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Association between the oxidative balance score and all-cause and cardiovascular mortality in populations with cardiovascular-kidney-metabolic syndrome stages 0–3: a prospective cohort study

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Association between the oxidative balance score and all-cause and cardiovascular mortality in populations with cardiovascular-kidney-metabolic syndrome stages 0–3: a prospective cohort study

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Recall international standards which contribution qualifies for authorship.

Abstract

Background: This study aims to investigate the association between the Oxidative Balance Score (OBS) and mortality outcomes in individuals with cardiovascular-kidney-metabolic (CKM) syndrome stages 0–3.

Methods: Using data from ten National Health and Nutrition Examination Survey cycles (1999-2018), we analyzed 17677 participants with CKM syndrome stages 0–3. OBS was calculated using 20 components (16 nutritional elements and 4 lifestyle factors). Cox proportional hazards models evaluated associations between OBS and

mortality outcomes, adjusting for relevant covariates.

Results: During the follow-up period (mean 122.4 months), there were 1983 deaths (8.16% of participants), of which 439 (1.71%) were due to cardiovascular disease. Multifactorial Cox regression showed that each standard deviation increment in the OBS corresponded to a significant 13% decrease in all-cause mortality risk (HR 0.87, 95% CI 0.82-0.92, P<0.001) and an 18% reduction in cardiovascular mortality risk (HR 0.82, 95% CI 0.72-0.92, P<0.001). When examining quartiles, individuals in the highest OBS quartile exhibited a 33% reduced risk of all-cause mortality (HR 0.67, 95% CI 0.57-0.79, P for trend <0.001) and a 34% lower cardiovascular mortality risk (HR 0.66, 95% CI 0.46-0.94, P for trend <0.001) compared to those in the lowest quartile. Subgroup analyses indicated that this protective relationship was most evident in CKM syndrome stages 1 and 2, with a significant interaction detected between OBS and CKM stage for all-cause mortality (P for interaction <0.05).

Conclusions: The study demonstrated that elevated OBS was significantly associated with reduced risks of both all-cause and cardiovascular mortality among populations with CKM syndrome stages 0–3.

Keywords: Cardiovascular-kidney-metabolic syndrome; Oxidative Balance Score; Mortality; Cardiovascular disease; Oxidative stress.

Introduction

In 2023, the American Heart Association (AHA) conceptualization of cardiovascular-kidney-metabolicceted syste (CKM) syndrome represents a significant

advancement in understanding interconnected health conditions[1]. This framework characterizes CKM as a multifamic disorder where obesity, metabolic disturbances, renal impairment, diabetes, and cardiovascular pathologies interact through shared pathophysiological mechanisms. The prevalence of CKM syndrome stages 0–3 reached approximately 90.8% between 2011-2020, highlighting its status as a critical public health concern[2]. Mortality data underscores the severity of this condition: patients with diabetes experience a 10-year mortality of 11.5%, while this figure escalates dramatically to 31.1% when diabetes co-occurs with chronic kidney disease (CKD)[3]. Heart failure and atherosclerotic cardiovascular complications constitute the predominant causes of death in these populations[4, 5]. To facilitate clinical classification, the AHA developed a five-tier staging system, with stages 0–3 representing the progression from initial risk factor presence without end-organ damage to established multi-organ involvement[1]. According to the AHA Scientific Advisory Panel, management strategies for individuals with CKM syndrome stages 0–3 should prioritize cardiovascular event prevention[1].

Research indicates that oxidative stress serves as a fundamental mechanism underlying both the initiation and advancement of CKM syndrome and its constituent disorders[6]. This pathological state, defined by dysregulation between reactive oxygen species (ROS) generation and antioxidant protective systems, triggers cellular injury, compromises endothelial function, and perpetuates inflammatory processes[7, 8]. In the context of CKD, heightened oxidative stress hastens the deterioration of renal function while simultaneously intensifying cardiovascular pathology[9].

Likewise, oxidative mechanisms underlie the development of insulin resistance, facilitating the onset and progression of diabetes[10, 11]. Within cardiovascular tissues, elevated ROS concentrations promote atherogenesis, adverse myocardial structural changes, and heart failure[12]. The Oxidative Balance Score (OBS) has been developed as an integrative metric that combines various pro-oxidant and antioxidant elements, encompassing nutritional factors, behavioral determinants, and supplementation practices[13]. This aggregate measure offers a comprehensive evaluation of oxidative status, where elevated OBS values reflect enhanced antioxidant capacity, while reduced scores indicate predominant pro-oxidant activity[13]. Contemporary investigations have demonstrated inverse relationships between OBS magnitude and the occurrence of diabetes, kidney dysfunction, and adverse cardiovascular events[14-16]. Nevertheless, the potential association between OBS and mortality outcomes, specifically in populations with CKM syndrome stages 0–3, remains unexplored, despite substantial evidence linking oxidative mechanisms to the pathobiology of this multisystem condition.

Therefore, this study aims to examine the relationship between OBS and mortality outcomes—both overall and cardiovascular-specific—among individuals diagnosed with CKM syndrome stages 0–3, utilizing the comprehensive dataset available through the National Health and Nutrition Examination Survey (NHANES). Our central hypothesis proposes that elevated OBS values, indicative of optimized oxidative equilibrium, will correlate with reduced mortality risk, potentially with differential impacts across the spectrum of CKM staging. Elucidating the connections

between oxidative status parameters and survival outcomes within the CKM syndrome population may yield critical insights for patient risk assessment and guide the formulation of specifically tailored antioxidant therapeutic strategies.

Methods

Study population

This study utilizes data from the NHANES, which gathers extensive health information from a representative sample of the non-institutionalized United States population. NHANES employs a sophisticated, multi-level probability sampling methodology with stratification to ensure nationally representative findings[17]. NHANES adheres to the ethical principles outlined in the Helsinki Declaration and has received formal approval from the National Center for Health Statistics Ethics Review Board. Written informed consent was obtained from all participants prior to data collection. Comprehensive methodological protocols and the complete datasets used in this analysis are publicly available through the official NHANES website (www.cdc.gov/nchs/nhanes/).

