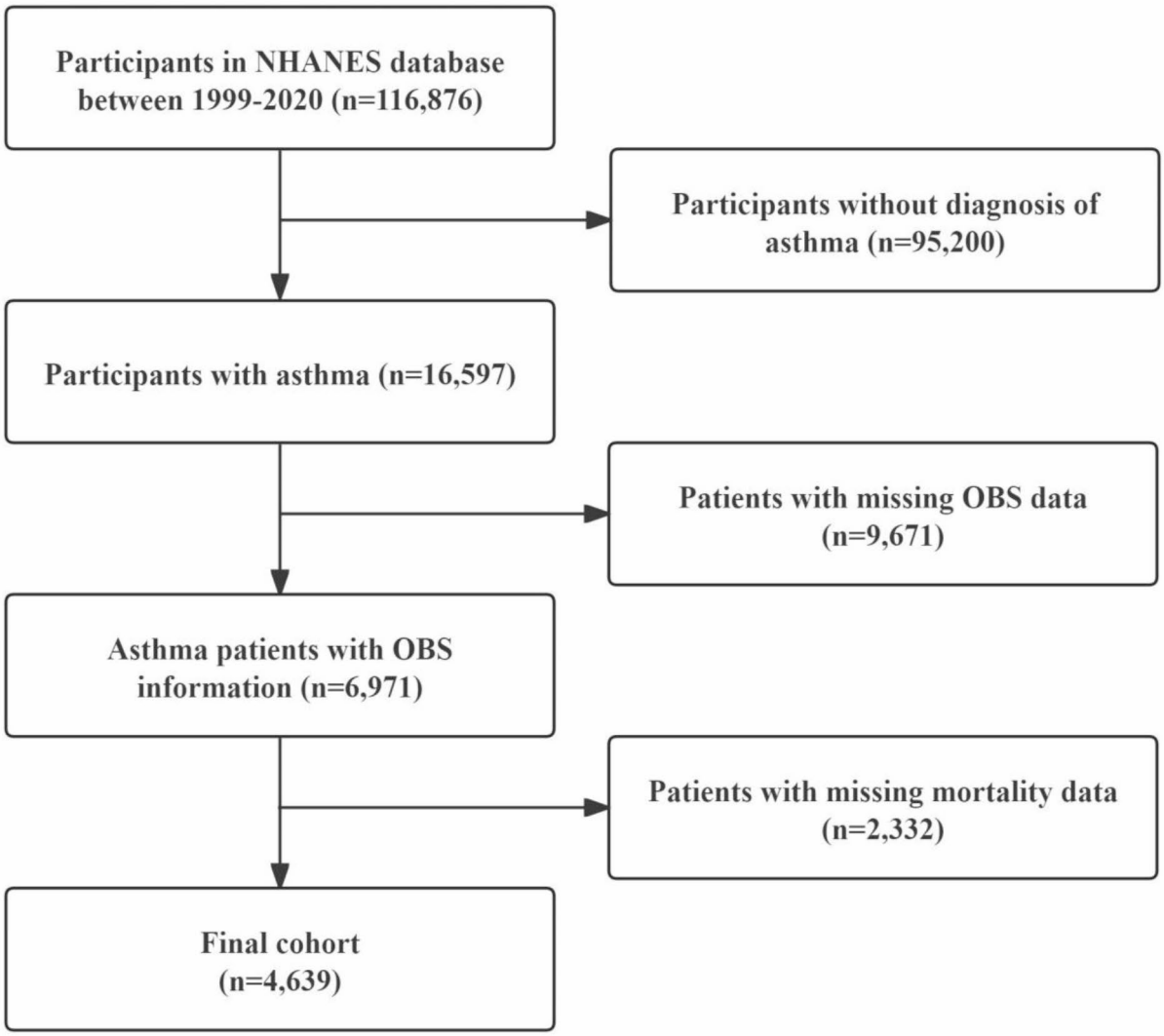

Fig. 1. Flow diagram.

status (never/moderate/heavy). (4) Comorbidities: diabetes (yes/no), hypertension (yes/no), and heart failure (yes/no). (5) Physical fitness measures: body mass index (BMI). For more details on the variable collection methods, please refer to the NHANES Survey Methods and Analysis Guide.

