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Alcohol drinking triggered decrease of oxidative balance score is associated with high all-cause and cardiovascular mortality in hypertensive individuals: findings from NHANES 1999–2014

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ABSTRACT

BACKGROUND Oxidative stress is closely associated with hypertensive outcomes. The oxidative balance score (OBS) measures oxidative stress exposure from dietary and lifestyle elements. The objective of this study was to investigate the association between OBS and mortality in hypertensive patients.

METHODS This study included 7823 hypertensive patients from the National Health and Nutrition Examination Survey (NHANES) 1999–2014. Several models, including Cox regression, restricted cubic splines (RCS), Kaplan–Meier survival analysis, subgroup, and sensitivity analyses, were exploited to investigate the relationship between OBS and the risk of mortality.

RESULTS Controlling for all potential confounders, a significantly inverse association was observed between elevated OBS and all-cause [hazard ratio (HR) = 0.90, 95% CI: 0.85–0.95] and cardiovascular mortality (HR = 0.85, 95% CI: 0.75–0.95). With adjustment for covariates, significant associations between lifestyle OBS and mortality risks diminished, whereas associations between dietary OBS and these mortality risks remained robust (all-cause mortality: HR = 0.91, 95% CI: 0.86–0.96; cardiovascular mortality: HR = 0.85, 95% CI: 0.76–0.96). RCS demonstrated a linear relationship between OBS and all-cause and cardiovascular mortality risk ($P_{nonlinear}$ = 0.088 and $P_{nonlinear}$ = 0.447, respectively). Kaplan–Meier curves demonstrated that the mortality rate was lower with a high OBS (P < 0.001). The consistency of the association was demonstrated in subgroup and sensitivity analyses. RCS after stratification showed that among current drinkers, those with higher OBS had a lower risk of mortality compared with former or never drinkers.

CONCLUSIONS In hypertensive individuals, there was a negative association between OBS and all-cause and cardiovascular mortality. Encouraging hypertensive individuals, especially those currently drinking, to maintain high levels of OBS may be beneficial in improving their prognosis.

Hypertension is a serious health problem for individuals.[1] Long-term hypertension can cause serious cardiovascular complications, such as stroke, coronary artery disease, and heart failure. It is well-documented that timely and effective antihypertensive treatment exerts a determinant effect in reducing the morbidity and mortality of hypertensive complications. However, statistics revealed that only 14%

of the 1.4 billion hypertensive patients worldwide can effectively control their blood pressure within the normal range.[2–5] Although the management of hypertension has been greatly developed in recent years, the impact of the disease on cardiovascular and renal mortality continues to grow.[6] The mortality rate of hypertensive patients is related to various relevant risk factors,[7] including physical activity,[8] dietary patterns,[9] excessive alcohol intake,[10] triglyceride glycemic index,[11] and geriatric nutrition risk index.[12] It is vital to hinder the deterioration of hypertension by better understanding these risk factors.

The pathologic mechanisms of hypertension are multifactorial. Specifically, oxidative stress is regarded as a significant risk factor.[13–15] Oxidative stress occurs when there is an overproduction of reactive oxygen species or a deficiency in antioxidants.[16] The disturbance between oxidative and antioxidative balance can promote endothelial dysfunction and vascular stiffness, accelerating vascular aging.[17] The deterioration of vascular function and structure, along with disturbances in blood pressure, can be caused by all factors contributing to oxidative stress. There is evidence that reported dietary factors and lifestyles can reduce oxidative levels and ameliorate oxidative-related vascular dysfunction.[18,19] Several studies found excessive oxidative stress plays a multifaceted role in increasing mortality risk in populations,[20,21] by inducing cell death endothelial dysfunction, and mitochondrial dysfunction.[15,22,23] This mechanism may still be applicable in hypertensive populations.

The oxidative balance score (OBS) is an individual indicator for evaluating individual oxidative balance, reflecting the equilibrium between pro-oxidants and antioxidants in diet and lifestyles. Twenty different dietary factors and lifestyle components are included in OBS.[24] Generally, higher OBS means greater antioxidant exposure.[25] Previous research has reported that OBS is closely related with cardiovascular-related diseases, such as atherosclerosis, hypertension, and diabetes mellitus (DM).[25–28] It has been reported that there is a negative association between OBS and hypertension.[29] Lee, *et al*.[30] utilizing data from a Korean cohort, also found that OBS is inversely associated with the risk of developing new-onset hypertension. Nonetheless, it remains unclear about the association between OBS and mortality risk in hypertensive patients. Therefore, we designed this study using the National Health and Nutrition Examination Survey (NHANES) database population to investigate this association.

METHODS

Study Population

The NHANES program is contrived to assess the health and nutritional condition of United States individuals. This study used "stratified multistage probability sampling" to collect resources in multiple ways, including interviews, examinations, dietary questionnaires, and laboratory tests. Through a multilevel stratified probability design, 5000 participants were sampled annually, and each performed a standardized questionnaire and physical examination. The specific study design and methods of data collection have been documented before.[31] For further details about the NHANES survey, please visit https://www.cdc.gov/nchs/nhanes/index.htm. From 1999 to 2014, information of 18,338 hypertensive patients was available from the NHANES database. We excluded 9907 participants who did not complete OBS data and excluded 1508 participants who missed outcome or survival data or any covariates (n = 1508). The study ultimately included 7823 participants (Figure 1). In addition, written informed consent was provided to all participants.

