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Association between the oxidative balance score and all-cause and cardiovascular mortality in patients with diabetes and prediabetes

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ABSTRACT

Background: Few studies have examined the link between systemic oxidative stress and mortality risk in diabetes and prediabetes patients. The Oxidative Balance Score (OBS) is a novel measure of systemic oxidative stress, with higher scores indicating greater antioxidant exposure. This study investigates the relationship between OBS and all-cause and cardiovascular mortality in these patients.
Methods: This study analyzed 10,591 diabetes and prediabetes patients from the 1999–2018 National Health and Nutrition Examination Survey (NHANES). The endpoints were all-cause and cardiovascular mortality, determined from the National Death Index (NDI). OBS was calculated using 20 dietary and lifestyle factors. Kaplan-Meier survival analysis, multivariable Cox regression models, restricted cubic splines (RCS), and subgroup analyses were used to assess the relationship between OBS and mortality risks.
Results: Over an average follow-up of 99.8 months, 2900 (26.4 %) participants died, including 765 (8.9 %) from cardiovascular diseases. Kaplan-Meier analysis showed the lowest all-cause and cardiovascular mortality in the highest OBS quartile (Q4) and the highest mortality in the lowest quartile (Q1) ($p < 0.001$). In the fully adjusted model, multivariable Cox regression revealed that each unit increase in OBS was linked to a 1.8 % decrease in all-cause mortality risk (HR 0.982, 95 % CI 0.976–0.987, $p < 0.0001$) and a 4 % decrease in cardiovascular mortality risk (HR 0.960, 95 % CI 0.949–0.970, $p < 0.0001$). Compared to Q1, those in Q4 had significantly lower all-cause mortality (HR 0.719, 95 % CI 0.643–0.804, $p < 0.0001$, p for trend <0.0001) and cardiovascular mortality (HR 0.567, 95 % CI 0.455–0.705, $p < 0.0001$, p for trend <0.0001). These findings were consistent across subgroups. RCS curves showed a negative correlation between OBS and both mortality types.
Conclusion: Higher OBS is linked to reduced all-cause and cardiovascular mortality in diabetes and prediabetes patients.

1. Introduction

In recent decades, the prevalence of diabetes and its complications has emerged as a significant global public health concern [1,2]. According to the 10th edition of the International Diabetes Federation (IDF) Diabetes Atlas, the global number of adults with diabetes reached 536.6 million in 2021, accounting for 10.5 % of the global adult population [1]. It is projected that by 2045, this number will rise to 783.2 million [1]. Prediabetes is defined as blood glucose levels above normal but below the threshold for diabetes, associated with a high risk of developing diabetes [3]. Numerous epidemiological studies have linked diabetes with increased risks of cardiovascular diseases, cerebrovascular diseases, renal dysfunction, and retinopathy [4–6]. Furthermore, individuals with prediabetes experience damage to their heart, blood vessels, and kidneys [7,8]. Additionally, diabetes patients exhibit higher rates of cardiovascular and all-cause mortality [9]. Evidence suggests that oxidative stress plays a crucial role in the development and progression of diabetes and prediabetes [10]. Oxidative stress can mediate insulin resistance, which forms the physiological basis for the development of diabetes and prediabetes, through the inhibition of insulin

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signaling and the dysregulation of adipokine factors [11,12]. Moreover, oxidative stress may contribute to the development of microvascular and macrovascular complications of diabetes [13].

Oxidative stress levels in the body can be influenced by a multitude of factors. Antioxidant factors commonly include specific antioxidant nutrients and physical activity, whereas pro-oxidant factors encompass behaviors like smoking, alcohol consumption, obesity, and the consumption of certain pro-oxidant nutrients [14]. However, the impact of individual factors on the body's oxidative/antioxidative status is limited [14]. The Oxidative Balance Score (OBS), calculated from 20 different dietary and lifestyle components of antioxidants and pro-oxidants, highlights the overall balance between pro-oxidants and antioxidants at the dietary and lifestyle levels [14]. It serves as a comprehensive indicator to assess an individual's overall oxidative/antioxidant status [14]. Generally, a higher OBS indicates stronger antioxidant activity, while a lower OBS indicates stronger pro-oxidant activity. Recent studies have confirmed a lower incidence of diabetes associated with higher OBS scores [15]. Furthermore, OBS has been negatively correlated with the incidence of other diseases such as chronic kidney disease [16], hypertension [17], and depression [18].

However, no studies have explored the relationship between OBS and mortality risk among patients with diabetes and prediabetes. Therefore, this study aims to investigate the association between OBS and all-cause mortality as well as cardiovascular mortality among individuals with diabetes and prediabetes using data from the National Health and Nutrition Examination Survey.

2. Method

2.1. Study population

The National Health and Nutrition Examination Survey (NHANES) is a nationally representative survey conducted by the National Center for Health Statistics (NCHS), part of the Centers for Disease Control and Prevention (CDC) in the United States. Its primary objective is to assess the health and nutritional status of non-institutionalized individuals across the country. Data collection methods include structured household interviews, mobile examination center visits, and laboratory testing, utilizing a complex, stratified, multistage probability sampling design. The NHANES research protocol is approved by the NCHS Ethics Review Board, and all participants provide written informed consent.