Statistical analysis

The baseline characteristics of the subjects were statistically described according to the quartiles of OBS and survival status. Continuous variables were presented as mean ± standard error, while categorical variables were shown as numbers (percentages). Analysis of variance was applied to compare continuous variables, whereas the chi-square test was utilized to assess the statistical discrepancies among categorical variables across different groups. Kaplan-Meier (KM) survival analyses were used to compare the probability of survival in patients with asthma after grouping them according to OBS quartiles. Cox proportional hazard regression models along with its 95% confidence interval (CI) were employed to investigate the relationship between OBS and cardiovascular disease mortality and all-cause mortality within the asthma population. Furthermore, three models were formulated to delve into the association between the OBS index and cardiovascular mortality and all-cause mortality in asthma patients. Crude model: no adjustment; Model 1: adjusted for age, sex, race, and PIR. Model 2: adjusted for age, sex, race, PIR, education, marital status, hypertension, heart failure, diabetes, lymphocytes, leukocytes, neutrophils, and eosinophils. To further elucidate the prognostic impact of the different components of OBS, the present study delved into the relationship between the OBS dietary and OBS lifestyle with cardiovascular mortality and all-cause mortality in asthmatics, using the three models described above. Upon multivariate adjustment, the restricted cubic spline regression model was utilized to assess the non-linear connection between the OBS index and both all-cause mortality and cardiovascular mortality in

asthmatic individuals. Finally, subgroup analyses and interaction tests, focusing on categories like age, sex, BMI, hypertension, diabetes, and heart failure, were conducted.

All analyses were done using R software (version 4.1.1) and all data were weighted in the manner officially recommended by the NHANES database and were considered statistically significant if the p-value was less than 0.05.

Result

Baseline characteristics of participants

This cohort study involved 4,639 participants, with an average age of 42.55 years, where approximately 43.46% were male. Table 1 presents the foundational metrics classified by quartiles of the OBS indicator. Compared with asthmatics in the low OBS quartile, those in the high quartile had a higher PIR, lower BMI, had lower WBC, lymphocyte, and neutrophil, had a higher number of Non-Hispanic White, never been married, more than high school, never smoked, and were low to moderate drinkers of alcohol. They also had higher rates of freedom from complications and low all-cause and cardiovascular mortality.

The initial attributes of the participants based on their survival status are detailed in Table 2. Participants who survived were younger, had a higher PIR, had higher lymphocyte and lower neutrophils, and had higher OBS index and its fractions. Those with more married, higher education, never smoked, and moderate alcohol consumption. had lower rates of comorbidities.

Association of OBS with all-cause and cardiovascular mortality in asthma patients

KM curves showed that asthmatics in lower OBS quartiles had higher all-cause (P log-rank < 0.001) and cardiovascular mortality (P log-rank = 0.008) (Fig. 2). We used three Cox regression models to analyze the relationship between OBS and mortality. In model 2, after adjusting for numerous confounders, OBS was inversely associated with all-cause mortality (HR: 0.95, 95% CI: 0.94, 0.97), and participants in Q4 had lower all-cause mortality compared with Q1 (Q4, HR: 0.37, 95% CI: 0.26, 0.53) (Table 3). The association of OBS with cardiovascular mortality was also inversely (HR: 0.94, 95% CI: 0.98), and participants in Q4 had lower cardiovascular mortality compared to Q1 (Q4, HR: 0.43, 95% CI: 0.19, 0.98) (Table 4).

Table 5 assessed the impacts of dietary OBS and lifestyle OBS on all-cause and cardiovascular mortality among asthma patients, revealing that upon adjustment for confounders, both dietary and lifestyle interventions exhibited a negative association with mortality ($P < 0.05$).

Dose-response relationship

To examine the dose-response associations between OBS and all-cause and cardiovascular mortality in asthma cases, we used the RCS model (Fig. 3). The RCS graph for all-cause mortality indicated that, upon adjusting all covariates within the aforementioned primary analysis Model 2, the overall pattern appeared linear (P non-linear = 0.058), and the RCS graph for cardiovascular mortality indicated there was a linear relationship (P non-linear = 0.092).

Subgroup analysis

In asthma subgroups classified by age, sex, BMI, hypertension, diabetes, and heart failure, OBS was negatively associated with all-cause mortality in all subgroups of asthmatics, and the interaction results showed that BMI mediated the negative association between OBS and all-cause mortality in asthmatics, specifically, the negative association between OBS and all-cause mortality in patients who were obese was more significant (P for interaction < 0.05) (Fig. 4). Similarly, OBS was negatively associated with the risk of cardiovascular mortality in asthma patients in all subgroups, but no significant interaction was found.

Discussion

By examining data from 4,639 NHANES participants, we found consistent independent negative associations between OBS and all-cause and cardiovascular mortality in patients with asthma. In addition, dietary OBS and lifestyle OBS significantly reduced the risk of death in asthmatics. In subgroup analyses, the negative association between OBS and risk of all-cause mortality was found to be more significant in obese asthmatics. Our groundbreaking study identifies the link between OBS and increased risk of death in asthma patients, providing a quantifiable indicator of dietary and lifestyle modifications to optimize prognosis in this high-risk group of patients.