This study used data from 10 NHANES cycles (from 1999-2000 to 2017-2018). From the initial 101316 participants, we excluded pregnant individuals and participants aged <20 years. We excluded those with missing data on key variables necessary for determining CKM syndrome stages, including anthropometric measurements, metabolic parameters, glycemic markers, blood pressure values, kidney function indicators, and smoking status information. In addition, we excluded participants who had missing OBS. Following the CKM syndrome staging assessment,

we excluded additional participants with established clinical cardiovascular disease (CVD) and those without applicable follow-up data. The final analytic sample comprised 17677 participants with CKM syndrome stages 0–3. Figure 1 presents the study population selection process.

Definitions of CKM syndrome stages 0 to 3

The AHA has established a staging system for CKM syndrome in its presidential advisory[18]. This classification ranges from Stage 0 to Stage 3. Individuals at Stage 0 demonstrate no CKM risk factors. At Stage 1, populations exhibit excessive adiposity or adipose tissue dysfunction. Progression to Stage 2 is marked by the presence of metabolic abnormalities or CKD of moderate to high risk. Stage 3 represents subclinical cardiovascular disease, identified either through an elevated 10-year cardiovascular risk (≥20% according to the PREVENT equation) or CKD, categorized as very high risk[19]. The classification of CKD follows the guidelines established by Kidney Disease Improving Global Outcomes, utilizing the estimated glomerular filtration rate (eGFR) and the urine albumin-to-creatinine ratio[20]. The 2021 CKD Epidemiology Collaboration creatinine equation, which excludes race and ethnicity variables, was employed for eGFR determination[21]. Supplementary Tables 1 and 2 provide the PREVENT equation parameters and detailed staging criteria.

Definition of OBS

The OBS evaluates 20 distinct components: 16 nutritional elements and 4 lifestyle factors[22]. These are categorized as either antioxidant-promoting (15 components) or oxidative stress-inducing (5 components). Nutritional information

was gathered from the baseline dietary recall interview, encompassing dietary fiber, carotenoids (assessed as retinol equivalents), several B vitamins (riboflavin, niacin, B6, folate, and B12), antioxidant vitamins (C and E—measured as Alpha-Tocopherol Equivalents), essential minerals (calcium, magnesium, zinc, copper, selenium), and factors that potentially influence oxidative status (total fat and iron). Lifestyle evaluation included exercise patterns, anthropometric measurements [using body mass index (BMI)], alcohol consumption, and smoking behavior (quantified via cotinine levels). Within this framework, total fat, iron, BMI, alcohol intake, and cotinine were identified as oxidative stress-inducing, while all other components were classified as antioxidant-promoting.

For the evaluation of alcohol consumption, participants were divided into three groups based on research literature[22]: abstainers (2 points), moderate consumers (women: ≤15g/day; men: ≤30g/day) (1 point), and heavy consumers (women: >15g/day; men: >30g/day) (0 points). The remaining elements were assessed using sex-specific tertile distributions. Antioxidant-promoting components were scored progressively (0-2 points) from lowest to highest tertiles, while oxidative stress-inducing elements were scored in reverse, with greater exposure receiving lower scores[22]. The total OBS was derived by summing individual component values, resulting in a possible range of 3-36, where higher scores reflect enhanced antioxidative capacity. Comprehensive details of the scoring system are available in Supplementary Table 3.

Outcomes

Our study focused on two main endpoints: all-cause mortality and deaths attributable to cardiovascular conditions. We accessed mortality data through the CDC's National Death Index (NDI) database in the United States. The observation period for each participant extended from their initial baseline interview until either their death or December 31, 2019, which represents the latest NDI database update. To identify deaths specifically related to cardiovascular causes, we utilized the International Classification of Diseases, 10th Revision (ICD-10) coding system. The relevant cardiovascular mortality codes included I00–I09 (rheumatic heart disease), I11 (hypertensive heart disease), I13 (hypertensive heart and kidney disease), and I20–I51 (ischemic and other forms of heart disease).

Data collection

We collected comprehensive participant information, including demographic characteristics, physical assessment metrics, laboratory values, lifestyle factors, and health conditions. Demographic information encompassed age, sex, racial background, educational attainment, and marital status. Physical assessments included body mass index, abdominal circumference, and blood pressure parameters (systolic and diastolic, averaged from three separate readings). Laboratory analyses measured kidney function (estimated glomerular filtration rate, urine albumin-to-creatinine ratio), serum uric acid levels, glycemic indicators (fasting glucose, HbA1c), and lipid profile components (triglycerides, total cholesterol, HDL-C, and LDL-C). We also documented lifestyle behaviors (tobacco and alcohol use) and recorded the presence of chronic conditions. Hypertension was identified when participants exhibited

systolic readings ≥130 mmHg or diastolic readings ≥80 mmHg, reported prior physician diagnosis, or used antihypertensive therapy. Diabetes was established through fasting glucose exceeding 126 mg/dL, HbA1c ≥6.5%, self-reported medical diagnosis, or use of glucose-regulating medications. Metabolic syndrome diagnosis required the presence of at least three of these criteria: elevated waist circumference (≥102 cm in males, ≥88 cm in females); reduced HDL-C (<40 mg/dL in males, <50 mg/dL in females); triglycerides ≥150 mg/dL; elevated blood pressure (as defined for hypertension); or fasting glucose ≥100 mg/dL. Detailed methodological protocols for all measurements are publicly available through the Centers for Disease Control and Prevention's NHANES website (www.cdc.gov/nchs/nhanes/).

Statistical analysis

Statistical analysis followed methodological guidelines established by the Centers for Disease Control and Prevention. To account for NHANES' complex multilevel stratified probability sampling framework, we incorporated appropriate strata, primary sampling units, and sampling weights throughout our analyses. We categorized participants into four equal groups based on the OBS quartiles (Q1-Q4). For continuous variables, we reported survey-weighted means with corresponding 95% confidence intervals, while categorical variables were expressed as counts with weighted percentages. To evaluate differences in baseline characteristics across OBS quartile groups, we employed survey-weighted linear regression techniques for continuous measurements and survey-weighted Chi-square testing for categorical variables.