Definition of OBS

Our OBS calculations took into account the effects of 16 dietary factors and 4 lifestyle elements, composed of 5 pro-oxidants and 15 antioxidants according to previous research and experience.[26] Information on 16 dietary factors, including carotene, dietary fiber, niacin, riboflavin, total folic acid, vitamin B6, vitamin B12, vitamin C, vitamin E, calcium, magnesium, selenium, copper, zinc, iron, and total fat, was collected from the first dietary survey interview. The 4 lifestyle elements consist of alcohol consumption, body mass index (BMI), physical activity, and smoking, with the extent of smoking indicated by the amount of cotinine. Among these 20 factors, iron, total fat, alcohol consumption, BMI, and smoking were 5 factors regarded as pro-oxidants, while the other 15 factors were regarded as antioxidants. We classified the drinking population into three groups: heavy drinkers (women: ≥ 15 g/d and men: ≥ 30 g/d), nonheavy drinkers (women: 0–15 g/d and men: 0–30 g/d), and nondrinkers. They were assigned with 0, 1, and 2 scores, respectively.[32] Other constituents were divided by gender and then by their tertiles into three groups, with antioxidants assigned scores of 0–2 and pro-oxidants assigned

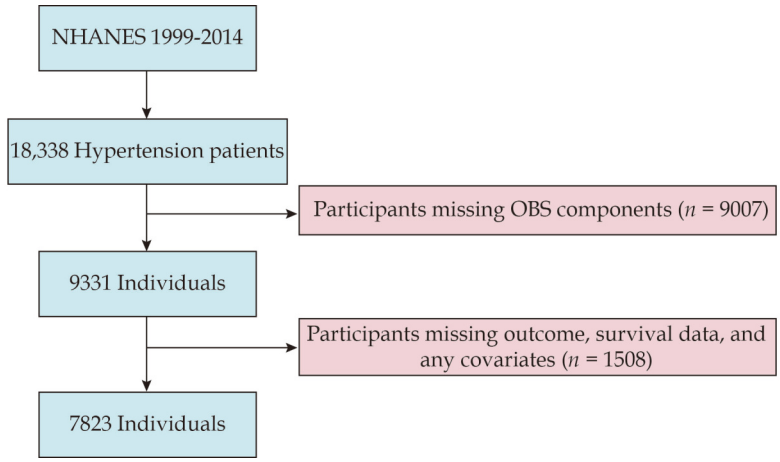

Figure 1 Flow diagram of study cohort selection. OBS: oxidative balance score.

scores of 2–0 in groups 1–3. Higher OBS scores indicate that antioxidant exposure is more significant.

Definition of Hypertension

Consistent with previous studies analyzing the NHANES database,[33,34] hypertension is diagnosed as follows: (1) average systolic blood pressure (SBP) ≥ 140 mmHg after at least 3 measurements; (2) average diastolic blood pressure (DBP) ≥ 90 mmHg after at least 3 measurements; (3) self-reported hypertension; and (4) use of prescription antihypertensive drugs.

Outcome Determination

The outcome variable in this study covered all deaths of participants from participating in the project to December 31, 2019, which was obtained from National Death Index data. The cause of mortality for each participant with varying disease was determined through ICD-10, with death from cardiovascular disease (CVD) determined with ICD-10 codes I00–I09, I11, I13, I20–I51, or I60–I69. In this study, a total of 1943 deaths were recorded, with 537 deaths resulting from CVD.

Covariate Evaluation

We included various covariates that could affect the results, including baseline data on general information [(age, gender, ethnicity, marital status, educational attainment, family poverty-income ratio (PIR), SBP, and DBP], lifestyle behaviors (smoking status, drinking status, and BMI), and medical history (DM and CVD). In general information, gender was divided into male or female. Ethnicity was classified as non-Hispanic white, non-Hispanic black, Mexican American, and others. Marriage status was categorized as living with others and living alone. Educational level was categorized as high school or lower and beyond high school. Three categories of the family PIR were identified: low (≤ 1), medium (> 1 and < 4), and high (≥ 4).[35] Both drinking status and smoking status were classified into two groups: former or never drinker (former or never smoker) and current drinker (current smoker). BMI was obtained by physical examination at the mobile medical examination center. Medical history was identified through medication use, index measurements, and self-reporting. The NHANES survey listed detailed information about the method of variable collection.