The data for this study were sourced from the NHANES database spanning ten cycles (1999–2000, 2001–2002, 2003–2004, 2005–2006, 2007–2008, 2009–2010, 2011–2012, 2013–2014, 2015–2016 and 2017–2018). Initially, a total of 101,316 participants were included. Exclusions were made for the following individuals: (1) pregnant participants (n = 840); (2) age <18 years (n = 42,081); (3) missing mortality data (n = 140); (4) insufficient dietary and lifestyle data required for calculating the Oxidative Balance Score (n = 11,642); and (5) individuals without diabetes or prediabetes (n = 36,022). Ultimately, our study included 10,591 participants (Fig. 1).

2.2. Definition of diabetes and prediabetes

Diabetes is defined as individuals meeting any of the following criteria: (1) fasting plasma glucose ≥7.0 mmol/L or 2-h post-oral glucose

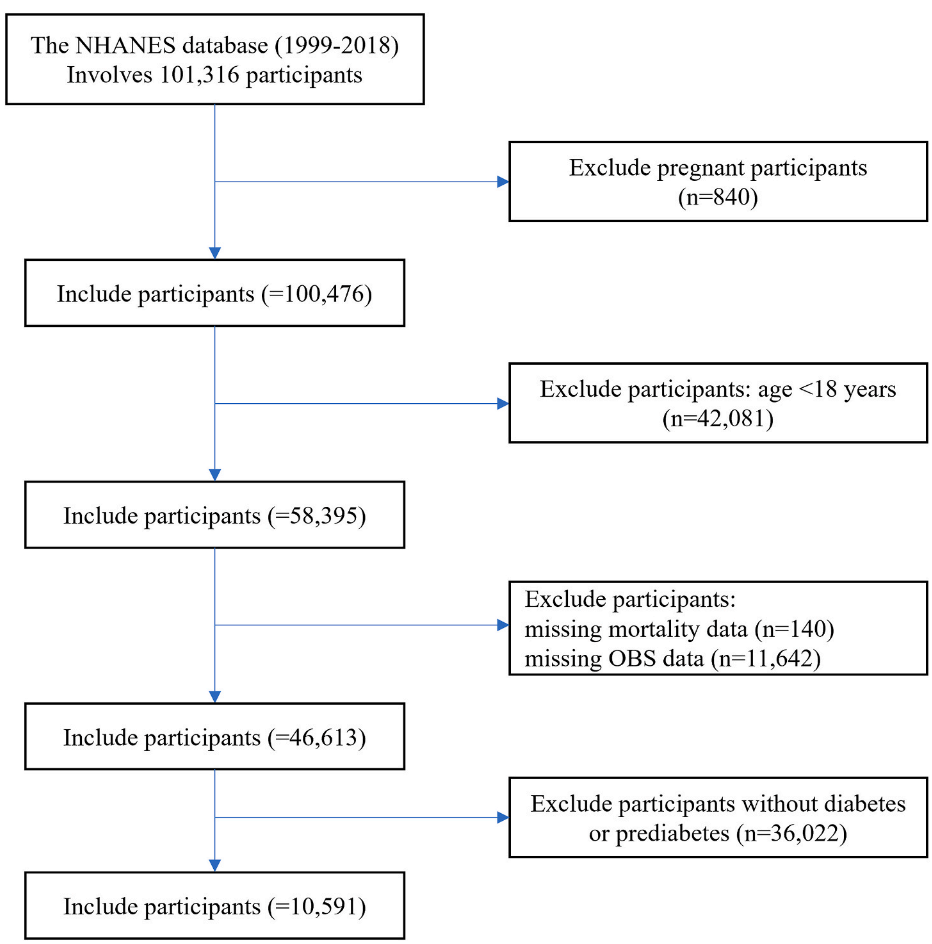

Fig. 1. Flowchart for selecting analyzed participants.

tolerance test level ≥11.1 mmol/L; (2) random plasma glucose ≥11.1 mmol/L; (3) glycated hemoglobin (HbA1c) ≥6.5 %; (4) self-reported diagnosis of diabetes ("Doctor told you have diabetes.") or currently using insulin.

Prediabetes is defined as individuals meeting any of the following criteria: (1) 2-h post-oral glucose tolerance test levels between 7.8 and 11.0 mmol/L; (2) fasting plasma glucose between 6.1 and 6.9 mmol/L; (3) HbA1c levels between 5.7 % and 6.4 %; (4) self-reported diagnosis of prediabetes ("Doctor told you have prediabetes.").

2.3. Exposure variable: oxidative balance score

The calculation of the Oxidative Balance Score (OBS) includes 16 dietary nutrients and 4 lifestyle factors, encompassing 15 antioxidative components and 5 pro-oxidative components [19]. The 16 nutrients are derived from the first dietary recall interview and include dietary fiber, carotenoids (retinol component, RE), riboflavin, niacin, vitamin B6, total folate, vitamin B12, vitamin C, vitamin E (Alpha-Tocopherol Equivalent, ATE), calcium, magnesium, zinc, copper, selenium, total fat, and iron. The 4 lifestyle factors are physical activity, Body Mass Index (BMI), alcohol consumption, and smoking, with the degree of smoking measured by cotinine levels. The 5 pro-oxidative components include total fat, iron, BMI, alcohol consumption, and cotinine, while the remaining factors are classified as antioxidative.

