Serum Bicarbonate Concentration and Cause-Specific Mortality: The National Health and Nutrition Examination Survey 1999–2010

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Abstract

Objective: To assess the association between serum bicarbonate concentration and cause-specific mortality in the US general population.

Methods: A total of 31,195 individuals enrolled in the National Health and Nutrition Examination Survey between 1999 and 2010 were followed for a median 6.7 (interquartile range, 3.7–9.8) years. Cause-specific mortality was defined as cardiovascular, malignancy, and

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noncardiovascular/nonmalignancy causes. Cox proportional hazards adjusted for demographics, comorbidities, medications, and renal function were used to test the association between baseline serum bicarbonate and the outcomes of interest.

Results: Of the 2798 participants who died, 722 had a cardiovascular- and 620 had a malignancy-related death. Compared with participants with serum bicarbonate 22 to 26 mEq/L, those with a level below 22 mEq/L had an increased hazard of all-cause and malignancy-related mortality (hazard ratio [HR], 1.54; 95% CI, 1.30–1.83; and HR, 1.46; 95% CI 1.00–2.13, respectively). The hazard for cardiovascular mortality was increased by 8% with each 1 mEq/L increase in serum bicarbonate above 26 mEq/L (HR, 1.08; 95% CI, 1.01–1.15). The findings were consistent in participants with or without chronic kidney disease, with no significant interactions observed.

Conclusion: In a large cohort of US adults, serum bicarbonate concentration level below 22 mEq/L was associated with malignancy-related mortality, whereas a concentration above 26 mEq/L was associated with cardiovascular mortality. Further studies to evaluate potential mechanisms for the differences in cause-specific mortality are warranted.

Chronic low serum bicarbonate concentration, often a manifestation of kidney function decline,[1] is associated with a multitude of deleterious effects, including chronic kidney disease (CKD) progression, skeletal muscle breakdown, bone demineralization, and all-cause mortality. [2–8] Whether an imbalance in acid base homeostasis, presenting as low serum bicarbonate concentration, is a cause or a consequence of other pathologic mechanisms linked to adverse clinical outcomes is unclear.

Studies in CKD cohorts have identified a link between serum bicarbonate and all-cause mortality, with an increased risk of death associated with both high and low serum bicarbonate concentration.[2,5] However, in non-CKD populations, the findings have been inconsistent.[6,9] In a previous National Health and Nutrition Examination Survey (NHANES) analysis, serum bicarbonate less than 22 mEq/L was not observed to be a predictor of mortality in individuals without CKD.[9] This was in contrast to an analysis of 2287 elderly participants in the Health, Aging, and Body Composition Study in which low serum bicarbonate concentration was associated with a 24% increase in all-cause mortality.[6] Neither study has systematically assessed the underlying cause of death.

Understanding the mortality associated with low serum bicarbonate concentration becomes important in the setting of Westernization of the world's diet. A heathy adult, consuming a typical Western diet that yields a high daily net acid load,[10] sustains a chronic, low degree metabolic acidosis and suffers from its related complications.[11] Prior studies have proposed that exposure to chronic acidosis may facilitate cancer cell clonal evolution and metastasis by inducing chromosomal instability and gene mutations.[12,13] However there is no firm evidence on the link between serum bicarbonate concentration and cancer, or cancer-related mortality. In the heart, acidosis has been associated with a reduction in Na+−K+−adenosine triphosphatase activity in myocardial cells,[14] and reduced contractility[15]; however, studies on the association between serum bicarbonate and cardiovascular mortality are limited.

The present study assessed the association between serum bicarbonate concentrations and cause-specific mortality in a large cohort of individuals representative of the US adult general population.

METHODS

Study Population

The NHANES survey is a program of studies designed to assess the health and nutritional status in the United States. The current version of the program (NHANES continuous) started in 1999, as a continuation of previous rounds (NHANES I, II, and III). In each cycle that spans 2 years, the program recruits approximately 10,000 participants living in the United States to conduct the studies. Through a multistage probability sample, this program is designed to provide a cohort representative of the civilian noninstitutionalized US population of all ages. NHANES continuous (1999–2010) is linked to the National Death Index through December 31, 2011. The current study enrolled 31,195 adult (18 years) participants in NHANES continuous, with available serum bicarbonate concentrations and mortality follow-up data (Figure 1).