Statistical Analysis

As the sampling approaches were complicated, we analyzed the study population with weighted statistics. In the process of baseline feature analysis, the weighted means (standard differences) was exploited for continuous variables, and the sample size (weighted percentage) was exploited for categorical variables. Generally, OBS was considered a continuous variable in the analysis. We employed One-way ANOVA, Kruskal-Wallis H test, or chi-square for analysis. In testing the differences in variable characteristics across OBS quartile groups (Q1, Q2, Q3, and Q4), weighted mean differences were analyzed using ANOVA for continuous variables, and weighted percentage differences were analyzed employing the Rao-Scott χ^2 test for categorical variables to characterize the overall population. The association between OBS and the risk of mortality in hypertensive patients was analyzed using weighted Cox regression models to estimate hazard ratio (HR) with 95% CI. Besides, we transformed

the continuous variable OBS into a categorical variable. We employed a weighted restricted cubic splines (RCS) regression to elucidate the dose-response relationship between OBS and the risk of mortality. We conducted three models in the present study, with Model 1 not adjusting for any confounding factors. Model 2 adjusted for age, sex, ethnicity, smoking status, drinking status, and BMI. Model 3 further adjusted for marital status, education level, PIR, CVD, DM, SBP, and DBP. In addition, we classified OBS into dietary OBS and lifestyle OBS and discussed their relationship with the mortality risk. We also implemented survival analyses by conducting weighted Kaplan–Meier curves and log-rank tests. Subgroup analyses further assessed the heterogeneity between OBS and mortality risk in hypertensive patients. Finally, we evaluated the robustness of the weighted Cox regression results through sensitivity analysis: (1) in order to minimize the possibility the reverse causality, we also eliminate hypertensive patients who died within the first two years of follow-up; and (2) the model was specifically adjusted to include the history of hypertension medication and lipid profiles such as low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, total cholesterol, and triglycerides. These factors have been identified as potentially influential factors based on suggestive biological connections.[36–40]

R statistical software 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria) was implemented for analysis. Results are significant with a two-sided *P*-value < 0.05.

RESULTS

Baseline Characteristics of Participants

In our study, we recruited a total of 7826 hypertensive patients. The baseline characteristics of grouped cohorts according to OBS levels were demonstrated in Table 1. Four groups were generated according to their OBS levels: Q1 (n = 2085), Q2 (n = 2053), Q3 (n = 1771), and Q4 (n = 1914). Most participants were non-Hispanic whites (76.81%). Almost all variables were statistically significant in the four OBS groups. When analyzing living conditions, we observed that participants in the highest quartile (Q4) of OBS had higher marriage rates, PIR, and education levels than those in the first quartile (Q1). Additionally, participants with higher OBS were often current drinkers but not current smokers. They also had lower BMI and SBP and lower rates of CVD and DM.

Table 1 Baseline characteristics of participants by OBS level.

Characteristics	OBS					*P*-value
	Total	Q1 (≤ 14)	Q2 (14 to ≤ 20)	Q3 (20 to ≤ 25)	Q4 (> 25)	
Number	7823	2085	2053	1771	1914	
Age, yrs	55.30 ± 0.31	54.92 ± 0.49	55.47 ± 0.47	55.81 ± 0.44	55.03 ± 0.56	0.402
Male	4258 (53.51%)	1211 (55.08%)	1124 (55.05%)	924 (50.50%)	999 (53.41%)	0.189
Race/Ethnicity						< 0.001
Non-Hispanic White	4248 (76.81%)	982 (70.84%)	1092 (75.96%)	1017 (78.98%)	1157 (80.55%)	
Non-Hispanic Black	1711 (10.66%)	610 (15.88%)	485 (12.04%)	318 (8.71%)	298 (6.86%)	
Mexican American	1025 (4.73%)	301 (5.00%)	262 (4.81%)	220 (4.14%)	242 (4.92%)	
Other race	839 (7.81%)	192 (8.28%)	214 (7.19%)	216 (8.17%)	217 (7.67%)	
Poverty-income ratio						< 0.001
Low	1213 (10.41%)	443 (15.59%)	325 (10.66%)	240 (9.27%)	205 (6.94%)	
Middle	4284 (49.71%)	1206 (54.48%)	1166 (51.76%)	936 (49.77%)	976 (43.97%)	
High	2326 (39.89%)	436 (29.92%)	562 (37.58%)	595 (40.96%)	733 (49.09%)	
Education level						< 0.001
High school or less	3860 (40.93%)	1288 (52.57%)	1049 (44.35%)	803 (39.55%)	720 (29.63%)	
More than high school	3963 (59.07%)	797 (47.43%)	1004 (55.65%)	968 (60.45%)	1194 (70.37%)	
Marital status						0.040
Living with others	5015 (67.51%)	1295 (65.01%)	1311 (66.73%)	1128 (67.01%)	1281 (70.67%)	
Living alone	2808 (32.49%)	790 (34.99%)	742 (33.27%)	643 (32.99%)	633 (29.33%)	

Continued

Characteristics	OBS					*P*-value
	Total	Q1 (≤ 14)	Q2 (14 to ≤ 20)	Q3 (20 to ≤ 25)	Q4 (> 25)	
Current smokers	1372 (18.06%)	516 (27.65%)	373 (18.35%)	294 (17.02%)	189 (10.94%)	< 0.001
Current drinkers	5037 (69.99%)	1221 (62.72%)	1313 (71.60%)	1188 (71.98%)	1315 (72.76%)	< 0.001
Body mass index, kg/m^2	30.10 ± 0.11	30.67 ± 0.21	30.43 ± 0.18	30.10 ± 0.23	29.34 ± 0.21	< 0.001
Systolic blood pressure, mmHg	133.76 ± 0.34	135.02 ± 0.64	133.55 ± 0.68	134.41 ± 0.58	132.39 ± 0.56	0.006
Diastolic blood pressure, mmHg	75.40 ± 0.29	75.64 ± 0.53	75.04 ± 0.46	75.34 ± 0.46	75.57 ± 0.43	0.676
Cardiovascular disease	1328 (14.12%)	404 (14.91%)	377 (16.70%)	286 (13.85%)	261 (11.41%)	0.002
Diabetes mellitus	1863 (18.38%)	565 (20.96%)	503 (19.48%)	388 (17.80%)	407 (15.80%)	0.003

Data are presented as weighted means ± SD or *n* (%). OBS: oxidative balance score.