Alcohol consumption is categorized into three groups following previous literature [19]: non-drinkers, light-to-moderate drinkers (females 0–15g/day, males 0–30g/day), and heavy drinkers (females ≥15g/day, males ≥30g/day), scored as 2, 1, and 0 points, respectively. The other components are scored based on tertiles, stratified by gender. For antioxidative components, scores are assigned as 0, 1, and 2 points for the lowest to the highest tertiles, respectively. In contrast, pro-oxidative components are scored inversely, with the highest tertile receiving 0 points and the lowest receiving 2 points [19]. The overall OBS was calculated by summing the scores of each component, with scores ranging from 3 to 36. Higher scores indicate greater antioxidant exposure. The scoring scheme for OBS components is detailed in Supplementary Table 1.

2.4. Ascertainment of mortality

Mortality information was obtained from the National Death Index (NDI) database [https://www.cdc.gov/nchs/data-linkage/mortality-public.htm], maintained by the Centers for Disease Control and Prevention (CDC) in the United States. The follow-up period was calculated from the date of the baseline interview to the date of death or December 31, 2019, which is the most recent update in the NDI database. Cardiovascular mortality was identified using the International Classification of Diseases, 10th Revision (ICD-10) codes, specifically I00–I09, I11, I13, and I20–I51.

2.5. Covariates

The covariates considered in this study include age, gender, race/ethnicity (Mexican American, other Hispanic, non-Hispanic White, non-Hispanic Black, and other races), education level (less than high school, high school or equivalent, and more than high school), marital status (married, single, living with a partner), poverty-to-income ratio (≤1.0, 1.0–3.0, >3.0), smoking history (defined as having smoked at least 100 cigarettes in one's lifetime), alcohol consumption history (defined as consuming at least 12 alcoholic drinks per year), and history of hypertension. The measurement procedures for these variables can be found on the CDC NHANES website at https://www.cdc.gov/nchs/nhanes/.

2.6. Statistical analysis

Statistical analyses were conducted in accordance with the guidelines provided by the CDC, available at https://www.cdc.gov/nchs/nhanes/tutorials/default.aspx. Baseline characteristics were expressed by quartiles of the OBS. Continuous variables were presented as mean ± standard deviation (SD), while categorical variables were presented as percentages. Chi-square tests were used to calculate p-values for categorical variables, and Kruskal-Wallis rank-sum tests were used for continuous variables. The log-rank test and Kaplan-Meier (K-M) survival analysis were applied to investigate differences in survival probabilities. Three multivariable Cox regression models (Model 1, Model 2, and Model 3) were developed to evaluate the relationship between OBS and all-cause mortality and cardiovascular mortality in patients with diabetes and prediabetes. Model 1 was unadjusted for covariates, Model 2 was adjusted for sex, age, and race/ethnicity, and Model 3 was adjusted for sex, age, race/ethnicity, education level, marital status, poverty-to-income ratio, smoking history, alcohol consumption history, and history of hypertension. The goodness-of-fit test using Schoenfeld residuals to validate the proportional hazards (PH) assumption. To visualize the association between OBS and all-cause mortality as well as cardiovascular mortality in patients with diabetes and prediabetes, restricted cubic splines with three knots based on the fully adjusted Cox model were constructed. Subgroup analyses and interaction tests were also conducted based on the fully adjusted model to investigate the relationship between OBS and mortality in different subgroups.

All statistical analyses were performed using Empower Stats software and R version 4.3.3. A two-tailed *p*-value of less than 0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics of the participants

Table 1 presents the baseline characteristics of the study population, categorized by quartiles of the OBS. The study included a total of 10,591 participants with diabetes or prediabetes. The average age of the selected participants was 59.78 years (±15.17), with non-Hispanic Whites constituting the majority of the study population. Compared to participants in the higher OBS quartiles (Q4), those in the lowest OBS quartile (Q1) were more likely to be male, older, non-Hispanic Black, have less than a high school education, be single, have a higher poverty-to-income ratio, have a history of hypertension, not consume alcohol, and be smokers. There was no statistically significant difference in alcohol consumption across the OBS groups.

3.2. Associations of the OBS with all-cause and cardiovascular mortality

During an average follow-up period of 99.8 months, out of the 10,591 participants with diabetes or prediabetes, 2900 (26.4 %) died, with 765 (8.9 %) deaths attributed to cardiovascular disease. The Kaplan-Meier (K-M) survival analysis demonstrated significant differences in all-cause and cardiovascular mortality rates among the four groups. Participants in the highest quartile (Q4) of the OBS had the lowest mortality rates, whereas those in the lowest quartile (Q1) had the highest mortality rates (log-rank $p < 0.001$). More details on the K-M curves are shown in Fig. 2.