Serum Bicarbonate Measurement

Blood was collected via a venipuncture from consenting NHANES participants. Vials were stored under appropriate frozen (−30°C) conditions and were shipped overnight to the NHANES Central Laboratory for testing. Serum bicarbonate concentrations were analyzed using the phosphoenolpyruvate carboxylase method on Hitachi 917 multichannel analyzer (Roche Diagnostics, Indianapolis, IN) from 1999 to 2001, using a pH-sensitive electrode on Beckman Synchron LX20 (Beckman Coulter Inc., Brea, CA) from 2002 to 2006, using LX20 and Beckman UniCel DxC800 Synchron (Beckman Coulter Inc.) from 2007 to 2008, and using the DxC800 Synchron system from 2009 to 2010. Baseline serum bicarbonate concentration was measured at study baseline and analyzed as a categorical variable by the following clinical relevant strata: low (<22 mEq/L), normal (22–26 mEq/L), and high (>26 mEq/L); as well as a continuous variable estimated using P-splines to allow for nonlinear effects.

Ascertainment of Overall and Cause-Specific Mortality Outcomes

Outcomes were defined as (1) all-cause mortality, (2) cardiovascular mortality, (3) malignancy-related mortality, and (4) other noncardiovascular/noncancer-related mortality. The underlying cause of death was coded according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD 10). Participants were linked to the National Death Index through December 31, 2011, by the National Center for Health Statistics as previously described.[16] Cardiovascular mortality was defined as death due to diseases of the heart, cerebrovascular disease, atherosclerosis, or other diseases of the circulatory system (ICD 10 codes: I00-I09, I11, I13, I20-I78). Cancer-related mortality was defined as death from any cancer (ICD 10 codes: C00-C97). Noncardiovascular/noncancer-related mortality included all other deaths (ie, chronic lower respiratory diseases [ICD 10 codes: J40-J47], Alzheimer's disease [ICD 10 code: G30], diabetes mellitus [ICD 10 codes: E10-E14], influenza and pneumonia [ICD 10 codes:

J09-J18], nephritis, nephrotic syndrome, and nephrosis [ICD 10 codes: N00-N07, N17-N19, N25N27], accidents [ICD 10 codes: V01-X59, Y85-Y86], and all other causes [residual]).

Covariates

Demographic variables including age, sex, race, along with comorbidities, body mass index, blood pressure, medication use, and laboratory data (total and high-density lipoprotein [HDL] cholesterol, creatinine, proteinuria, hemoglobin, C-reactive protein, and potassium) were obtained at study baseline. Estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease-Epidemiology Collaboration equation.[17] CKD was defined as eGFR less than 60 mL/min per 1.73 m^2. Comorbid conditions including diabetes, heart failure (HF), coronary artery disease (CAD), chronic obstructive pulmonary disease, and malignancy were all self-reported. Diabetes was defined as a self-reported history of diabetes, use of oral hypoglycemic agents or insulin, or fasting plasma glucose greater than or equal to 126 mg/dL. Hypertension was defined as systolic blood pressure greater than140 mm Hg and/or diastolic blood pressure greater than 90 mm Hg, current treatment for hypertension, or if the participant was ever told to take medication for high blood pressure or had hypertension. Cardiovascular disease was defined as a history of myocardial infarction, stroke, or congestive HF. History of smoking included previous and current smokers.

Statistical Analysis

Categorical variables are presented as percentage and continuous variables are presented as mean and 95% CIs. All analyses (unless specified otherwise) accounted for NHANES complex survey design, and followed the analytical guidelines as recommended by the National Center for Health Statistics.[18] We compared baseline characteristics across serum bicarbonate strata using χ^2 tests for categorical and one-way analysis of variance for continuous variables. We used the Poisson distribution to estimate mortality rates (per 1000 person-years of follow-up) and 95% CI for each leading cause of death within each serum bicarbonate stratum.[19,20]

Survival analyses were estimated using Cox proportional hazard models in gradually inclusive models defined a priori based on our assessment of the covariates' likelihood of being a confounder in the relationship between serum bicarbonate and each cause-specific mortality outcome. The relevant confounding variables used for adjustments included demographics (age, sex, and race/ethnicity), traditional cardiovascular risk factors (history of CAD, HF, diabetes, smoking, systolic blood pressure, total and HDL cholesterol, body mass index, malignancy, medications [angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, diuretics]), and kidney function (eGFR and log transformed spot urine albumin/creatinine). Residual plots were used to confirm model assumptions. Serum bicarbonate concentration of 22 to 26 mEq/L was used as the reference group. Demographics (age, sex, and race) were available for all patients. Data missingness was as follows (unweighted data): smoking (N=2601; 8.3%), diabetes (N=480; 1.5%), hypertension (N=213; 0.7%), alcohol (N=8531; 27.3%), history of CAD (N=2716; 8.7%), history of HF (N=2676; 8.6%), history of malignancy (N=2573; 8.2%), history of chronic obstructive pulmonary disease (N=2638; 8.5%), history of liver disease (N=2632; 8.4%), body mass index (N=619; 2%), heart rate (N=30,101; 3.5%), blood pressure (N=1303;