Restricted Cubic Splines Analyses

We exploited weighted RCS analyses to model the relationship of OBS with all-cause and cardiovascular mortality in hypertensive individuals. No nonlinear relationship between OBS and mortality risk was found ($P_{overall} < 0.05$, $P_{nonlinear} > 0.05$) (Figure 2A & 2B).

Kaplan-Meier Survival Analyses

We performed weighted Kaplan-Meier survival analyses for OBS and all-cause and cardiovascular mortality. Over an average follow-up period of 127 months, a total of 1943 individuals died from various causes, with 537 deaths attributed to CVD. The survival curve (Figure 3A & 3B) denoted that patients with high OBS hypertension had significantly lower all-cause ($P < 0.001$) and cardiovascular mortality ($P < 0.001$) and longer survival times.

Independent Role of OBS on Mortality

We implemented a weighted Cox regression model to analyze the HR of OBS and its association with the risk of all-cause and cardiovascular mortality (Table 2). In Model 1 (unadjusted model), OBS was negatively associated with all-cause mortality risk (HR = 0.83, 95% CI: 0.78–0.88). Each standard deviation increase in OBS led to a 17% decrease in all-cause mortality. The HR for the quartiles of OBS exhibited a significant downward trend from Q1 to Q4 ($P_{trend} < 0.001$). This association was also present and statistically significant in unadjusted models for cardiovascular mortality (HR = 0.80, 95% CI: 0.72–0.89, $P < 0.001$). After multivariate adjustment, in Model 3, the negative correlation trends between OBS and all-cause (HR = 0.90, 95% CI: 0.85–0.95, $P < 0.001$) and cardiovascular mortality (HR = 0.85, 95% CI: 0.75–0.96, $P =$

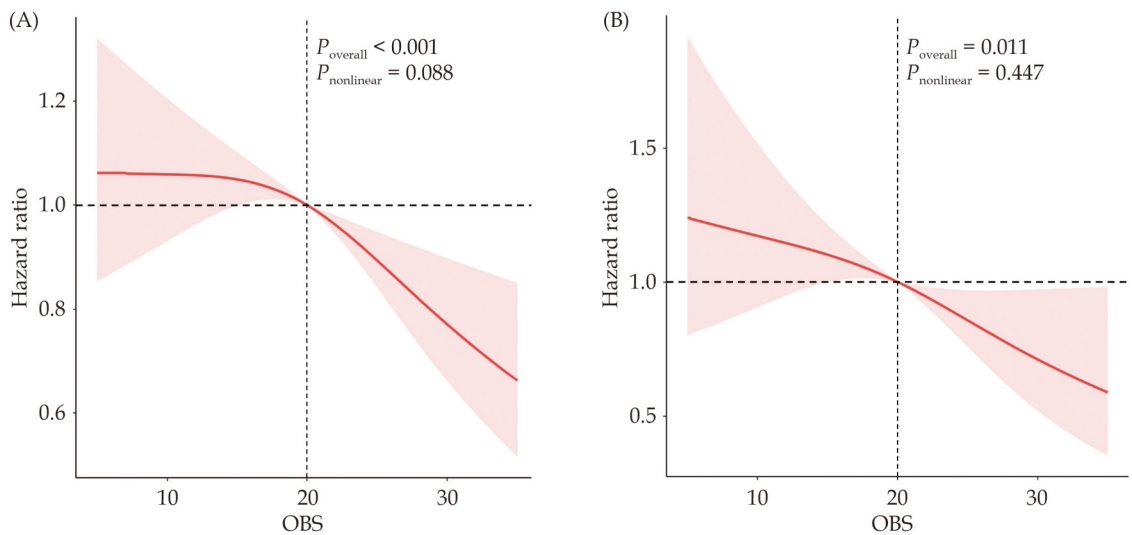

Figure 2 Nonlinear correlation between OBS and all-cause (A) and cardiovascular (B) mortality. OBS: oxidative balance score.