Table 2 illustrates the Cox regression models examining the association between OBS and all-cause mortality. In the unadjusted model (Model 1), we found that with an increase in OBS, the risk of all-cause mortality significantly decreased (HR 0.968, 95 % CI 0.963–0.973, $p < 0.0001$). Compared to the lowest quartile (Q1) of OBS, the highest quartile (Q4) was associated with a 46.8 % reduction in the risk of all-cause mortality (HR 0.532, 95 % CI 0.478–0.592, *p* for trend <0.0001). After adjusting for sex, age, and race in Model 2, each unit increase in OBS was associated with a 2.7 % reduction in the risk of all-cause mortality (HR 0.973, 95 % CI 0.967–0.978, $p < 0.0001$). In this model, participants in the OBS Q4 group had a 39.3 % lower risk of all-

Table 1
Baseline characteristics of the selected participants.

OBS	Q1	Q2	Q3	Q4	*P*-value
N	2486	2329	2919	2857	
Age, mean ± SD (years)	61.239 ± 15.097	60.795 ± 14.884	59.456 ± 15.350	58.020 ± 15.082	<0.001
Gender (%)					<0.001
Male	1387 (55.792 %)	1196 (51.353 %)	1440 (49.332 %)	1417 (49.597 %)	
Female	1099 (44.208 %)	1133 (48.647 %)	1479 (50.668 %)	1440 (50.403 %)	
Race/ethnicity (%)					<0.001
Mexican American	434 (17.458 %)	462 (19.837 %)	585 (20.041 %)	591 (20.686 %)	
Other Hispanic	205 (8.246 %)	221 (9.489 %)	272 (9.318 %)	234 (8.190 %)	
Non-Hispanic White	930 (37.409 %)	881 (37.827 %)	1248 (42.754 %)	1319 (46.167 %)	
Non-Hispanic Black	789 (31.738 %)	596 (25.590 %)	573 (19.630 %)	444 (15.541 %)	
Other Race	128 (5.149 %)	169 (7.256 %)	241 (8.256 %)	269 (9.415 %)	
Education (%)					<0.001
Less than high school	1154 (46.420 %)	854 (36.668 %)	915 (31.346 %)	679 (23.766 %)	
High school	592 (23.813 %)	572 (24.560 %)	682 (23.364 %)	641 (22.436 %)	
More than high school	735 (29.566 %)	898 (38.557 %)	1319 (45.187 %)	1535 (53.728 %)	
Not recorded	5 (0.201 %)	5 (0.215 %)	3 (0.103 %)	2 (0.070 %)	
Marital status (%)					<0.001
Married	1221 (49.115 %)	1293 (55.517 %)	1595 (54.642 %)	1740 (60.903 %)	
Single	1077 (43.323 %)	914 (39.244 %)	1157 (39.637 %)	972 (34.022 %)	
Living with a partner	141 (5.672 %)	91 (3.907 %)	126 (4.317 %)	119 (4.165 %)	
Not recorded	47 (1.891 %)	31 (1.331 %)	41 (1.405 %)	26 (0.910 %)	
Poverty to income ratio (%)					<0.001
≤1.0	678 (27.273 %)	491 (21.082 %)	552 (18.911 %)	409 (14.316 %)	
1.0–3.0	1095 (44.047 %)	1017 (43.667 %)	1216 (41.658 %)	1093 (38.257 %)	
>3.0	478 (19.228 %)	604 (25.934 %)	888 (30.421 %)	1142 (39.972 %)	
Not recorded	235 (9.453 %)	217 (9.317 %)	263 (9.010 %)	213 (7.455 %)	
Hypertension history (%)					<0.001
Yes	1571 (63.194 %)	1403 (60.240 %)	1731 (59.301 %)	1553 (54.358 %)	
No	903 (36.323 %)	918 (39.416 %)	1181 (40.459 %)	1298 (45.432 %)	
Not recorded	12 (0.483 %)	8 (0.343 %)	7 (0.240 %)	6 (0.210 %)	
Drinking (%)					0.056
Yes	1550 (62.349 %)	1479 (63.504 %)	1883 (64.508 %)	1911 (66.888 %)	
No	810 (32.582 %)	740 (31.773 %)	906 (31.038 %)	821 (28.736 %)	
Not recorded	126 (5.068 %)	110 (4.723 %)	130 (4.454 %)	125 (4.375 %)	
Smoking (%)					<0.001
Yes	1415 (56.919 %)	1205 (51.739 %)	1403 (48.064 %)	1258 (44.032 %)	
No	1043 (41.955 %)	1106 (47.488 %)	1493 (51.148 %)	1581 (55.338 %)	
Not recorded	28 (1.126 %)	18 (0.773 %)	23 (0.788 %)	18 (0.630 %)	
Condition (%)					<0.001
Diabetes	1894 (76.187 %)	1725 (74.066 %)	2070 (70.915 %)	1862 (65.173 %)	
Prediabetes	592 (23.813 %)	604 (25.934 %)	849 (29.085 %)	995 (34.827 %)	

Note: Q1–Q4: Grouped by quartile according to OBS.
Mean ± SD for continuous variables: *P* value was calculated by Kruskal-Wallis rank-sum test.
% for categorical variables: *P* value was calculated by chi-square test.

cause mortality compared to those in the Q1 group (HR 0.607, 95 % CI 0.544–0.677, *p* for trend <0.0001). In the fully adjusted model (Model 3), each unit increase in OBS was linked to a 1.8 % reduction in the risk of all-cause mortality (HR 0.982, 95 % CI 0.976–0.987, $p < 0.0001$). When comparing Q4 to Q1, the risk of all-cause mortality was reduced by 28.1 % (HR 0.719, 95 % CI 0.643–0.804, *p* for trend <0.0001).