OBS is a composite measure of antioxidant and pro-oxidant capacity in the context of diet and lifestyle. Dietary OBS contains a variety of antioxidant components, several of which have been shown in previous studies to be strongly associated with patient prognosis. For example, several studies have shown that increased dietary fiber intake leads to an increase in intestinal prebiotics[24,25]. These probiotics are intricately linked to the manifestation, progression, and prognosis of chronic airway inflammatory disorders through their involvement in the synthesis of purine metabolic enzymes and the release of inflammatory markers. A cross-sectional investigation by Shengmin Zhang et al., based on 12,276 individuals, indicated that a higher intake of dietary fiber correlates with a reduced risk of all-cause mortality among those with chronic inflammatory airway conditions. Some clinical investigations endorse the advantageous effects of vitamin B, C, D, and E supplements in modulating airway inflammation and antioxidation[26]. Increasing evidence highlights magnesium's multifaceted roles, including anti-inflammatory, bronchodilation, and antioxidant activities, potentially contributing positively to the management of asthma patients[27]. Mario Barbagallo's meta-analysis, encompassing 17 randomized controlled trials (800 participants), yielded mixed findings, concluding that magnesium supplementation significantly decreases multiple inflammatory cytokines within the body, such as plasma C-reactive protein, fibrinogen, IL-1,

	Total	OBS quartiles				
	(*n* = 4,639	Q1 (*n* = 1,189)	Q2 (*n* = 1,327)	Q3 (*n* = 1,040)	Q4 (*n* = 1,083)	*P* value
Age, years	42.55(0.32)	42.17(0.60)	42.71(0.51)	42.87(0.60)	42.41(0.58)	0.765
Sex, %						0.582
Female	2569(56.54)	655(57.40)	749(58.07)	569(55.03)	596(55.59)	
Male	2070(43.46)	534(42.60)	578(41.93)	471(44.97)	487(44.41)	
PIR	3.00(0.05)	2.43(0.07)	2.91(0.07)	3.20(0.07)	3.39(0.07)	< 0.001
BMI, kg/m^2	29.33(0.16)	30.65(0.29)	29.98(0.29)	29.05(0.24)	27.83(0.30)	< 0.001
WBC, $10^9/L$	7.37(0.04)	7.60(0.09)	7.47(0.07)	7.33(0.08)	7.13(0.08)	0.001
Lymphocyte, $10^9/L$	2.15(0.02)	2.22(0.03)	2.18(0.03)	2.14(0.03)	2.06(0.03)	< 0.001
Neutrophil, $10^9/L$	4.38(0.03)	4.53(0.07)	4.43(0.06)	4.34(0.06)	4.25(0.06)	0.018
Eosinophil, $10^9/L$	0.23(0.00)	0.23(0.01)	0.23(0.01)	0.24(0.01)	0.23(0.01)	0.678
Race, %						< 0.001
Mexican American	522(4.77)	143(5.27)	139(4.67)	124(5.17)	116(4.11)	
Non-Hispanic Black	1041(11.01)	351(16.40)	330(12.67)	178(8.36)	182(7.22)	
Non-Hispanic White	2317(72.68)	525(66.45)	648(71.57)	538(72.76)	606(78.82)	
Other Hispanic	358(4.97)	94(5.81)	105(5.13)	88(5.37)	71(3.78)	
Other Race	401(6.57)	76(6.08)	105(5.96)	112(8.34)	108(6.07)	
Marital status, %						< 0.001
Married	2397(58.40)	533(53.19)	684(62.15)	586(64.14)	594(63.02)	
Never married	1124(20.93)	318(23.71)	310(21.03)	229(19.68)	267(22.98)	
Widowed	862(16.59)	272(23.10)	245(16.82)	178(16.18)	167(14.00)	
Education level, %						< 0.001
High school	1737(32.33)	578(45.80)	526(35.03)	336(28.54)	297(21.89)	
Less than high school	225(2.49)	89(4.02)	63(2.76)	44(1.98)	29(1.41)	
More than high school	2674(65.15)	522(50.18)	736(62.21)	660(69.48)	756(76.69)	
Smoking status, %						< 0.001
Former	1100(25.00)	263(22.97)	309(24.98)	289(31.62)	239(24.33)	
Never	2208(50.50)	433(40.07)	630(51.39)	499(50.13)	646(65.20)	
Now	969(20.94)	371(36.96)	290(23.63)	172(18.25)	136(10.47)	
Drinking status, %						< 0.001
Nondrinker	1076(20.18)	300(25.79)	331(22.82)	222(19.29)	223(19.52)	
Moderate drinker	2152(52.83)	479(50.24)	594(53.51)	505(60.42)	574(62.78)	
Heavy drinker	849(19.79)	233(23.97)	255(23.67)	191(20.29)	170(17.70)	
Diabetes, %						< 0.001
No	3855(87.67)	971(86.03)	1098(88.28)	859(88.70)	927(92.68)	
Yes	641(10.76)	199(13.97)	192(11.72)	146(11.30)	104(7.32)	
Hypertension, %						< 0.001
No	2910(65.75)	687(60.62)	810(61.96)	672(69.37)	741(70.69)	
Yes	1729(34.25)	502(39.38)	517(38.04)	368(30.63)	342(29.31)	
Heart failure, %						0.015
No	3998(91.83)	978(95.83)	1132(95.98)	917(97.42)	971(98.18)	
Yes	167(2.95)	59(4.17)	55(4.02)	29(2.58)	24(1.82)	
All-cause mortality, %						< 0.001
No	4195(92.84)	1032(88.78)	1195(91.96)	944(93.11)	1024(96.80)	
Yes	444(7.16)	157(11.22)	132(8.04)	96(6.89)	59(3.20)	
Cardiovascular mortality, %						0.005
No	4529(98.30)	1146(97.36)	1291(97.79)	1023(98.84)	1069(99.12)	
Yes	110(1.70)	43(2.64)	36(2.21)	17(1.16)	14(0.88)	