Our analyses evaluated the OBS as both a continuous and categorical predictor. To compare event rates between groups, we constructed Kaplan-Meier survival curves and employed log-rank tests. The association between OBS and outcomes was assessed through Cox proportional hazards models, providing hazard ratios (HRs) with corresponding 95% confidence intervals (CIs). We verified the proportional hazards assumption using Schoenfeld residual analysis, which confirmed no significant violations. Our analytical approach involved three progressive models: an unadjusted baseline (Model 1), followed by adjustment for demographic factors including age, gender, and race (Model 2), and finally, a comprehensive model (Model 3) controlling for multiple covariates age, gender, race, educational attainment, marital status, smoking habits, alcohol consumption, presence of hypertension, diabetes, metabolic syndrome, body mass index, waist circumference, systolic and diastolic blood pressure, glycated hemoglobin, fasting blood glucose, total cholesterol, HDL and LDL cholesterol, triglycerides, uric acid, and estimated glomerular filtration rate. To examine potential non-linear relationships between OBS and clinical outcomes, we implemented restricted cubic spline regression with knots positioned at the 10th, 50th, and 90th percentiles of the OBS distribution.

Several baseline variables in the NHANES dataset contained missing values, though none exceeded 9% missingness (detailed in Supplementary Table 4). To address this, we implemented multiple imputation techniques using the "MICE" package in R. The imputation process employed wholly conditional specification methods appropriate for data with arbitrary missing patterns, generating 20 complete

datasets for both continuous and categorical variables.

To assess the consistency of our findings and identify potential effect modifications, we conducted stratified analyses across various subpopulations. These subgroup analyses were performed according to age (dividing participants at the 65-year threshold), gender, smoking status (smokers versus non-smokers), presence or absence of hypertension, diabetic status, and across the spectrum of CKM syndrome stages (0 through 3).

To validate our findings, we implemented various sensitivity analyses. Initially, we reanalyzed the data without applying multiple imputation techniques for missing covariate values. Subsequently, we conducted an additional analysis excluding mortality events occurring within the first 24 months of follow-up to address potential reverse causality.

Statistical computations were performed using R software version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was established at $P < 0.05$, with all statistical tests being two-sided.

Results

Baseline characteristics of the participants

Table 1 summarizes the baseline demographic and clinical characteristics of our study cohort (N=17677) with CKM syndrome stages 0-3, stratified by OBS quartiles. Participants in the highest OBS quartile (Q4) compared to those in the lowest quartile (Q1) were characterized by advanced age, female predominance, non-Hispanic white ethnicity, higher educational attainment, and greater likelihood of being married. The

distribution of CKM syndrome showed higher proportions of stages 0 and 1 in Q4. These individuals displayed more favorable metabolic profiles, including reduced BMI, smaller waist circumference, lower SBP, decreased glycemic markers (HbA1c, FBG), improved lipid parameters (lower TC, LDL, TG; higher HDL), reduced UA levels, and enhanced renal function (higher eGFR). Additionally, Q4 participants had a lower prevalence of smoking, hypertension, diabetes, and metabolic syndrome, while alcohol consumption was more common in this group.

Associations of the OBS with all-cause and cardiovascular mortality

Throughout the median follow-up duration of 122.4 months, we documented 1983 deaths in our cohort, representing an all-cause mortality rate of 8.16%. Of these, 439 fatalities (1.71%) were cardiovascular in origin. Kaplan-Meier survival analysis revealed distinct mortality patterns across OBS quartiles (Figure 2). A clear inverse relationship emerged between OBS levels and mortality risk. Specifically, individuals in the uppermost OBS quartile (Q4) exhibited the most favorable survival outcomes, while those in the lowest quartile (Q1) demonstrated substantially higher mortality rates for both all-cause and cardiovascular endpoints.

Table 2 presents the findings from Cox regression analyses evaluating the relationship between OBS and mortality outcomes. The unadjusted analysis (Model 1) revealed that per standard deviation increase in OBS, there was a significant 17% decrease in all-cause mortality risk (HR 0.83, 95% CI 0.79-0.87, P<0.001) and a 23% decrease in cardiovascular mortality risk (HR 0.77, 95% CI 0.69-0.86, P<0.001). When comparing extreme quartiles, individuals in the highest OBS quartile (Q4)

exhibited a 43% reduction in all-cause mortality (HR 0.57, 95% CI 0.49-0.67, *P* for trend <0.001) and a 47% reduction in cardiovascular mortality (HR 0.53, 95% CI 0.38-0.75, *P* for trend <0.001) relative to those in the lowest quartile (Q1). In Model 2, which adjusted for demographic factors (age, gender, and race), the protective associations persisted. Each standard deviation increment in OBS was linked to a 20% lower all-cause mortality risk (HR 0.80, 95% CI 0.76-0.84, *P*<0.001) and a 24% lower cardiovascular mortality risk (HR 0.76, 95% CI 0.67-0.85, *P*<0.001). The highest OBS quartile demonstrated a 46% reduction in all-cause mortality (HR 0.54, 95% CI 0.46-0.62, *P* for trend <0.001) and a 47% reduction in cardiovascular mortality (HR 0.53, 95% CI 0.37-0.75, *P* for trend <0.001) compared to the lowest quartile. The fully adjusted model (Model 3), incorporating comprehensive sociodemographic and clinical covariates, continued to demonstrate significant inverse associations. Per standard deviation increase in OBS, there was a 13% reduction in all-cause mortality risk (HR 0.87, 95% CI 0.82-0.92, *P*<0.001) and an 18% reduction in cardiovascular mortality risk (HR 0.82, 95% CI 0.72-0.92, *P*<0.001). Subjects in the highest OBS quartile experienced a 33% lower all-cause mortality risk (HR 0.67, 95% CI 0.57-0.79, *P* for trend <0.001) and a 34% lower cardiovascular mortality risk (HR 0.66, 95% CI 0.46-0.94, *P* for trend <0.001) compared to those in the lowest quartile.

Employing restricted cubic spline analysis based on the fully adjusted Cox regression model (Model 3), we identified a significant inverse relationship between OBS and mortality outcomes. Figure 3 illustrates this negative correlation pattern for

both all-cause and cardiovascular mortality among populations with cardiovascular-kidney-metabolic (CKM) syndrome stages 0–3.

Sensitivity analyses

To evaluate the consistency of the relationship between OBS and mortality outcomes, we performed stratified analyses across different CKM syndrome stages (0–3), with findings summarized in Table 3. The results demonstrated that the inverse association between OBS and mortality persisted with statistical significance across most subgroups examined. Particularly noteworthy was the observation that OBS maintained significant protective associations with both all-cause and cardiovascular mortality among populations with intermediate CKM syndrome severity (stages 1 and 2). However, this protective relationship was not statistically significant in populations at either extreme of the spectrum—those with CKM syndrome stages 0 or 3. Our interaction analysis revealed a significant effect modification between OBS and CKM syndrome stage for all-cause mortality (P for interaction<0.05). In contrast, no significant interaction was detected for cardiovascular mortality (P for interaction>0.05).