Table 2 also shows the Cox regression models assessing the relationship between OBS and cardiovascular mortality. In the unadjusted model (Model 1), we observed a significant reduction in the risk of cardiovascular mortality with increasing OBS (HR 0.956, 95 % CI 0.946–0.966, $p < 0.0001$). Compared to OBS Q1, the Q4 group exhibited a 58.3 % lower risk of cardiovascular mortality (HR 0.417, 95 % CI 0.339–0.514, p for trend <0.0001). After adjusting for sex, age, and race in Model 2, each unit increase in OBS was associated with a 4 % reduction in the risk of cardiovascular mortality (HR 0.960, 95 % CI 0.949–0.970, $p < 0.0001$). Participants in the Q4 group had a 53.5 % lower risk of cardiovascular mortality compared to those in the Q1 group (HR 0.465, 95 % CI 0.376–0.575, *p* for trend <0.0001). In the fully adjusted model (Model 3), each unit increase in OBS corresponded to a 3 % reduction in the risk of cardiovascular mortality (HR 0.970, 95 % CI 0.959–0.981, $p < 0.0001$). The risk of cardiovascular mortality in the OBS Q4 group was 43.3 % lower than in the Q1 group (HR 0.567, 95 % CI 0.455–0.705, *p* for trend <0.0001). The PH assumption was confirmed to be met using the Schoenfeld goodness-of-fit test (GLOBAL $p = 0.3072$ and 0.3637). We also conducted RCS analysis based on the fully adjusted Cox regression model (Model 3), revealing a negative correlation between OBS and both all-cause and cardiovascular mortality in patients with diabetes and prediabetes (Fig. 3).

3.3. Subgroup analysis

We conducted a stratified analysis to assess the robustness of the regression results on the relationship between OBS and mortality among patients with diabetes and prediabetes across different subgroups. The results are presented in Table 3. The analysis indicated that in most subgroups, the relationship between OBS and mortality remained consistent, showing a negative correlation, and these associations were statistically significant. Additionally, education level appeared to

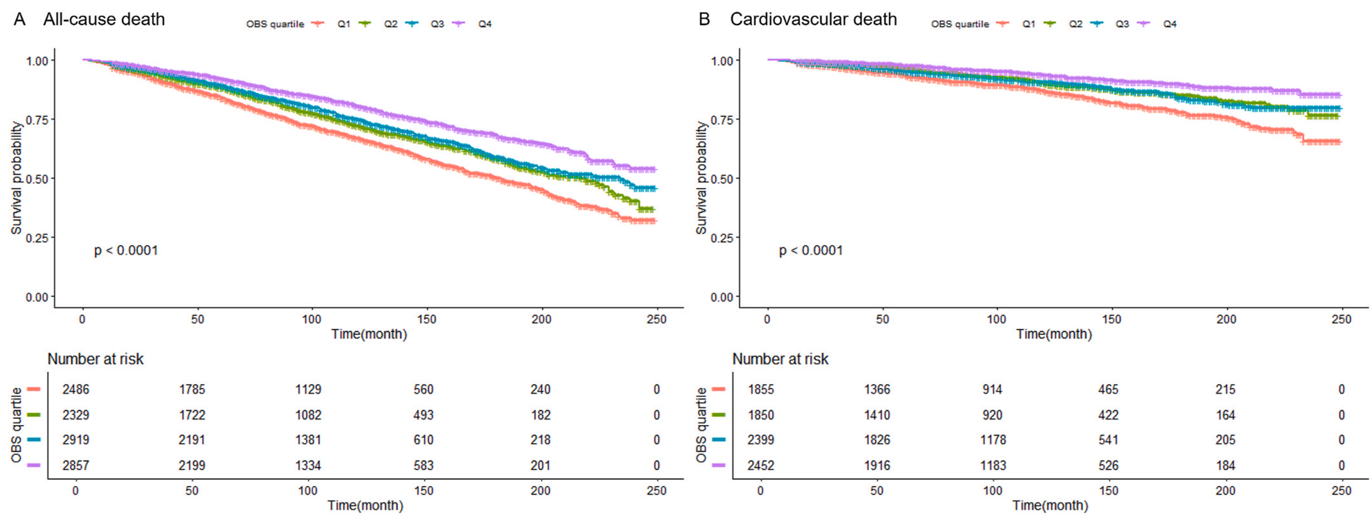

Fig. 2. K–M analyses for mortality among the four groups. Q1–Q4 quartiles 1–4, OBS oxidative balance score **A** All-cause mortality. **B** cardiovascular mortality hyperglycemia ratio.

Table 2
Multivariable Cox regression models analysis of the relationship between OBS and mortality in diabetes and prediabetes.