4.2%), glomerular filtration rate (GFR) (N=0; 0%), urine albumin to creatinine ratio (N=506; 1.6%), hemoglobin (N=56; 0.2%), albumin (N=0; 0%), cholesterol (N=1; 0%), potassium (N=2; 0%), and C-reactive protein (N=14; 0%). No assumptions were used for missing data and listwise deletion method was used for missing variables in multivariable models.

For survival analyses, the event was defined as the death from any cause (all-cause mortality) or cause-specific deaths (cardiovascular disease [CVD], cancer, and non-CVD/noncancer), censoring for other events (including deaths from other causes). In nonlinear modeling, the association between serum bicarbonate concentrations and all-cause and cause-specific mortality was explored using penalized spline regression models.[21] To our knowledge, there is no widely available package to visualize splines under complex survey methods; therefore, splines were performed on unweighted data. Because listwise deletion was used for missing data, effect estimates from incremental models may not be comparable; therefore, sensitivity analyses were performed after excluding participants with missing data from the list of covariates. Additionally, analyses were replicated using Fine-Gray method to consider competing causes of death.[22]

In secondary analyses, we examined the association between baseline serum bicarbonate and cause-specific mortality rates in subgroups by age, sex, race, CKD, and diabetes status. Subgroup analyses were performed after excluding participants with history of lung disease at baseline.

All analyses were conducted using SPSS, R, SAS, and Stata. All tests were two-sided, and P<.05 was considered statistically significant.

RESULTS

Of the total 31,195 participants, 52% were women, and 11% were African Americans. Mean age SD was 45.3 (95% CI, 45.1–45.5) years. A small proportion (6.2%) had CKD. Serum bicarbonate mean ± SD was 24.5 ± 0.05. Compared with participants with normal (22–26 mEq/L), or high (>26 mEq/L) serum bicarbonate, participants with low (<22 mEq/L) serum bicarbonate concentration at study baseline were more likely to be younger, women, non-black, and with higher eGFR. Participants with high serum bicarbonate level were more likely to have hypertension or history of malignancy at baseline. Baseline characteristics of the study population are presented in Table 1.

Causes of Death Mortality Rates by Serum Bicarbonate Concentration

Over a median follow-up of 6.7 (interquartile range [IQR], 3.7–9.8) years, 2798 patients died (unweighted). The leading causes of death were CVD (n=722) and malignant neoplasms (n=620) (unweighted). The overall crude unweighted mortality rates per 1000 person-years of follow-up were 14.1 (95% CI, 13.5–14.6) for all-cause deaths, 3.6 (95% CI, 3.4–3.9) for CVD deaths, and 3.1 (95% CI, 2.9–3.3) for malignancy-related deaths. Mortality rates per 1000 person-years across the serum bicarbonate strata overall and by cause-specific mortality are depicted in Table 2.

Serum Bicarbonate Concentration and All-Cause Mortality

Kaplan-Meier survival curves by baseline serum bicarbonate strata are presented in Figure 2. Participants with serum bicarbonate concentration less than 22 mEq/L had a significantly reduced overall survival compared with participants in the normal or high bicarbonate groups (P<.001) (Figure 2).

In multivariable adjusted Cox regression models (model 3), the hazard for all-cause mortality was 54% higher (hazard ratio [HR], 1.54; 95% CI, 1.30–1.83; *P*<.001) for participants with serum bicarbonate concentration less than 22 mEq/L compared with participants with serum bicarbonate level from 22 to 26 mEq/L. Participants with serum bicarbonate concentration greater than 26 mEq/L had similar hazard of all-cause mortality compared with those in the normal bicarbonate group (HR, 1.04; 95% CI, 0.97–1.11; *P*=.26). Table 3 and Supplemental Table 1 (available online at http://www.mayoclinicproceedings.org) show the incrementally adjusted effect size estimates after excluding participants with missing data. Unadjusted and fully adjusted (model 3) penalized splines models (unweighted) showed a statistically significant U-shaped association between serum bicarbonate concentration and all-cause mortality (Figure 3).