Our sensitivity analyses confirmed the robustness of our findings. The strength and direction of associations remained largely consistent in analyses using non-imputed data and after excluding mortality events from the initial 2-year follow-up period (Supplementary Tables 5–6).

Discussion

Our research represents the first thorough investigation examining OBS in relation to mortality outcomes among individuals with CKM syndrome stages 0-3. The results revealed a notable inverse relationship between OBS and both all-cause and cardiovascular mortality, suggesting that a better oxidative balance correlates with lower mortality risk in this patient population. Quantitatively, each standard deviation increment in OBS was linked to a 13% decrease in all-cause mortality risk and an 18% reduction in cardiovascular mortality risk after adjusting for a comprehensive set of sociodemographic and clinical variables. Moreover, subjects in the highest OBS quartile demonstrated 33% reduced all-cause mortality risk and 34% lower cardiovascular mortality risk compared to those in the lowest quartile. The protective associations remained consistent throughout multiple sensitivity analyses, underscoring the robustness of these observations.

The protective association observed between elevated OBS and decreased mortality risk has sound biological foundations, considering oxidative stress's well-documented role in CKM syndrome pathophysiology. Oxidative stress reflects an imbalance where ROS production exceeds antioxidant defense capabilities, resulting in cellular injury, compromised endothelial function, and persistent inflammation[7, 8]. These processes are fundamental to both development and progression across all CKM syndrome components. In renal physiology, heightened oxidative stress hastens kidney function deterioration through various mechanisms, including direct cellular damage, inflammatory responses, and tissue fibrosis[9]. Oxidative stress similarly impairs insulin sensitivity and damages pancreatic β-cells,

which are critical factors in diabetes pathogenesis and progression[10, 23]. In cardiovascular pathology, ROS enhances atherosclerotic processes, vascular inflammatory responses, and cardiac remodeling, thereby elevating the risk of adverse cardiovascular outcomes[24, 25]. Our results corroborate previous investigations examining relationships between oxidative stress and specific CKM syndrome elements. Wu and colleagues documented a sex-specific inverse relationship between OBS and diabetes prevalence in their cross-sectional evaluation of U.S. population data[14]. Additionally, research by Xu et al. revealed that subjects with higher OBS demonstrated reduced metabolic syndrome susceptibility and lower all-cause mortality risk among those with established metabolic syndrome[26]. The present investigation expands upon these earlier findings by specifically addressing CKM syndrome as an integrated clinical entity and exploring the relationship between oxidative balance indicators and mortality outcomes across different syndrome stages.

Notably, our stratified analysis demonstrated varying protective associations between OBS and mortality across different CKM syndrome stages. The inverse correlation between OBS and both all-cause and cardiovascular mortality was strongest in individuals with CKM syndrome stages 1 and 2, while this relationship lacked statistical significance in those with stages 0 and 3. We identified a significant interaction between OBS and CKM syndrome stage for all-cause mortality, though no such interaction emerged for cardiovascular mortality. This variability across CKM stages suggests that oxidative balance may influence mortality risk differently depending on the disease stage, possibly reflecting distinct pathophysiological

mechanisms and risk profiles at each stage. The non-significant association observed in stage 0 populations (those without CKM health risk factors) may suggest that oxidative balance exerts less influence on mortality outcomes in metabolically healthy individuals. Conversely, for those in stage 1 (characterized by excessive or dysfunctional adiposity) and stage 2 (presenting with metabolic risk factors or moderate to high-risk CKD), oxidative stress appears to substantially contribute to mortality risk. The absence of a significant relationship in stage 3 populations with existing subclinical CVD might indicate that once vascular damage has developed, oxidative stress becomes relatively less influential on mortality outcomes than other established risk factors or that advanced pathological alterations respond less effectively to variations in oxidative balance.

The protective relationship observed between elevated OBS and decreased mortality in populations with CKM syndrome likely involves several interrelated pathways. Enhanced oxidative balance may protect against insulin resistance through preservation of insulin signaling cascades and prevention of ROS-mediated phosphorylation of insulin receptor substrate-1 (IRS-1) at serine/threonine residues, which otherwise disrupt normal insulin action[27, 28]. A favorable oxidative environment might also suppress the activation of key inflammatory mediators, particularly NF-κB and c-Jun N-terminal kinase pathways, which play crucial roles in propagating inflammatory responses and aggravating insulin resistance[29]. With respect to renal physiology, optimal oxidative homeostasis could shield kidney structures from oxidative injury—a recognized driver of CKD progression[9].

Moreover, better oxidative status potentially maintains endothelial integrity, diminishes vascular inflammatory processes, and attenuates atherogenesis, collectively contributing to reduced cardiovascular mortality risk[30].

This study has several strengths. First, we utilized data from a large, nationally representative sample with a relatively long follow-up period, enhancing the generalizability of our findings. Second, our analysis incorporated comprehensive adjustment for potential confounders, including sociodemographic factors, lifestyle habits, and clinical parameters. Third, composite OBS rather than individual oxidative stress markers provide a more holistic assessment of oxidative status, capturing the combined effect of multiple pro-oxidant and antioxidant exposures. Finally, our stratified analyses across different CKM syndrome stages offer insights into the stage-specific associations between oxidative balance and mortality risk.

However, some limitations should be acknowledged. First, the observational nature of our study precludes causal inference, and residual confounding cannot be ruled out despite our extensive adjustment for potential confounders. Second, OBS was calculated based on a single baseline assessment, and changes in dietary patterns or lifestyle factors during the follow-up period were not accounted for. Third, the OBS components in our study, while comprehensive, may not capture all relevant pro-oxidant and antioxidant exposures. Fourth, the classification of CKM syndrome stages was based on clinical criteria and may not perfectly reflect the underlying pathophysiological processes. Lastly, despite using a nationally representative sample,

our findings may not be fully generalizable to populations with different dietary patterns, lifestyle habits, or genetic backgrounds.