Table 1. Baseline characteristics and outcomes for patients with asthma grouped by the OBS quartiles. WBC, white blood cell; BMI, body mass index; PIR, poverty income ratio. Continuous variables are expressed as means (standard errors). Categorical variables are presented as numbers (percentages). OBS quartiles: Q1 ≤ 14, 14 < Q2 ≤ 21, 21 < Q3 ≤ 26, and 26 < Q4.

	Total	Survival	Death	
	(*n* = 4,639)	(*n* = 4,195)	(*n* = 444)	*P* value
Age, years	42.55(0.32)	41.17(0.35)	60.36(0.88)	< 0.001
Sex, %				0.608
Female	2569(56.54)	2364(56.65)	205(55.17)	
Male	2070(43.46)	1831(43.35)	239(44.83)	
PIR	3.00(0.05)	3.05(0.05)	2.38(0.10)	< 0.001
BMI, kg/m^2	29.33(0.16)	29.27(0.17)	30.20(0.49)	0.075
WBC, $10^9/L$	7.37(0.04)	7.36(0.05)	7.58(0.14)	0.138
Lymphocyte, $10^9/L$	2.15(0.02)	2.16(0.02)	1.99(0.04)	< 0.001
Neutrophil, $10^9/L$	4.38(0.03)	4.36(0.03)	4.69(0.11)	0.007
Eosinophil, $10^9/L$	0.23(0.00)	0.23(0.00)	0.24(0.01)	0.392
OBS	21.06(0.17)	21.30(0.18)	17.97(0.35)	< 0.001
OBS. dietary	16.95(0.15)	17.15(0.16)	14.34(0.34)	< 0.001
OBS. lifestyle	4.11(0.04)	4.15(0.04)	3.64(0.09)	< 0.001
Race, %				0.088
Mexican American	522(4.77)	484(4.94)	38(2.54)	
Non-Hispanic Black	1041(11.01)	966(11.21)	75(8.39)	
Non-Hispanic White	2317(72.68)	2032(72.17)	285(79.24)	
Other Hispanic	358(4.97)	334(4.99)	24(4.69)	
Other Race	401(6.57)	379(6.68)	22(5.14)	
Marital status, %				< 0.001
Married	2397(58.40)	2174(61.26)	223(56.05)	
Never married	1124(20.93)	1074(22.60)	50(11.86)	
Widowed	862(16.59)	705(16.14)	157(32.09)	
Education level, %				< 0.001
High school	1737(32.33)	1553(31.61)	184(41.72)	
Less than high school	225(2.49)	168(2.21)	57(6.10)	
More than high school	2674(65.15)	2472(66.18)	202(52.18)	
Smoking status, %				< 0.001
Former	1100(25.00)	919(24.95)	181(38.11)	
Never	2208(50.50)	2070(54.06)	138(31.25)	
Now	969(20.94)	852(20.99)	117(30.64)	
Drinking status, %				< 0.001
Nondrinker	1076(20.18)	885(20.03)	191(42.89)	
Moderate drinker	2152(52.83)	1973(58.17)	179(41.70)	
Heavy drinker	849(19.79)	796(21.80)	53(15.40)	
Diabetes, %				< 0.001
No	3855(87.67)	3547(90.27)	308(73.64)	
Yes	641(10.76)	508(9.73)	133(26.36)	
Hypertension, %				< 0.001
No	2910(65.75)	2778(68.23)	132(33.64)	
Yes	1729(34.25)	1417(31.77)	312(66.36)	
Heart failure, %				< 0.001
No	3998(91.83)	3624(97.68)	374(87.10)	
Yes	167(2.95)	107(2.32)	60(12.90)	

Table 2. Baseline characteristics and outcomes of asthma patients grouped by whether they died. OBS, oxidative balance score; WBC, white blood cell; BMI, body mass index; PIR, poverty income ratio. Continuous variables are expressed as means (standard errors). Categorical variables are presented as numbers (percentages).

etc[28]. Studies conducted in China also suggest that magnesium injections correlate with improved outcomes in acute asthma patients. Similarly, the impact of lifestyle on patient prognosis has been extensively studied. The influence of lifestyle on asthma patients' outcomes has been extensively studied. Xiaoxv Yin's cross-sectional analysis of 223,951 UK Biobank participants revealed that unhealthy lifestyle aspects, including smoking, insufficient exercise, poor diet, and extended sedentary time, negatively impact adult asthma prognosis[29].