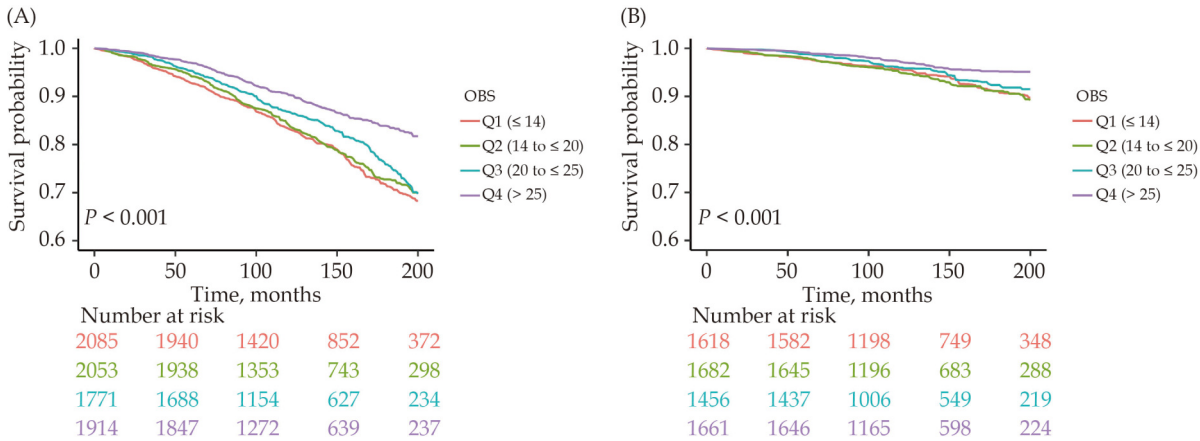

Figure 3 Kaplan–Meier survival curve between OBS and all-cause (A) and cardiovascular (B) mortality. OBS: oxidative balance score.

0.006) remained statistically significant, which indicate that the association was robustness.

Association between Dietary and Lifestyle Elements of OBS and Mortality

We also distinguished dietary and lifestyle elements of OBS and then conducted subsequent analyses (Tables 3 & 4). In the unadjusted model, significant negative association between OBS and all-cause and cardiovascular mortality. Both of these trends were statistically significant (P_{trend} < 0.001). In the final adjustment (Model 3), compared with the Q1 group, the HRs of all-cause and cardiovascular mortality were 0.77 (95% CI: 0.66–0.90) and 0.60 (95% CI: 0.44–0.83) in the Q4 group, respectively. Nonetheless, our results demonstrated that the association between lifestyle elements of OBS and all-cause and cardiovascular mortality was non-significant (Q4 *vs.* Q1). The protective prognostic effect of lifestyle OBS appears to be weaker in hypertensive patients when compared to dietary OBS.

Table 2 Association between OBS and mortality.

Variable	Events	Model 1		Model 2		Model 3	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
All-cause mortality							
OBS per standard differences		0.83 (0.78–0.88)	< 0.001	0.87 (0.83–0.92)	< 0.001	0.90 (0.85–0.95)	< 0.001
Q1 (≤ 14)	649 (25.40%)	Reference		Reference		Reference	
Q2 (14 to ≤ 20)	517 (21.27%)	0.95 (0.81–1.11)	0.503	1.05 (0.89–1.24)	0.592	1.03 (0.87–1.22)	0.709
Q3 (20 to ≤ 25)	432 (19.21%)	0.85 (0.72–0.99)	0.038	0.92 (0.80–1.07)	0.290	0.96 (0.83–1.11)	0.561
Q4 (> 25)	345 (12.60%)	0.55 (0.46–0.66)	< 0.001	0.68 (0.58–0.79)	< 0.001	0.74 (0.63–0.86)	< 0.001
P_{trend}		< 0.001		< 0.001		< 0.001	
Cardiovascular mortality							
OBS per standard differences		0.80 (0.72–0.89)	< 0.001	0.83 (0.74–0.93)	0.002	0.85 (0.75–0.95)	0.006
Q1 (≤ 14)	182 (6.40%)	Reference		Reference		Reference	
Q2 (14 to ≤ 20)	146 (6.11%)	1.06 (0.79–1.43)	0.698	1.10 (0.81–1.49)	0.537	1.05 (0.76–1.44)	0.782
Q3 (20 to ≤ 25)	117 (4.85%)	0.84 (0.63–1.12)	0.240	0.91 (0.68–1.24)	0.557	0.87 (0.64–1.19)	0.390
Q4 (> 25)	92 (3.06%)	0.50 (0.37–0.70)	< 0.001	0.59 (0.42–0.83)	0.002	0.63 (0.45–0.88)	0.007
P_{trend}		< 0.001		< 0.001		0.003	

Model 1: not adjusted. Model 2: adjusted for age, sex, race, smoking status, drinking status, and body mass index. Model 3: adjusted for variables in Model 2 plus the marital status, education level, poverty-income ratio, cardiovascular disease, diabetes mellitus, systolic blood pressure, and diastolic blood pressure. OBS: oxidative balance score.

Table 3 Association between dietary OBS and mortality.

Variable	Events	Model 1		Model 2		Model 3	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
All-cause mortality							
OBS per standard differences		0.80 (0.75–0.85)	< 0.001	0.88 (0.83–0.93)	< 0.001	0.91 (0.86–0.96)	< 0.001
Q1 (≤ 14)	639 (25.86%)	Reference		Reference		Reference	
Q2 (14 to ≤ 20)	522 (21.65%)	0.91 (0.78–1.06)	0.243	1.00 (0.86–1.17)	0.950	1.02 (0.87–1.19)	0.803
Q3 (20 to ≤ 25)	445 (18.14%)	0.76 (0.66–0.88)	< 0.001	0.88 (0.76–1.02)	0.099	0.94 (0.81–1.08)	0.361
Q4 (> 25)	337 (12.91%)	0.52 (0.43–0.63)	< 0.001	0.70 (0.60–0.83)	< 0.001	0.77 (0.66–0.90)	< 0.001
P_{trend}		< 0.001		< 0.001		< 0.001	
Cardiovascular mortality							
OBS per standard differences		0.77 (0.69–0.86)	< 0.001	0.84 (0.75–0.95)	0.004	0.85 (0.76–0.96)	0.008
Q1 (≤ 14)	177 (6.47%)	Reference		Reference		Reference	
Q2 (14 to ≤ 20)	152 (6.39%)	1.05 (0.80–1.38)	0.719	1.13 (0.85–1.51)	0.398	1.09 (0.82–1.45)	0.568
Q3 (20 to ≤ 25)	125 (4.71%)	0.78 (0.59–1.02)	0.068	0.91 (0.67–1.22)	0.516	0.90 (0.67–1.20)	0.468
Q4 (> 25)	83 (2.88%)	0.44 (0.31–0.62)	< 0.001	0.58 (0.41–0.82)	0.002	0.60 (0.44–0.83)	0.002
P_{trend}		< 0.001		< 0.001		0.003	