Conclusions

In conclusion, our study demonstrates a significant inverse association between OBS and all-cause and cardiovascular mortality in populations with CKM syndrome stages 0–3, with the protective effect most pronounced in stages 1 and 2. These findings suggest that maintaining a favorable oxidative balance through dietary and lifestyle modifications may be an important strategy for reducing mortality risk in this population.

Declarations

Data availability

Data from the NHANES are publicly available online (www.cdc.gov/nchs/nhanes/).

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Competing interests

The authors declare no competing interests.

Ethics approval and consent to participate

The data utilized in this research comes from the NHANES, a publicly available database that received approval from the National Center for Health Statistics' Institutional Review Board, and all participants provided written informed consent at the time of participation.

Authors' contributions

Feng Gao participated in study design and manuscrpt draft. Tian Rui and Yue Zhang are contribute to the performance of research and data collection. Bicong Gao and Xiaochen Wang participated in the data collection. Yating Chen is contributed to study design and perfomance of research. Feng Gao is the senior author of this manuscript and contributed to the study design ,implementation and manuscrpt draft.All authors reviewed the article and approved the submitted publication.

Consent for publication

Not applicable.

References

1. Ndumele CE, Neeland IJ, Tuttle KR, Chow SL, Mathew RO, Khan SS, Coresh J, Baker-Smith CM, Carnethon MR, Després JP *et al*: **A Synopsis of the Evidence for the Science and Clinical Management of Cardiovascular-Kidney-Metabolic (CKM) Syndrome: A Scientific Statement From the American Heart Association**. *Circulation* 2023, **148**(20):1636-1664.
2. Aggarwal R, Ostrominski JW, Vaduganathan M: **Prevalence of Cardiovascular-Kidney-Metabolic Syndrome Stages in US Adults, 2011-2020**. *Jama* 2024, **331**(21):1858-1860.
3. Afkarian M, Sachs MC, Kestenbaum B, Hirsch IB, Tuttle KR, Himmelfarb J, de Boer IH: **Kidney disease and increased mortality risk in type 2 diabetes**. *Journal of the American Society of Nephrology : JASN* 2013, **24**(2):302-308.
4. **Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013**. *Lancet (London, England)* 2015, **385**(9963):117-171.
5. Packham DK, Alves TP, Dwyer JP, Atkins R, de Zeeuw D, Cooper M, Shahinfar S, Lewis JB, Lambers Heerspink HJ: **Relative incidence of ESRD versus cardiovascular mortality in proteinuric type 2 diabetes and nephropathy: results from the DIAMETRIC (Diabetes Mellitus Treatment for Renal Insufficiency Consortium) database**. *American journal of kidney diseases : the official journal of the National Kidney Foundation* 2012, **59**(1):75-83.

6. Ratliff BB, Abdulmahdi W, Pawar R, Wolin MS: **Oxidant Mechanisms in Renal Injury and Disease**. *Antioxidants & redox signaling* 2016, **25**(3):119-146.
7. Liguori I, Russo G, Curcio F, Bulli G, Aran L, Della-Morte D, Gargiulo G, Testa G, Cacciatore F, Bonaduce D *et al*: **Oxidative stress, aging, and diseases**. *Clinical interventions in aging* 2018, **13**:757-772.
8. Forrester SJ, Kikuchi DS, Hernandes MS, Xu Q, Griendling KK: **Reactive Oxygen Species in Metabolic and Inflammatory Signaling**. *Circulation research* 2018, **122**(6):877-902.
9. Daenen K, Andries A, Mekahli D, Van Schepdael A, Jouret F, Bammens B: **Oxidative stress in chronic kidney disease**. *Pediatric nephrology (Berlin, Germany)* 2019, **34**(6):975-991.
10. Tangvarasittichai S: **Oxidative stress, insulin resistance, dyslipidemia and type 2 diabetes mellitus**. *World journal of diabetes* 2015, **6**(3):456-480.
11. Pitocco D, Tesauro M, Alessandro R, Ghirlanda G, Cardillo C: **Oxidative stress in diabetes: implications for vascular and other complications**. *International journal of molecular sciences* 2013, **14**(11):21525-21550.
12. Münzel T, Gori T, Keaney JF, Jr., Maack C, Daiber A: **Pathophysiological role of oxidative stress in systolic and diastolic heart failure and its therapeutic implications**. *European heart journal* 2015, **36**(38):2555-2564.
13. Hernández-Ruiz Á, García-Villanova B, Guerra-Hernández EJ, Carrión-García CJ, Amiano P, Sánchez MJ, Molina-Montes E: **Oxidative Balance Scores (OBSs) Integrating Nutrient, Food and Lifestyle Dimensions: Development of the NutrientL-OBS and FoodL-OBS**. *Antioxidants (Basel, Switzerland)* 2022, **11**(2).
14. Wu C, Ren C, Song Y, Gao H, Pang X, Zhang L: **Gender-specific effects of oxidative balance score on the prevalence of diabetes in the US population from NHANES**. *Frontiers in endocrinology* 2023, **14**:1148417.
15. Wen H, Li X, Chen J, Li Y, Yang N, Tan N: **Association of oxidative balance score with chronic kidney disease: NHANES 1999-2018**. *Frontiers in endocrinology* 2024, **15**:1396465.
16. Lakkur S, Judd S, Bostick RM, McClellan W, Flanders WD, Stevens VL, Goodman M: **Oxidative stress, inflammation, and markers of cardiovascular health**. *Atherosclerosis* 2015, **243**(1):38-43.
17. Patel CJ, Pho N, McDuffie M, Easton-Marks J, Kothari C, Kohane IS, Avillach P: **A database of human exposomes and phenomes from the US National Health and Nutrition Examination Survey**. *Scientific data* 2016, **3**:160096.
18. Ndumele CE, Rangaswami J, Chow SL, Neeland IJ, Tuttle KR, Khan SS, Coresh J, Mathew RO, Baker-Smith CM, Carnethon MR *et al*: **Cardiovascular-Kidney-Metabolic Health: A Presidential Advisory From the American Heart Association**. *Circulation* 2023, **148**(20):1606-1635.
19. Khan SS, Matsushita K, Sang Y, Ballew SH, Grams ME, Surapaneni A, Blaha MJ, Carson AP, Chang AR, Ciemins E *et al*: **Development and Validation of the American Heart Association's PREVENT Equations**. *Circulation* 2024, **149**(6):430-449.
20. **KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease**. *Kidney international* 2024, **105**(4s):S117-s314.
21. Inker LA, Eneanya ND, Coresh J, Tighiouart H, Wang D, Sang Y, Crews DC, Doria A, Estrella MM, Froissart M *et al*: **New Creatinine- and Cystatin C-Based Equations to**

Estimate GFR without Race. *The New England journal of medicine* 2021, **385**(19):1737-1749.