Serum Bicarbonate Concentration and Cardiovascular Mortality

There was no significant association between serum bicarbonate concentration and CVD mortality when serum bicarbonate concentration was analyzed as a categorical predictor using cox-regression estimates (Table 3 and Figure 2) or in Fine-Gray analysis accounting for competing causes of death (Supplemental Table 2 [available online at http://www.mayoclinicproceedings.org]). In a nonlinear approach, using penalized splines we observed an increased risk of CVD mortality for participants with high baseline serum bicarbonate concentration (Figure 3). Multivariable adjusted linear splines revealed an 8% increase in CVD mortality with each 1 mEq/L higher serum bicarbonate concentration above 26 mEq/L (HR, 1.08; 95% CI, 1.01–1.15; *P*=.04).

Serum Bicarbonate Concentration and Cancer Mortality

Participants with serum bicarbonate concentration less than 22 mEq/L had a significantly increased risk of cancer mortality compared with participants in the normal or high bicarbonate group (*P*=.01) (Figure 2). The hazard for cancer mortality was 46% higher for participants with serum bicarbonate concentration less than 22 mEq/L (HR, 1.46; 95% CI, 1.00–2.13; *P*=.05) compared with participants in the normal group (Table 3). The results were replicated using competing risk analyses (Supplemental Table 3 [available online at http://www.mayoclinicproceedings.org]). Findings from penalized spline analyses were generally congruent with the categorical results, indicating a higher risk of cancer mortality for participants with low serum bicarbonate (Figure 3).

Serum Bicarbonate and Noncardiovascular/Noncancer Mortality

The number of events for each other cause of death was small and did not allow individual comparisons (Table 2). Taken as a group, noncardiovascular/noncancer mortality was higher for participants with low serum bicarbonate at baseline compared with participants with normal serum bicarbonate (HR, 1.74; 95% CI, 1.40–2.17; *P*<.001). There was no association

for participants with high serum bicarbonate compared with participants with normal serum bicarbonate (HR, 1.01; 95% CI, 0.92–1.12; *P*=77).

Subgroup Analyses

The association between serum bicarbonate concentrations and cause-specific mortality was consistent in subgroups by age, sex, race, CKD, and diabetes status. There was an increase in the risk of cancer mortality in participants younger than 65 years and in men with low serum bicarbonate concentration, although the differences were not statistically significant (Figure 4). Supplemental Table 3 depicts the association between serum bicarbonate and mortality outcomes after excluding participants with lung disease at baseline.

DISCUSSION

In this large cohort representative of the US general population with and without CKD, after accounting for significant confounders, serum bicarbonate concentration less than 22 mEq/L was associated with all-cause and cancer-related mortality, but not with cardiovascular mortality. However, each 1 mEq/L higher serum bicarbonate concentration above 26 mEq/L was associated with an 8% increase in cardiovascular mortality; and a U-shaped association was observed between serum bicarbonate concentration and all-cause mortality. These findings were consistent in individuals with and without CKD. To our knowledge, this is the first largescale study to investigate the cause-specific mortality associated with serum bicarbonate concentration.

Both low and high bicarbonate concentrations are associated with increased all-cause mortality in CKD.[2,5] The association between serum bicarbonate concentration and all-cause mortality in the non-CKD population is not well established. In a study of 15,836 NHANES III participants, serum bicarbonate concentrations less than 22 mEq/L were associated with a 2.6-fold increased hazard of death in individuals with CKD.[9] However, serum bicarbonate was not an independent predictor of overall mortality in the non-CKD subgroup.[9] Less than 10% in our cohort had CKD; still, in subgroup analysis, we observed no interaction by CKD status. It is unclear whether the analyses are underpowered to detect significant interactions. At the other end of the spectrum, metabolic alkalosis was shown to be associated with all-cause mortality in healthy older individuals.[6] The current study validates the U-shaped association between serum bicarbonate concentration and overall mortality and further refines it by adding the causes of death.