Model 1: not adjusted. Model 2: adjusted for age, sex, race, smoking status, drinking status, and body mass index. Model 3: adjusted for variables in Model 2 plus the marital status, education level, poverty-income ratio, cardiovascular disease, diabetes mellitus, systolic blood pressure, and diastolic blood pressure. OBS: oxidative balance score.

Table 4 Association between lifestyle OBS and mortality.

Variable	Events	Model 1		Model 2		Model 3	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
All-cause mortality							
OBS per standard differences		1.13 (1.05–1.21)	< 0.001	0.94 (0.88–1.01)	0.080	0.96 (0.90–1.03)	0.298
Q1 (≤ 14)	774 (19.62%)	Reference		Reference		Reference	
Q2 (14 to ≤ 20)	465 (19.35%)	1.14 (0.97–1.33)	0.103	0.83 (0.70–0.98)	0.026	0.86 (0.73–1.02)	0.088
Q3 (20 to ≤ 25)	427 (18.85%)	1.30 (1.09–1.55)	0.004	0.88 (0.76–1.02)	0.087	0.93 (0.81–1.08)	0.341
Q4 (> 25)	277 (18.83%)	1.37 (1.12–1.67)	0.002	0.78 (0.63–0.95)	0.013	0.85 (0.69–1.03)	0.102
P_{trend}		< 0.001		0.016		0.137	
Cardiovascular mortality							
OBS per standard differences		0.77 (0.69–0.86)	< 0.001	0.84 (0.75–0.95)	0.004	0.85 (0.76–0.96)	0.008
Q1 (≤ 14)	219 (5.08%)	Reference		Reference		Reference	
Q2 (14 to ≤ 20)	138 (5.73%)	1.31 (1.01–1.71)	0.044	0.88 (0.67–1.17)	0.378	0.93 (0.69–1.26)	0.638
Q3 (20 to ≤ 25)	111 (4.62%)	1.28 (0.95–1.72)	0.107	0.84 (0.63–1.11)	0.217	0.93 (0.69–1.26)	0.642
Q4 (> 25)	69 (4.28%)	1.26 (0.89–1.78)	0.202	0.64 (0.41–0.98)	0.039	0.74 (0.49–1.13)	0.159
P_{trend}		0.076		0.039		0.206	

Model 1: not adjusted. Model 2: adjusted for age, sex, race, smoking status, drinking status, and body mass index. Model 3: adjusted for variables in Model 2 plus the marital status, education level, poverty-income ratio, cardiovascular disease, diabetes mellitus, systolic blood pressure, and diastolic blood pressure. OBS: oxidative balance score.

Stratification Analyses

Stratification analyses were conducted to determine the influence of confounding factors on the association between OBS and all-cause and cardiovascular mortality (Figure 4A & 4B). Significant interactions were found between OBS and race, education level, and drinking