22. Zhang W, Peng SF, Chen L, Chen HM, Cheng XE, Tang YH: **Association between the Oxidative Balance Score and Telomere Length from the National Health and Nutrition Examination Survey 1999-2002**. *Oxidative medicine and cellular longevity* 2022, **2022**:1345071.

23. Newsholme P, Cruzat VF, Keane KN, Carlessi R, de Bittencourt PI, Jr.: **Molecular mechanisms of ROS production and oxidative stress in diabetes**. *The Biochemical journal* 2016, **473**(24):4527-4550.

24. Förstermann U, Xia N, Li H: **Roles of Vascular Oxidative Stress and Nitric Oxide in the Pathogenesis of Atherosclerosis**. *Circulation research* 2017, **120**(4):713-735.

25. Steven S, Frenis K, Oelze M, Kalinovic S, Kuntic M, Bayo Jimenez MT, Vujacic-Mirski K, Helmstädter J, Kröller-Schön S, Münzel T *et al*: **Vascular Inflammation and Oxidative Stress: Major Triggers for Cardiovascular Disease**. *Oxidative medicine and cellular longevity* 2019, **2019**:7092151.

26. Xu Z, Lei X, Chu W, Weng L, Chen C, Ye R: **Oxidative balance score was negatively associated with the risk of metabolic syndrome, metabolic syndrome severity, and all-cause mortality of patients with metabolic syndrome**. *Frontiers in endocrinology* 2023, **14**:1233145.

27. Houstis N, Rosen ED, Lander ES: **Reactive oxygen species have a causal role in multiple forms of insulin resistance**. *Nature* 2006, **440**(7086):944-948.

28. Evans JL, Maddux BA, Goldfine ID: **The molecular basis for oxidative stress-induced insulin resistance**. *Antioxidants & redox signaling* 2005, **7**(7-8):1040-1052.

29. Shoelson SE, Lee J, Goldfine AB: **Inflammation and insulin resistance**. *The Journal of clinical investigation* 2006, **116**(7):1793-1801.

30. Stocker R, Keaney JF, Jr.: **Role of oxidative modifications in atherosclerosis**. *Physiological reviews* 2004, **84**(4):1381-1478.

Table 1. Baseline characteristics of the selected participants.

Variables	OBS quartile				*P* value
	Q1	Q2	Q3	Q4	
N	4355	4230	4347	4745	
Age, years	43.23(42.63,43.84)	45.61(44.87,46.35)	45.81(45.11,46.52)	45.70(45.10,46.31)	<0.001
Gender (%)					<0.001
Female	2021(47.22)	2193(51.74)	2296(52.37)	2515(52.62)	
Male	2334(52.78)	2038(48.26)	2051(47.63)	2230(47.38)	
Race (%)					<0.001
Non-Hispanic white	1577(59.92)	1765(65.54)	2025(70.42)	2401(74.86)	

Non-Hispanic black	1063(15.54)	946(13.33)	758(9.44)	595(6.33)	
Mexican American	822(9.89)	824(8.29)	797(8.10)	850(7.86)	
Others	893(14.65)	696(12.84)	767(12.05)	899(10.96)	
Education (%)					<0.001
College or above	1704(47.03)	1971(53.59)	2408(61.40)	3095(72.58)	
High school or equivalent	1122(28.24)	1060(27.11)	993(24.88)	863(17.47)	
Less than high school	1529(24.73)	1200(19.30)	946(13.72)	787(9.95)	
Marital status (%)					<0.001
Married	2099(48.77)	2224(55.31)	2420(58.76)	2797(62.25)	
Separated	966(19.00)	930(18.55)	836(15.86)	773(13.43)	
Never married	1290(32.23)	1077(26.15)	1091(25.38)	1175(24.32)	
Smoking (%)					<0.001
No	3088(67.84)	3236(74.70)	3541(80.37)	4175(88.29)	
Yes	1267(32.16)	994(25.30)	806(19.63)	570(11.71)	
Drinking (%)					0.009
No	1344(24.67)	1276(24.47)	1195(23.17)	1234(21.30)	
Yes	3011(75.33)	2954(75.53)	3152(76.83)	3511(78.70)	
Hypertension (%)					<0.001
No	2641(65.66)	2455(64.07)	2674(65.52)	3174(70.63)	
Yes	1714(34.34)	1776(35.93)	1673(34.48)	1571(29.37)	
Diabetes (%)					<0.001
No	3557(86.52)	3470(86.79)	3672(88.28)	4169(90.86)	
Yes	798(13.48)	761(13.21)	675(11.72)	576(9.14)	
Metabolic syndrome (%)					<0.001
No	2686(64.42)	2526(62.92)	2720(65.03)	3345(72.05)	
Yes	1669(35.58)	1705(37.08)	1627(34.97)	1400(27.95)	