Exposure	Model 1	Model 2	Model 3
	HR (95 % CI) *P* value	HR (95 % CI) *P* value	HR (95 % CI) *P* value
Cardiovascular death			
OBS	0.956 (0.946, 0.966) <0.00001	0.960 (0.949, 0.970) <0.00001	0.970 (0.959, 0.981) <0.00001
OBS (Quartile)			
Q1 (3–12)	Reference	Reference	Reference
Q2 (13–18)	0.648 (0.532, 0.789) 0.00002	0.671 (0.550, 0.817) 0.00008	0.739 (0.606, 0.903) 0.00300
Q3 (19–23)	0.663 (0.553, 0.795) <0.00001	0.745 (0.619, 0.896) 0.00182	0.833 (0.690, 1.004) 0.05522
Q4 (24–36)	0.417 (0.339, 0.514) <0.00001	0.465 (0.376, 0.575) <0.00001	0.567 (0.455, 0.705) <0.00001
P for Trend	<0.00001	<0.00001	<0.00001
All-cause death			
OBS	0.968 (0.963, 0.973) <0.00001	0.973 (0.967, 0.978) <0.00001	0.982 (0.976, 0.987) <0.00001
OBS (Quartile)			
Q1 (3–12)	Reference	Reference	Reference
Q2 (13–18)	0.778 (0.703, 0.861) <0.00001	0.783 (0.707, 0.867) <0.00001	0.833 (0.752, 0.923) 0.00049
Q3 (19–23)	0.706 (0.640, 0.778) <0.00001	0.765 (0.693, 0.845) <0.00001	0.830 (0.751, 0.918) 0.00027
Q4 (24–36)	0.532 (0.478, 0.592) <0.00001	0.607 (0.544, 0.677) <0.00001	0.719 (0.643, 0.804) <0.00001
P for Trend	<0.00001	<0.00001	<0.00001

Model 1, unadjusted; Model 2, adjusted for age, gender, race; Model 3, adjusted for age, gender, race, education, marital status, poverty to income ratio, hypertension history, drinking, smoking.

interact with OBS, suggesting a potential moderating effect (p for interaction <0.05).

4. Discussion

This study is the first to evaluate the relationship between the OBS and survival outcomes among patients with diabetes and prediabetes based on a large sample from the NHANES. Among the 10,591 participants with diabetes or prediabetes across 10 NHANES cycles (1999–2018), a negative correlation was observed between OBS and both all-cause and cardiovascular mortality. This relationship was found to be highly robust, indicating that higher OBS scores are associated with lower risks of both types of mortality. Our findings underscore the importance of adhering to an antioxidant-rich diet and lifestyle as a preventive strategy for managing diabetes and prediabetes.

Insulin resistance plays a pivotal role in the pathogenesis of diabetes and prediabetes [11,12]. Oxidative stress is considered a detrimental factor contributing to insulin resistance. Under physiological conditions, there is a balance between the production of reactive oxygen species (ROS) and cellular antioxidant defense mechanisms [20]. When this balance is disrupted, leading to an excess production of ROS beyond the neutralizing capacity of the antioxidant system, oxidative stress occurs, which can inhibit insulin signaling and reduce insulin sensitivity [21]. ROS can induce serine/threonine phosphorylation of insulin receptor substrate-1 (IRS-1), which inhibits its tyrosine phosphorylation and disrupts insulin signaling [22]. Normally, insulin binding to its receptor leads to tyrosine phosphorylation of IRS-1, activating the downstream PI3K/Akt pathway. However, ROS-induced aberrant phosphorylation hampers this process [23]. Additionally, ROS can activate both the NF-κB (nuclear factor κB) and JNK (c-Jun N-terminal kinase) signaling pathways, which play critical roles in regulating inflammatory responses and insulin signaling [24]. Activation of NF-κB induces the expression of various inflammatory cytokines, such as TNF-α and IL-6, which further inhibit insulin signaling [24]. Simultaneously, activation of JNK leads to serine/threonine phosphorylation of IRS-1, exacerbating insulin resistance [24]. Additionally, β-cells are particularly susceptible to oxidative stress due to their low levels of antioxidant enzymes, such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) [25]. Oxidative stress can diminish the expression of these critical β-cell genes, induce cell death, decrease insulin production, and impair glucose-stimulated insulin secretion [25–27]. Furthermore, oxidative stress can activate inflammatory responses, leading to the production of inflammatory mediators such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) [28,29]. These inflammatory mediators exacerbate oxidative stress, creating a vicious cycle that can trigger insulin resistance and promote the development of diabetes [30]. Under hyperglycemic conditions, this inflammatory response may further deteriorate, accelerating the progression of chronic complications associated with diabetes [30]. Moreover, this subclinical inflammation can damage β-cells in the pancreas, impairing normal insulin secretion and ultimately leading to elevated blood glucose levels [31]. Interestingly, chronic inflammation observed in various conditions, such as diabetes and atherosclerosis, is often driven by excessive mitochondrial ROS production [32,33].