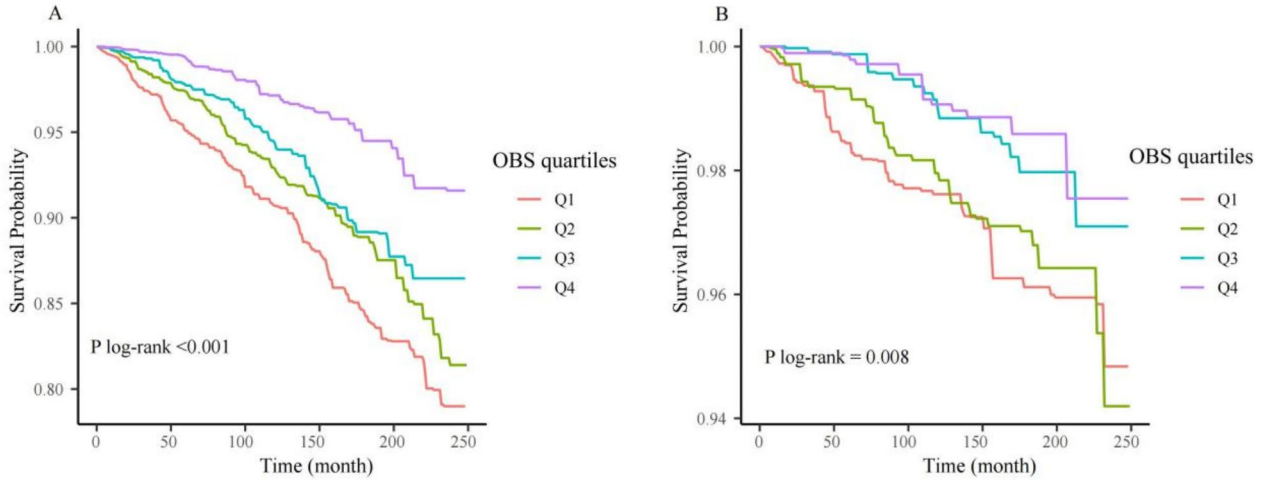

Fig. 2. Kaplan-Meier survival analysis curves for mortality. (A: All-cause mortality; B: Cardiovascular mortality).

	Crude model		Model 1		Model 2	
	95%CI	*P*	95%CI	*P*	95%CI	*P*
OBS	0.94(0.93,0.96)	< 0.001	0.95(0.94,0.97)	< 0.001	0.95(0.94,0.97)	< 0.001
OBS quartiles						
Q1	ref		ref		ref	
Q2	0.75(0.56,1.00)	0.051	0.87(0.65,1.16)	0.332	0.89(0.66,1.20)	0.447
Q3	0.62(0.46,0.82)	0.001	0.72(0.52,1.01)	0.054	0.76(0.55,1.05)	0.098
Q4	0.31(0.21,0.46)	< 0.001	0.41(0.29,0.58)	< 0.001	0.37(0.26,0.53)	< 0.001
P for trend		< 0.001		< 0.001		< 0.001

Table 3. Relationship between OBS and all-cause mortality in patients with asthma. Crude model: no adjusted. Model 1: adjust age, sex, race, and PIR. Model 2: adjust age, sex, race, PIR, education level, marital status, heart failure, diabetes, hypertension, lymphocyte, WBC, neutrophil, and eosinophil. WBC, white blood cell; PIR, poverty income ratio.

	Crude model		Model 1		Model 2	
	95%CI	*P*	95%CI	*P*	95%CI	*P*
OBS	0.94(0.91,0.97)	< 0.001	0.95(0.91,0.98)	0.01	0.94(0.91,0.98)	0.003
OBS quartiles						
Q1	ref		ref		ref	
Q2	0.87(0.51,1.50)	0.624	1.09(0.64,1.87)	0.743	1.21(0.68, 2.15)	0.520
Q3	0.44(0.23,0.83)	0.012	0.55(0.28,1.10)	0.089	0.61(0.29, 1.29)	0.195
Q4	0.36(0.17,0.78)	0.010	0.51(0.24,1.08)	0.079	0.43(0.19, 0.98)	0.045
P for trend		< 0.001		0.016		0.013

Table 4. Relationship between OBS and cardiovascular mortality in patients with asthma. Crude model: no adjusted. Model 1: adjust age, sex, race, and PIR. Model 2: adjust age, sex, race, PIR, education level, marital status, heart failure, diabetes, hypertension, lymphocyte, WBC, neutrophil, and eosinophil.. WBC, white blood cell; PIR, poverty income ratio.