BMI, kg/m^2	28.92(28.62,29.22)	29.10(28.83,29.36)	28.83(28.55,29.12)	27.66(27.40,27.92)	<0.001
Waist circumference, cm	98.43(97.72,99.15)	98.99(98.28,99.69)	98.28(97.55,99.00)	95.65(94.98,96.32)	<0.001
SBP, mmHg	121.73(121.11,122.36)	121.62(120.96,122.28)	121.12(120.41,121.84)	118.67(118.13,119.21)	<0.001
DBP, mmHg	70.77(70.30,71.24)	71.01(70.50,71.52)	70.90(70.41,71.40)	70.64(70.20,71.08)	0.632
HbA1c, %	5.56(5.53,5.59)	5.56(5.52,5.59)	5.52(5.49,5.55)	5.46(5.43,5.49)	<0.001
FBG, mg/dL	104.56(103.61,105.52)	104.97(103.82,106.13)	103.56(102.58,104.54)	101.43(100.55,102.31)	<0.001
TC, mg/dL	195.09(193.14,197.04)	198.37(196.70,200.04)	196.51(194.73,198.28)	194.32(192.77,195.87)	0.003
HDL, mg/dL	51.86(51.12,52.60)	52.36(51.72,53.01)	53.84(53.21,54.48)	56.06(55.46,56.67)	<0.001
LDL, mg/dL	117.85(116.25,119.45)	119.75(118.39,121.12)	117.49(116.08,118.90)	114.91(113.61,116.21)	<0.001
TG, mg/dL	132.55(127.15,137.94)	136.63(131.24,142.01)	129.77(126.17,133.38)	120.53(116.90,124.16)	<0.001
UA, mg/dL	5.55(5.50,5.60)	5.50(5.45,5.55)	5.45(5.40,5.51)	5.26(5.21,5.30)	<0.001
eGFR, mL/min/1.73 m^2	99.16(98.41,99.91)	97.11(96.25,97.98)	97.78(96.96,98.60)	98.00(97.27,98.73)	<0.001
OBS	6.25(6.10, 6.41)	15.20(15.13,15.28)	21.54(21.48,21.61)	28.42(28.32,28.51)	<0.001
CKM syndrome (%)					<0.001
Stage 0	375(10.91)	319(9.83)	418(12.32)	684(17.24)	
Stage 1	876(21.72)	779(20.54)	903(22.32)	1135(25.23)	
Stage 2	2699(62.37)	2767(64.79)	2743(61.64)	2702(55.12)	
Stage 3	405(5.00)	366(4.84)	283(3.71)	224(2.41)	
All-cause mortality (%)	556(9.18)	594(9.93)	467(8.14)	366(5.38)	<0.001
Cardiovascular mortality (%)	138(2.03)	136(2.18)	89(1.51)	76(1.11)	<0.001

526 Abbreviations: BMI, body mass index; CKM, Cardiovascular-kidney-metabolic; DBP, diastolic
527 blood pressure; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HbA1c,
528 glycated hemoglobin A1c; HDL, high density lipoprotein cholesterol; LDL, low density

lipoprotein cholesterol; OBS, Oxidative Balance Score; SBP, systolic blood pressure; TG, triglycerides; TC, total cholesterol.

All estimates accounted for complex survey designs.

Continuous variables were presented as weighted means (95% CI), and *P* values were obtained from survey-weighted linear regression. Categorical variables were presented as number (weighted percentages), and *P* values were obtained from the survey-weighted Chi-square test.

Table 2. Cox regression models analysis of the relationship between OBS and mortality in the population with CKM syndrome stages 0–3.

Exposure	Model 1		Model 2		Model 3	
	HR (95 % CI)	***P* value**	**HR (95 % CI)**	***P* value**	**HR (95 % CI)**	***P* value**
All-cause death						
OBS (per 1 SD)	0.83(0.79,0.87)	<0.001	0.80(0.76,0.84)	<0.001	0.87(0.82,0.92)	<0.001
OBS (Quartile)						
Q1	Reference		Reference		Reference	
Q2	0.95(0.81,1.12)	0.571	0.82(0.71,0.95)	0.009	0.90(0.77,1.05)	0.168
Q3	0.82(0.70,0.96)	0.016	0.74(0.65,0.85)	<0.001	0.86(0.74,1.00)	0.046
Q4	0.57(0.49,0.67)	<0.001	0.54(0.46,0.62)	<0.001	0.67(0.57,0.79)	<0.001
P for Trend		<0.001		<0.001		<0.001
Cardiovascular death						
OBS (per 1 SD)	0.77(0.69,0.86)	<0.001	0.76(0.67,0.85)	<0.001	0.82(0.72,0.92)	<0.001
OBS (Quartile)						
Q1	Reference		Reference		Reference	
Q2	0.93(0.68,1.28)	0.663	0.81(0.58,1.13)	0.214	0.89(0.64,1.22)	0.453
Q3	0.68(0.50,0.92)	0.014	0.64(0.48,0.87)	0.003	0.70(0.52,0.93)	0.015
Q4	0.53(0.38,0.75)	<0.001	0.53(0.37,0.75)	<0.001	0.66(0.46,0.94)	0.023
P for Trend		<0.001		<0.001		<0.001

Model 1, unadjusted; Model 2, adjusted for age, gender, race; Model 3, adjusted for model 2 covariates and education, marital status, smoking, drinking, hypertension, diabetes, metabolic

syndrome, BMI, waist circumference, SBP, DBP, HbA1c, FBG, TC, HDL, LDL, TG, UA and eGFR.

Table 3. Stratified analysis of the relationship between OBS and mortality in the population with CKM syndrome stages 0–3.

Exposure	All-cause mortality			Cardiovascular mortality		
	HR (95 % CI)	*P* value	*P* for interaction	HR (95 % CI)	*P* value	*P* for interaction
Age (years)			0.051			0.245
< 65	0.89(0.81,0.98)	0.013		0.82(0.64,1.04)	0.095	
≥ 65	0.87(0.80,0.94)	<0.001		0.82(0.72,0.93)	0.002	
Gender			0.861			0.543
Female	0.85(0.77,0.93)	<0.001		0.84(0.72,0.98)	0.026	
Male	0.89(0.81,0.97)	0.008		0.81(0.66,1.00)	0.053	
Smoking			0.274			0.925
No	0.89(0.84,0.95)	<0.001		0.86(0.75,0.99)	0.032	
Yes	0.96(0.83,1.10)	0.533		0.89(0.63,1.24)	0.485	
Hypertension			0.122			0.213
No	0.83(0.75,0.92)	<0.001		0.73(0.61,0.87)	<0.001	
Yes	0.90(0.83,0.98)	0.013		0.87(0.74,1.03)	0.099	
Diabetes			0.147			0.387
No	0.84(0.78,0.90)	<0.001		0.85(0.73,0.98)	0.030	
Yes	0.95(0.83,1.08)	0.402		0.75(0.59,0.95)	0.015	
CKM syndrome			0.016			0.074
Stage 0	0.88(0.65,1.18)	0.390		1.55(0.64,3.74)	0.329	
Stage 1	0.72(0.58,0.88)	0.002		0.62(0.45,0.86)	0.004	
Stage 2	0.87(0.81,0.94)	<0.001		0.78(0.66,0.93)	0.006	
Stage 3	0.96(0.86,1.07)	0.422		0.85(0.70,1.04)	0.110	