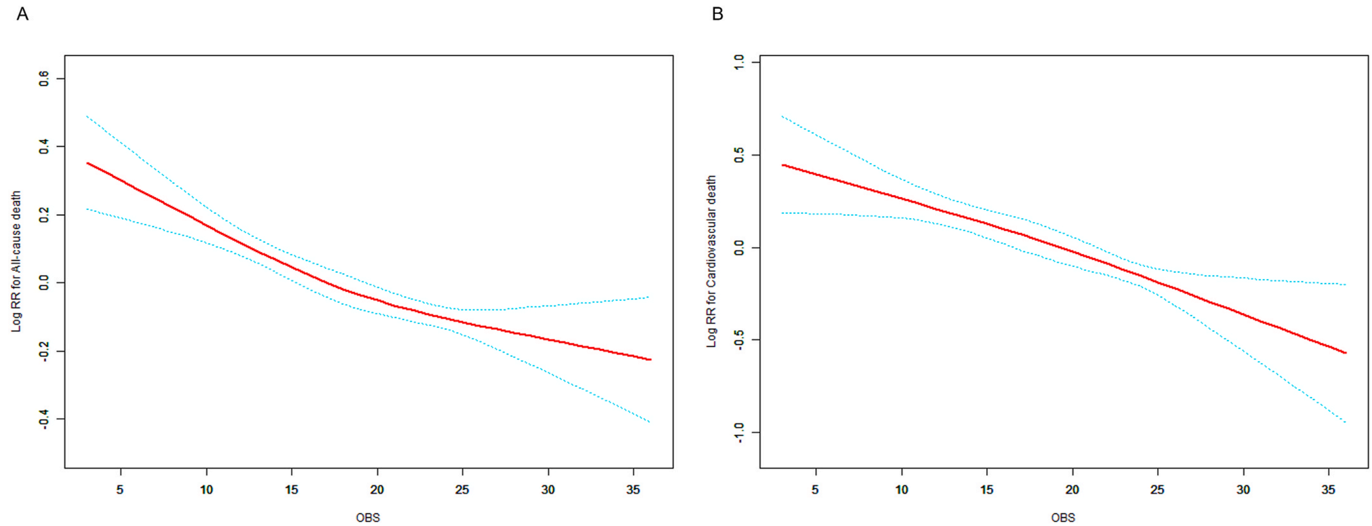

Fig. 3. The association of OBS with all-cause (A) and cardiovascular mortality (B) among diabetes and prediabetes visualized by restricted cubic spline.

Our study indicates that a high OBS, which reflects greater exposure to antioxidant factors, acts as a protective factor against mortality in patients with diabetes and prediabetes, aligning with findings from previous research. Recently, a cross-sectional study by Wu et al. involving 5233 individuals from the U.S. population found a gender-dependent negative association between OBS and diabetes prevalence [15]. Xu et al. reported that individuals with higher OBS had lower susceptibility to metabolic syndrome (MetS) in a study involving 11,171 participants, and that increased OBS was associated with reduced risk of all-cause mortality in MetS subjects [34]. Given that insulin resistance is a core feature of MetS, Xu's findings corroborate our results. Additionally, two cohort studies by Xuan et al. involving 2125 diabetes patients in Germany reported that levels of oxidative stress biomarkers were associated with major cardiovascular events and all-cause mortality, highlighting that an imbalance in the redox system is a significant contributor to premature death in diabetes patients [35]. Although research on the impact of OBS on mortality among diabetes and prediabetes patients is limited, several studies have examined the relationship between individual OBS components and mortality. A meta-analysis focusing on diabetic patients demonstrated that a high-fiber diet with antioxidant properties can improve blood glucose control, lipid profiles, and reduce premature mortality [36]. A cohort study by Liu et al. found that lower levels of serum vitamin B12 and folate were significantly associated with increased cardiovascular disease mortality risk in diabetes patients [37]. Additionally, there is evidence that diet and physical activity can reduce or delay the onset of diabetes in individuals with impaired glucose tolerance (IGT) [38]. Smoking has been shown to significantly increase the risk of total mortality and cardiovascular events in diabetes patients, whereas smoking cessation is associated with risk reduction [39].

This study has several strengths. First, we utilized a large sample size with a long follow-up period, resulting in stable and reliable outcomes with strong statistical power. Second, by using OBS, a composite index, to assess oxidative stress rather than relying on a single indicator, we could more comprehensively understand the relationship between oxidative stress and mortality in patients with diabetes and prediabetes. Third, the use of a nationally representative, high-quality sample enhances the generalizability of our findings. However, there are some limitations to this study. Due to database constraints, it was challenging to include all dietary and lifestyle factors related to oxidative stress in the OBS calculation. For instance, certain components like flavonoids were not fully recorded in the database. Moreover, the NHANES database does not provide specific data to distinguish between Type 1 Diabetes Mellitus (T1DM) and Type 2 Diabetes Mellitus (T2DM). Therefore, our results cannot be explicitly generalized to differentiate between T1DM and T2DM. Additionally, although we adjusted for several potential confounders in our multivariable models, OBS may still be influenced by other factors. Lastly, our investigation is based on NHANES data, which is specific to the U.S. population, and the results may not be generalizable to other populations.

5. Conclusion

In conclusion, our study of 10 NHANES cycles (1999–2018) involving 10,591 participants demonstrates a negative correlation between OBS and all-cause mortality as well as cardiovascular mortality among diabetes and prediabetes patients. Higher OBS scores, indicating greater exposure to antioxidant factors relative to pro-oxidant factors in diet and lifestyle, were associated with lower risks of all-cause and cardiovascular mortality. These findings underscore the importance of adhering to antioxidant-rich diets and lifestyles in strategies aimed at preventing and managing diabetes and prediabetes.