Charlotte Suppli Ulrik's Danish study highlighted that self-reported leisure-time physical activity reduces mortality risk for asthma patients[30]. Notably, previous studies have only examined the association between antioxidant diet or lifestyle and patient prognosis in isolation, ignoring the interaction between the two.

In recent years, researchers have increasingly focused their attention on the role of OBS in disease development. Among the published articles, several studies have examined the association between OBS and all-cause mortality in patients with diabetes, kidney disease, metabolic syndrome, and cardiovascular disease. In a study from across the United States that included patients with diabetes and prediabetes, xu et al. found

	OBS ingredient	Crude model		Model 1		Model 2	
		95%CI	*P*	95%CI	*P*	95%CI	*P*
All-cause mortality	Lifestyle	0.91(0.83,1.00)	0.048	0.86(0.78,0.94)	0.001	0.89(0.80,0.98)	0.014
	Dietary	0.94(0.93,0.96)	< 0.001	0.96(0.94,0.97)	< 0.001	0.95(0.94,0.97)	< 0.001
Cardiovascular mortality	Lifestyle	0.85(0.74,0.99)	0.037	0.78(0.66,0.91)	0.002	0.81(0.67, 0.98)	0.029
	Dietary	0.94(0.90,0.97)	< 0.001	0.96(0.92,1.00)	0.029	0.95(0.91,0.99)	0.010

Table 5. Relationship between OBS ingredient and mortality in patients with asthma. Crude model: no adjusted. Model 1: adjust age, sex, race, and PIR. Model 2: adjust age, sex, race, PIR, education level, marital status, heart failure, diabetes, hypertension, lymphocyte, WBC, neutrophil, and eosinophil. WBC, white blood cell; PIR, poverty income ratio.

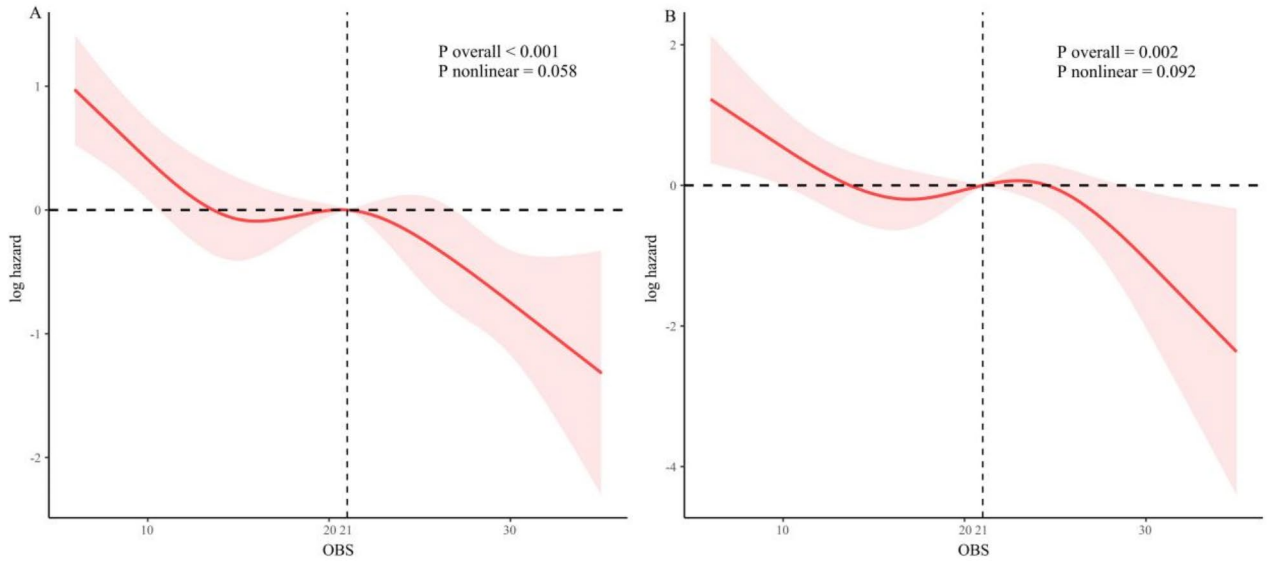

Fig. 3. RCS analysis of the association between OBS and mortality. The association was adjusted for age, sex, race, PIR, education level, marital status, heart failure, diabetes, hypertension, lymphocyte, WBC, neutrophil, and eosinophil. The median OBS was chosen as the reference. (A: All-cause mortality; B: Cardiovascular mortality).

a 1.8% decrease in the risk of all-cause mortality and a 4% decrease in the risk of cardiovascular death in this population for each unit increase in OBS after surveying 10,591 participants[31]. Another study from the Seguimiento Universidad de Navarra (SUN) Study, a Mediterranean cohort of Spanish graduates, found a strong negative correlation between obs and all-cause, CVD, and cancer mortality[32]. The results of our study are similar to previous findings. In our study, we considered a combination of dietary and lifestyle oxidative antioxidants by means of the OBS score and related it to the prognosis of asthma patients and found that OBS significantly reduced the risk of cardiovascular and all-cause mortality in asthma patients.