Few studies have evaluated the association between serum bicarbonate concentration and CVD with conflicting results. In a cohort of patients with type 2 diabetes, serum bicarbonate concentration was inversely associated with incident coronary disease.[23] In contrast, no significant association between bicarbonate and CVD was observed in patients with diabetic kidney disease[24] or in healthy older individuals.[6]

In a study of 3939 participants in the Chronic Renal Insufficiency Cohort study, high serum bicarbonate concentration was associated with increased risk of HF events, but no association with atherosclerotic events, including CAD, was found.[3] In a subsequent study, persistently elevated serum bicarbonate concentrations above 26 mEq/L during follow-up

remained a robust predictor of incident HF events after adjustments for multiple confounders including diuretic type and doses.[4] These studies and others clearly established a link between serum bicarbonate concentration and CVD in CKD. However, this is not well studied in individuals without CKD. The prevalence of CKD in the current study was less than 9% and thus many of the mortality events observed were reflective of a non-CKD population. Whereas low serum bicarbonate concentration was not a predictor of CVD mortality, the current study enhances the earlier findings by showing an association between high serum bicarbonate concentrations and increased cardiovascular mortality in a primarily non-CKD population. Because arterial blood gas was not measured, it is difficult to ascertain if high serum bicarbonate level was a compensatory mechanism for an underlying respiratory acidosis or a reflection of metabolic alkalosis.

Cancer-related mortality was higher in the low bicarbonate group compared with the normal bicarbonate group. The association remained unaltered in increasingly adjusted models, including accounting for eGFR, albuminuria, comorbidities, and medications. The potential mechanisms responsible for this association remain speculative and cannot be proven in this epidemiological cohort, but a few points are important to make. Animal studies suggest that acidosis can induce and propagate carcinogenesis.[25] Acid-base disequilibrium modulates molecular activity including adrenal glucocorticoid, insulin growth factor, and adipocyte cytokine signaling, and may result in dysregulated cellular metabolism and osteoclast activation that can induce carcinogenesis.[26] Additionally, acidity generated by the tumor microenvironment can drive local invasion of tumor cells by degrading the extracellular matrix.[27,28] Also, several families of receptors and ion channels that help cells sense extracellular acidosis have been described in cancer cells.[29] pH-sensing G protein-coupled cell receptors including GPR4, TDAG8 (GPR65), OGR1 (GPR68), and G2A (GPR132) are recently discovered pH sensors that are activated by an acidic milieu and may play a role in tumor development, inflammation, and angiogenesis.[30–32]

Although no statistically significant interaction by sex was observed, men with serum bicarbonate levels below 22 mEq/L had an increased risk of cancer mortality compared to women. The rationale for such potential sex disparity remains unclear, but one can speculate that carcinogenesis in male-specific cancers, such as prostate cancer, finds acidosis a favorable milieu. CKD has been shown to be associated with an increased risk of genitourinary cancers, but not prostate cancer. This raises the possibility that the association with cancer death may be driven by mechanisms other than the chronic metabolic acidosis in the context of declining GFR.

The risk of cancer mortality was also higher for low serum bicarbonate group in participants younger than 65 years, although the difference with the older group was not statistically significant. A potential explanation can reside in the high-energy, high-protein, high-fat (Westernized) diet likely to be consumed in higher amounts by a younger population, therefore increasing the exposure to metabolic acidosis, but also to potentially carcinogenic compounds that are found in meats, including N-nitroso compounds, heterocyclic amines, or polycyclic aromatic hydrocarbons.

Treatment with oral sodium bicarbonate increases tumor pH and reduced lymph node involvement, tumor extravasation, colonization, and distant metastasis formation in animal models.[33] The role of sodium bicarbonate use in human cancer treatment is currently under investigation (extended use of sodium bicarbonate in patients with cancer, Clinicaltrials.gov: NCT02531919).

In our study, the association between low serum bicarbonate concentration and cancer deaths were similar in CKD and non-CKD groups, making kidney function a less likely confounder. Diabetes has been shown to increase cancer risk,[34] mostly due to chronic inflammation. Higher level of C-reactive protein, a measure of inflammatory state, was found to be prevalent in participants with low serum bicarbonate in our cohort. However, we observed no interaction by diabetes status.

The strengths of this study include a large cohort of individuals representative of the US general population with and without CKD with available serum bicarbonate concentration measurements and cause-specific mortality data. However, few limitations should be acknowledged. The observational study design precludes potential causality between serum bicarbonate concentration and cause-specific mortality. Data on the type of malignancy was not available and the cause of death obtained from the National Death Index may not have been accurately adjudicated. However, these death indexes have been previously used and considered reliable for CVD and cancer mortality.[35,36] The lack of available arterial blood gas analysis precluded the assessment of acid-base status. It is possible that participants with low bicarbonate level had an underlying respiratory alkalosis; and high bicarbonate level could be a compensatory mechanism for respiratory acidosis. Additionally, the study is based on a single measurement of serum bicarbonate, which may not be reflective of the temporal variability. Nevertheless, the NHANES dataset was prospectively collected for research purposes, which limits the bias introduced by a retrospective review.