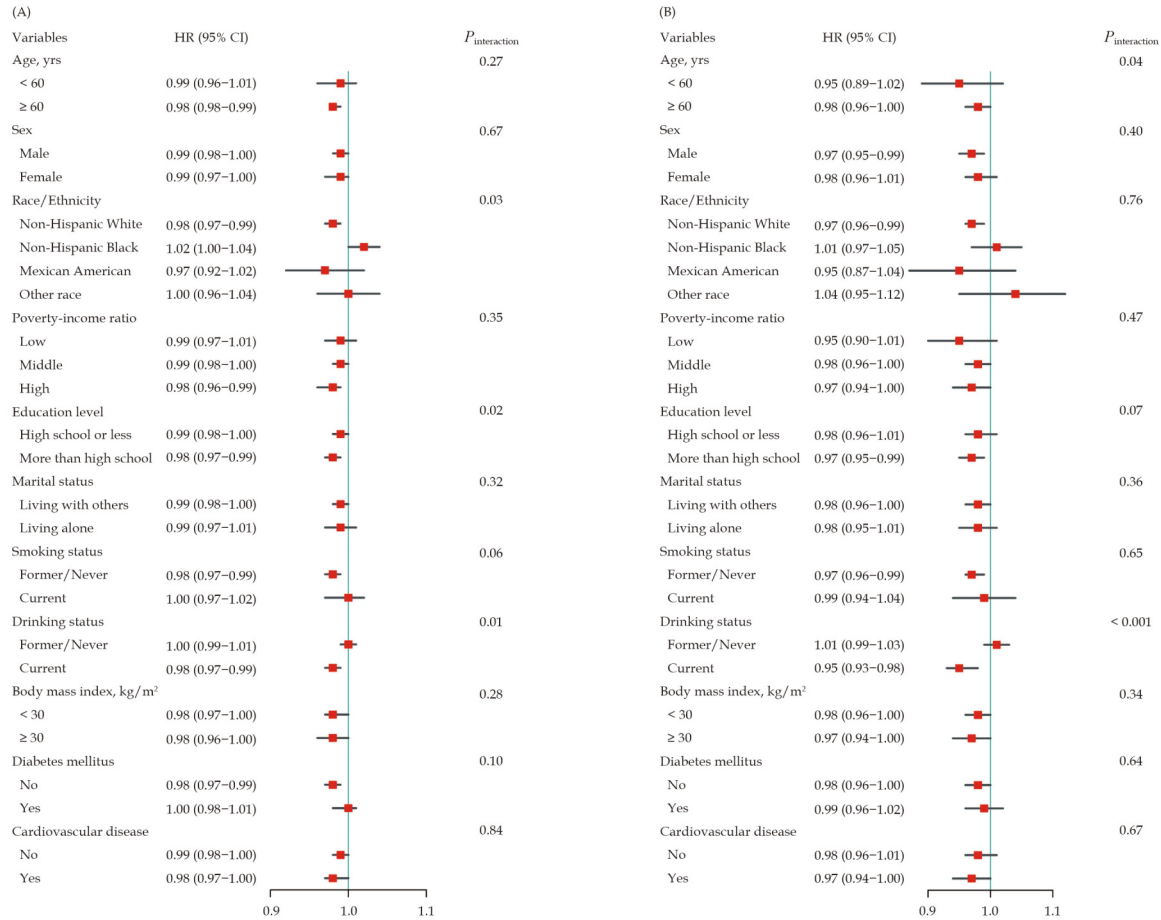

Figure 4 Subgroup analyses between OBS and all-cause (A) and cardiovascular (B) mortality. OBS: oxidative balance score.

status with all-cause mortality risk ($P_{interaction} < 0.05$). Similarly, OBS exhibited significant interactions with age and drinking status with cardiovascular mortality risk ($P_{interaction} < 0.05$). We discovered that drinking status affects the association between OBS and all-cause and cardiovascular mortality. RCS analyses also demonstrated that elevated levels of OBS were linked to notably reduced HRs for all-cause and cardiovascular mortality in current drinkers, in contrast to former or never drinkers (supplemental material, Figure 1S). In addition, we observed a nonlinear association between OBS and all-cause mortality among former or never drinkers. Segmented regression analyses indicated that the point of inflection for OBS in former or never drinkers was 19. Specifically, when OBS was less than 19, the risk of all-cause mortality increased with increasing levels of OBS. However, when the OBS was greater than 19, the risk of all-cause mortality tended to decrease. No linear or nonlinear associations were observed between OBS and cardiovascular mortality among former or never drinkers ($P_{overall} > 0.05$, $P_{nonlinear} > 0.05$) (supplemental material, Figure 2S).

Sensitivity Analyses

Moreover, we assessed the robustness of the results with several sensitivity tests. Consistent with the previous results, OBS was negatively associated with risk of all-cause mortality (HR = 0.91, 95% CI: 0.86–0.96, $P < 0.001$) and cardiovascular mortality (HR = 0.88, 95% CI: 0.79–0.99, $P = 0.031$) in the fully adjusted model after excluding patients who died within two years of follow-up ($n = 7769$) (supplemental material, Table 1S). When blood lipids and the history of hypertension medication were considered, the reduction in OBS and the risk of all-cause (HR = 0.90, 95% CI: 0.84–0.97, $P = 0.008$) and cardiovascular mortality (HR = 0.83, 95% CI: 0.70–0.98, $P = 0.028$) remanied significant (supplemental material, Table 2S).

DISCUSSION

Main Results and Public Health Implications

This nationally representative research showed a negative correlation between OBS levels and all-cause and

cardiovascular mortality in hypertensive patients. The protective prognostic effect of lifestyle OBS may be weaker compared to dietary OBS. The protective effects of OBS were stronger among hypertensive individuals who were current drinkers compared with former drinkers or never drinkers. In conclusion, our findings suggest that increasing OBS levels can be an effective way to improve the prognosis of hypertensive populations. This underscores the potential benefits of adopting an antioxidant-rich diet and lifestyle for hypertensive patients, particularly those who consume alcohol.

Comparison with Other Studies

Growing evidence of the high potential of OBS in the assessment of various diseases provides a solid foundation for our pioneering study on the relationship between OBS and mortality in hypertensive patients. A cross-sectional study of 6222 adults from the NHANES database found a significant negative correlation between OBS and free and total thyroxine.[41] Liu, *et al*.[42] demonstrated a nonlinear relationship between dietary OBS and migraine incidence, suggesting that adhering to an antioxidant-rich diet may help alleviate migraines. Furthermore, studies by Lee, *et al*.[30] and Annor, *et al*.[29] have shown that individuals with higher levels of OBS have a lower risk of developing hypertension. Previous research has also indicated that OBS is a good predictor of mortality in patients with metabolic syndrome,[43] and those with nonalcoholic fatty liver disease.[44] However, the relationship between OBS and prognosis in hypertensive patients had not been explored until our study. Our findings, for the first time, revealed that higher OBS was associated with lower mortality in hypertensive patients. Promoting healthy antioxidant practices and dietary habits is a crucial strategy for enhancing the prognosis of hypertensive patients.