Oxidative stress plays a crucial role in the development and progression of asthma inflammation. Excessive ROS directly attack airway epithelial cells and endothelial cells, leading to cell membrane lipid peroxidation, oxidative modification of proteins, and DNA damage, which can lead to cellular dysfunction and even death. This cellular damage disrupts the structural integrity of the airway, making the airway more susceptible to external stimuli and exacerbating the inflammatory response[12,33]. In addition, oxidative stress activates a variety of inflammatory cells such as eosinophils, neutrophils, and macrophages. These cells release more ROS and inflammatory mediators in response to oxidative stress, creating a vicious cycle that further exacerbates airway inflammation[34]. Whereas antioxidant supplementation can modulate immune activity in asthma patients, vitamin E can reduce the production of inflammatory cytokines such as tumor necrosis factor α and interleukin 6 by inhibiting the nuclear factor κB signaling pathway[35]. In addition, antioxidants have positive effects on the proliferation, differentiation and function of immune cells. For example, vitamin A promotes the proliferation and differentiation of T-cells, enhances their antigen-presenting capacity, and promotes T helper 2 cell responses[36].

The precise mechanism linking OBS to decreased all-cause mortality in asthmatics remains unclear, yet this observation is tentatively attributed to several potential pathways: (1) Antioxidants mitigate oxidative stress by balancing ROS production and defense mechanisms, crucial for asthma management. Smoking and alcohol consumption exacerbates oxidative stress; antioxidants counteract this, minimizing cellular damage[37,38].

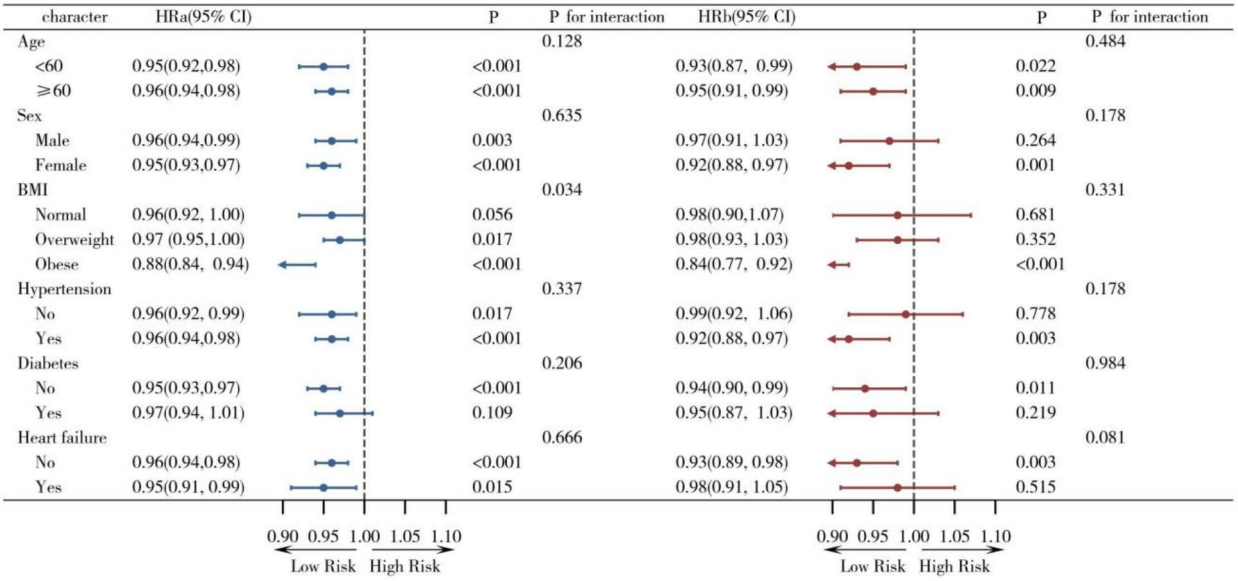

Fig. 4. Forest plots of hazard ratios for the mortality in different subgroups. (HRa: All-cause mortality; HRb: Cardiovascular mortality).