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Ethics approval and consent to participate

The National Health and Nutrition Examination Survey (NHANES) is a publicly accessible database approved by the Institutional Review Board (IRB) of the National Center for Health Statistics. All participants provided written informed consent during their participation in the national survey. As secondary analysis does not require additional IRB approval, this study was exempt from further ethical review and approval.

Disclosure statement

The authors have nothing to disclose.

CRediT authorship contribution statement

Zichen Xu: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal

Table 3
Stratified analysis of the relationship between OBS and mortality in diabetes and prediabetes.

	Cardiovascular mortality	All-cause mortality
	HR (95 % CI) P value	HR (95 % CI) P value
Age		
≤60	0.947 (0.923, 0.972) <0.0001	0.976 (0.963, 0.988) 0.0002
>60	0.971 (0.960, 0.983) <0.0001	0.980 (0.974, 0.986) <0.0001
P for interaction	0.0801	0.5448
Gender		
Male	0.970 (0.956, 0.984) <0.0001	0.980 (0.973, 0.988) <0.0001
Female	0.970 (0.954, 0.987) 0.0005	0.983 (0.975, 0.992) 0.0001
P for interaction	0.9636	0.5933
Race		
Mexican American	0.961 (0.929, 0.994) 0.0213	0.982 (0.967, 0.997) 0.0166
Other Hispanic	1.019 (0.954, 1.088) 0.5835	0.995 (0.966, 1.024) 0.7243
Non-Hispanic White	0.972 (0.958, 0.986) <0.0001	0.978 (0.971, 0.986) <0.0001
Non-Hispanic Black	0.960 (0.936, 0.984) 0.0014	0.990 (0.977, 1.002) 0.1101
Other Race	0.983 (0.910, 1.061) 0.6556	0.964 (0.931, 0.999) 0.0440
P for interaction	0.5119	0.3854
Education		
Less than high school	0.982 (0.965, 0.999) 0.0377	0.989 (0.980, 0.998) 0.0147
High school	0.981 (0.960, 1.004) 0.0992	0.985 (0.974, 0.997) 0.0149
More than high school	0.948 (0.930, 0.967) <0.0001	0.971 (0.962, 0.981) <0.0001
P for interaction	0.0441	0.0646
Marital status		
Married	0.970 (0.954, 0.985) 0.0002	0.980 (0.972, 0.988) <0.0001
Single	0.975 (0.960, 0.991) 0.0025	0.983 (0.975, 0.992) 0.0001
Living with a partner	0.857 (0.774, 0.949) 0.0031	0.982 (0.940, 1.026) 0.4210
P for interaction	<0.0001	0.7672
Poverty to income ratio		
Low	0.970 (0.946, 0.993) 0.0124	0.979 (0.966, 0.991) 0.0011
Middle	0.976 (0.960, 0.992) 0.0032	0.984 (0.976, 0.992) 0.0001
High	0.967 (0.945, 0.989) 0.0038	0.981 (0.969, 0.993) 0.0016
P for interaction	0.4581	0.8882
Smoking		
Yes	0.963 (0.948, 0.978) <0.0001	0.979 (0.972, 0.987) <0.0001
No	0.978 (0.962, 0.995) 0.0096	0.986 (0.977, 0.995) 0.0020
P for interaction	0.1649	0.7281
Drinking		
Yes	0.964 (0.949, 0.978) <0.0001	0.979 (0.972, 0.987) <0.0001
No	0.978 (0.960, 0.996) 0.0151	0.983 (0.973, 0.993) 0.0007
P for interaction	0.2947	0.1042
Hypertension history		
Yes	0.972 (0.965, 0.980) <0.0001	0.982 (0.975, 0.989) <0.0001
No	0.967 (0.959, 0.975) <0.0001	0.982 (0.972, 0.992) 0.0004
P for interaction	0.5017	0.1683
Diabetes status		
Diabetes	0.968 (0.956, 0.980) <0.0001	0.983 (0.976, 0.989) <0.0001
Prediabetes	0.982 (0.959, 1.006) 0.1393	0.978 (0.966, 0.990) 0.0004
P for interaction	0.3275	0.4325

Stratified analysis was constructed based on model 3. In each case, the model was not adjusted for the stratification variable itself.

analysis, Data curation, Conceptualization. **Daoqin Liu:** Writing – review & editing, Software, Formal analysis, Data curation, Conceptualization. **Ying Zhai:** Writing – review & editing, Visualization, Validation, Supervision, Software, Formal analysis, Data curation, Conceptualization. **Yu Tang:** Writing – review & editing, Software, Resources, Project administration, Formal analysis, Data curation. **Luqing Jiang:** Validation, Software, Resources, Investigation, Formal analysis, Data curation. **Lei Li:** Writing – review & editing, Supervision, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Qiwen Wu:** Writing – review & editing, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no competing interests.

Data availability

Data will be made available on request.

Acknowledgments

Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.redox.2024.103327.

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