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

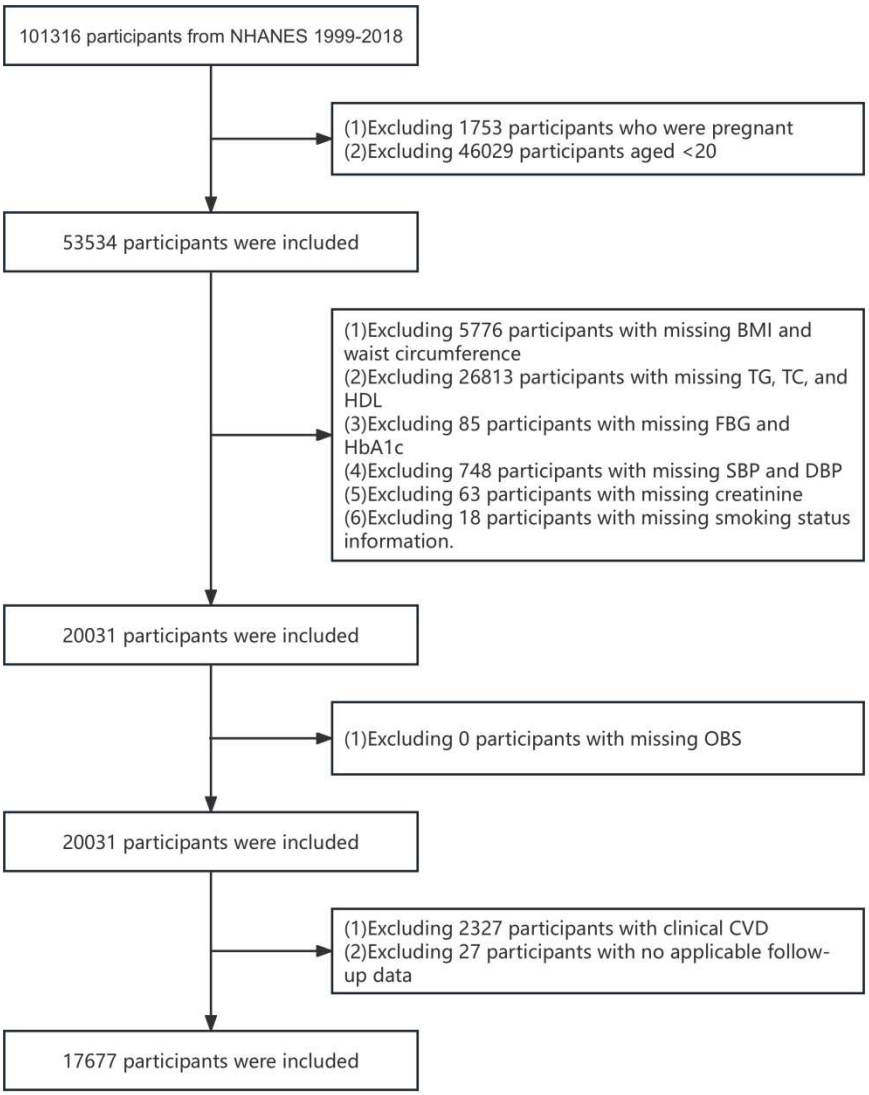


Figure 1. Flowchart of the study population

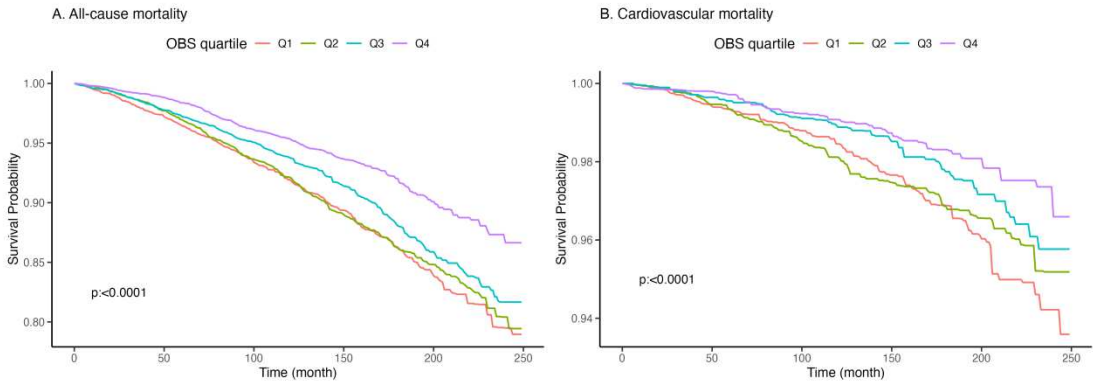


Figure 2. K–M analyses for all-cause (A) and cardiovascular mortality (B) among the four OBS quartile groups in the population with CKM syndrome stages 0–3.

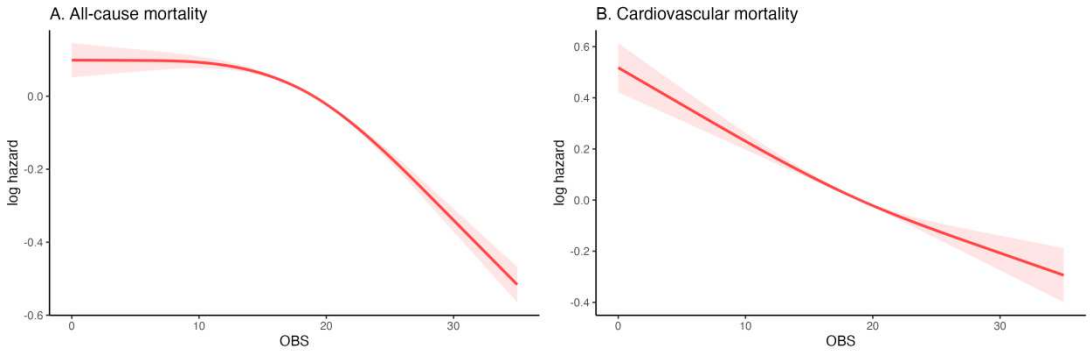


Figure 3. Dose-response relationship between OBS and all-cause (A) and cardiovascular mortality (B) in the population with CKM syndrome stages 0–3. Restricted cubic spline was used to explore nonlinear associations. The model was adjusted for age, gender, race, education, marital status, smoking, drinking, hypertension, diabetes, metabolic syndrome, BMI, waist circumference, SBP, DBP, HbA1c, FBG, TC, HDL, LDL, TG, UA and eGFR.

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