Potential Mechanisms

A crucial finding of our study is that higher OBS is correlated with reduced all-cause and cardiovascular mortality in hypertensive patients. Conclusions from basic research also confirm the relationship between oxidative stress and hypertension. Increasing evidence shows that oxidative damage is the decisive element in the pathogenesis of hypertension. Free radicals can damage the vascular endothelium, promote the formation of thrombi, and change the vasodilatory function of blood vessels.[45,46] ROS and redox signaling play an essential role in several processes, including endothelial injury, vascular stiffness, sympathetic nervous system activation, immune cell activation, and inflammation, which underlie the pathophysiology of hypertension.[47–49] ROS can also degrade some factors that relax blood vessels, such as NO, causing vasoconstriction and increased tension.[23] In addition, oxidative stress is also correlated with atherosclerosis, and ROS can oxidize low-density lipoprotein into oxidatively modified low-density lipoprotein. The deposition of oxidatively modified low-density lipoprotein particles can damage the vascular endothelium and induce the aggregation of macrophages, causing atherosclerosis.[50] To conclude, oxidative stress participates in the pathogenesis of various types of hypertension and is the decisive factor in the occurrence and prognosis of hypertension.

Our study also revealed an interesting finding: lifestyle OBS appears to have a weaker prognostic protective effect in hypertensive patients than dietary OBS. In this regard, we believe that there may be a synergistic effect among the various components in the dietary OBS scoring system to protect the body from oxidative damage, making it more protective. This is mainly manifested in the following aspects. First, there is a mutual regeneration effect between certain antioxidants. For example, vitamin C can regenerate vitamin E, and glutathione can regenerate vitamin C.[51] In turn, vitamin C and vitamin E can activate the activity of the glutathione antioxidant system.[52,53] Second, different antioxidants have different targets. For example, vitamin C mainly scavenges water-soluble free radicals, and vitamin E mainly scavenges fat-soluble free radicals.[54] The use of multiple antioxidants allows for simultaneous attacks on different oxidative reaction sites, increasing antioxidant coverage of a wide range of free radicals and providing more comprehensive protection. Although the underlying mechanisms of this synergistic effect need further investigation, it can at least be assumed that the combination of several antioxidant components provides better benefits than the individual factors.

In addition, our study was surprised to find that the protective effects of OBS were stronger among hypertensive individuals who were current drinkers. The impact of alcohol on oxidative stress in the body may be responsible for this. Alcohol exposure can increase ROS production and inhibit antioxidant activity, exacerbating oxidative stress levels.[55,56] Therefore, we speculate that for hypertensive individuals who drink alcohol, their ox-

idative stress levels are higher, so the protective effect produced by OBS may be more significant. The mechanism of alcohol consumption on the oxidative stress level of hypertensive patients and its effect on patient prognosis is worthy of further in-depth study. In our study, the data on drinking status was obtained from the Alcohol Use Questionnaire which primarily focused on lifetime and current (past 12 months) alcohol consumption. The questions did not capture specific details about the type of alcohol consumed, making it challenging to precisely define the drinking status. Therefore, more clinical trials and laboratory studies are warranted to investigate the exact association between alcohol intake and antioxidant capacity in hypertensive patients.

STRENGTHS AND LIMITATIONS

Our research has the following advantages. Firstly, this study has a large sample size, and relevant adjustments were made for statistical tests and various covariates to ensure the stability of our results. Secondly, we separately discuss the influence of diet-induced OBS and lifestyle-induced OBS on mortality, which contributes to a better understanding of the potential of dietary and lifestyle factors to reduce oxidative stress. Thirdly, the NHANES data use a rigorous multi-stage probability sampling design to ensure that our study's results are representative of the broader American population, which enhances the generalizability and applicability of the results.

Of course, this study also has limitations. Firstly, this study is an observational cohort study, hence it is hard to elaborate on the causal relationship and molecular mechanisms. Secondly, individual long-term routine intakes for this study were estimated by the average of two 24-hour dietary recalls. This could be influenced by nondifferential misclassification, nor can it be ruled out that patients have altered dietary patterns. Thirdly, since the data used in this study did not have detailed information on the stages of hypertension, we could not analyze the protective effect of OBS on patients with hypertension of different severities and the differences in correlation.

CONCLUSIONS

In conclusion, there was an inverse relationship between OBS and both all-cause and cardiovascular mortality in hypertensive patients. The intake of foods that contain antioxidants and maintain healthy lifestyles are believed to reduce the mortality rate of hypertensive patients and improve the prognosis of hypertensive patients.

AVAILIABILITY OF DATA AND MATERIALS

The datasets used and/or analyzed during the current study are available at https://www.cdc.gov/nchs/nhanes.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The protocols of NHANES were approved by the Institutional Review Board of the National Center for Health Statistics, CDC (https://www.cdc.gov/nchs/nhanes/irba98.htm). NHANES has obtained written informed consent from all participants.

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