Xiangjing Meng et al.'s research based on asthma mice suggests that inhibiting HMGB1 can improve TDI-induced ROS release, inflammatory response, and autophagy activation in human bronchial cells, thereby improving the prognosis of asthma mice[39]. (2) Enhancing metabolism: OBS incorporates antioxidants, significantly boosting insulin sensitivity and combating metabolic syndrome. Recent experiments underscore insulin resistance's role in airway remodeling, amplifying airway smooth muscle activity, escalating airway hyperreactivity, and stimulating pro-inflammatory mediator release from fat cells. These findings highlight hyperinsulinemia's deleterious effect on airway integrity and function, suggesting an insulin-resistant asthma subtype[40,41]. Antioxidants preserve metabolic balance, mitigating asthma incidence and enhancing patient outcomes. Based on a cross-sectional study of 625 people, Lisa G Wood's research team confirmed that insulin resistance is positively associated with the occurrence of moderate to severe asthma and is closely related to prognosis[42]. (3) Antioxidants and intestinal health synergy: Increased antioxidant consumption fosters bidirectional benefits for gut health. By mitigating oxidative stress and inflammation-triggered intestinal epithelial cell damage, antioxidants lower intestinal permeability, expedite cellular repair, and fortify the intestinal barrier. Moreover, they restrain the synthesis and discharge of inflammatory messengers, shield the intestinal microbiome, and preserve the equilibrium and cohesion of the intestinal ecosystem[43]. A thriving intestinal milieu enhances antioxidant absorption and utilization, amplifying their biological efficacy. Certain gut microbes can transform antioxidants into more potent compounds, boosting their overall antioxidant impact. Joseph H Skalski's prior research indicates that specific fungal overgrowths, notably Candida, heighten mortality risks in adult asthmatics, per findings published in JOF[44].

In subgroup analysis, antioxidant diet and lifestyle showed a stronger protective effect in women, suggesting greater benefits for female asthma patients in reducing all-cause mortality through dietary and lifestyle changes. This is partly due to women's higher antioxidant gene expression and enzyme activity, aiding in combatting oxidative stress. Additionally, higher smoking prevalence among men contributes to prolonged oxidative stress post-smoking or cessation, upping their mortality risk. However, the distinctiveness in OBS effects on mortality wasn't mirrored in the piezo resistance analysis of cardiovascular mortality, likely owing to variations in the specific occurrence and development mechanisms of CVD-related mortality. Our subgroup analyses also showed that the negative association between OBS and asthma mortality was more pronounced in obese patients. This may be related to the "obesity paradox", in which obese patients have lower mortality compared to patients with normal or low body weight[45], and obese individuals may have more adipose tissue, which to a certain extent provides additional energy and nutrients to help patients maintain essential functions and immune responses in the face of disease stres[46,47]. A previous study of COPD patients similarly showed the obesity paradox, which is consistent with our results[7].

This study is a cross-sectional investigation aiming to examine the link between OBS and cardiovascular and all-cause mortality among asthma patients. NHANES' rigorous data gathering protocol ensures data reliability and offers comprehensive details on confounding variables, thereby reducing measurement bias. The outcomes might assist healthcare providers and public health specialists in presenting the influence of overall dietary and exercise antioxidant levels on asthma patient prognosis and encourage healthier dietary and lifestyle modifications. Notably, our research highlights that OBS exhibits a notably stronger protective effect on females, enhancing the specificity of the findings. However, there are limitations to our study. First, the cross-sectional

nature of the study does not allow for the identification or validation of causal relationships. Second, OBS assessment based on dietary recall introduces recall bias. Third, despite adjusting for covariates, it may not be possible to exclude potential confounders, such as the duration of the patient's nutritional intake, and lipid status. Fourth, limitations of the retrospective study prevented us from exploring the reasons for the differences in all-cause and cardiovascular mortality due to noncardiovascular factors, and the classification of asthma as allergic or not, and as acute or chronic asthma. Fifth, there remains uncertainty in extrapolating study findings from the US population. Therefore, more large-scale randomized controlled trials or cohort studies that take the above limitations into account are needed in the future to validate the predictive significance of OBS for asthma patients in different populations and with different asthma types.

Conclusion

In conclusion, our findings indicate an inverse link between the OBS index and all-cause, cardiovascular mortality risks in asthmatic patients. This relationship's robustness was confirmed through various modeling techniques and adjustment stages, emphasizing its reliability. Further studies should delve deeper into the biological underpinnings of this connection for enhanced comprehension and precise clinical guidance.

Data availability

The datasets generated and analyzed for the current study are available in the NHANES repository. These data can be accessed using the following link: https://wwwn.cdc.gov/nchs/nhanes/Default.aspx.

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Author contributions

Wei Zhao was involved in the experiment design. Yiyuan Sun performed the data analysis. Wei Zhao and Yiyuan Sun wrote the manuscript together. Bohui Zhu reviewed the manuscript and provided critical suggestions.

Declarations

Ethics approval and consent to participate

The study analyzed data downloaded from the National Health and Nutrition Examination Survey public database. The National Center for Health Statistics Ethics Review Committee granted ethics approval. The methods involved in this study were conducted in accordance with relevant guidelines and regulations (Declaration of Helsinki). All individuals provided written informed consent before participating in the study. Details are available at https://www.cdc.gov/nchs/nhanes/irba98.htm. The current study was deemed exempt from further review because the data used are identified and publicly accessible.

Competing interests

The authors declare no competing interests.

Additional information

Correspondence and requests for materials should be addressed to B.Z.

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