CONCLUSION

In a large cohort of US adults with and without CKD, low serum bicarbonate concentration was an independent predictor of overall and malignancy-related deaths. The risk of cardiovascular mortality was increased for individuals with serum bicarbonate above 26 mEq/L. Further studies to confirm these findings and explain the potential mechanisms for the differences in cause-specific mortality are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations and Acronyms:

CKD   chronic kidney disease

CVD   cardiovascular disease

eGFR   estimated glomerular filtration rate

HR	hazard ratio
IQR	interquartile range
NHANES	National Health and Nutrition Examination Survey

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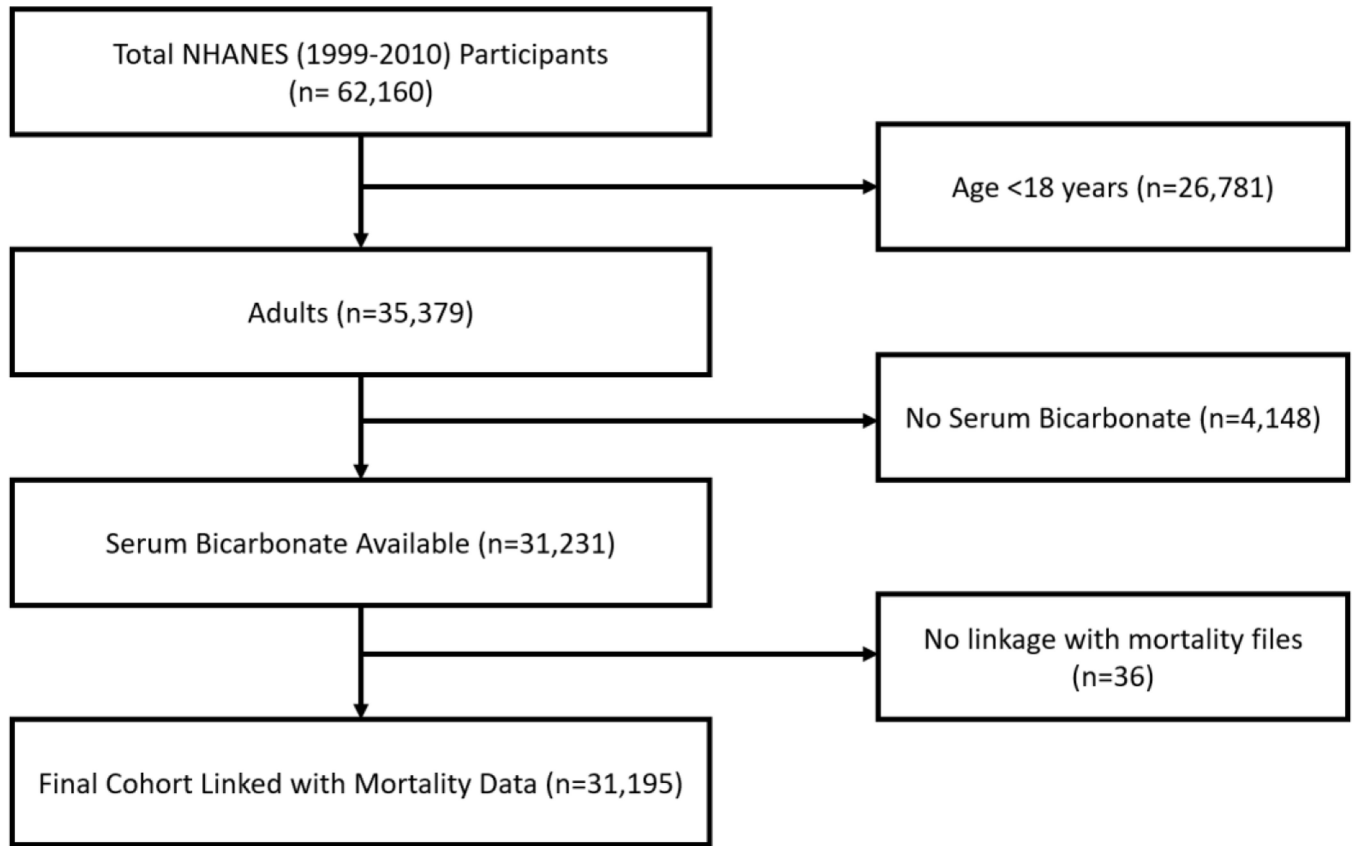
FIGURE 1.
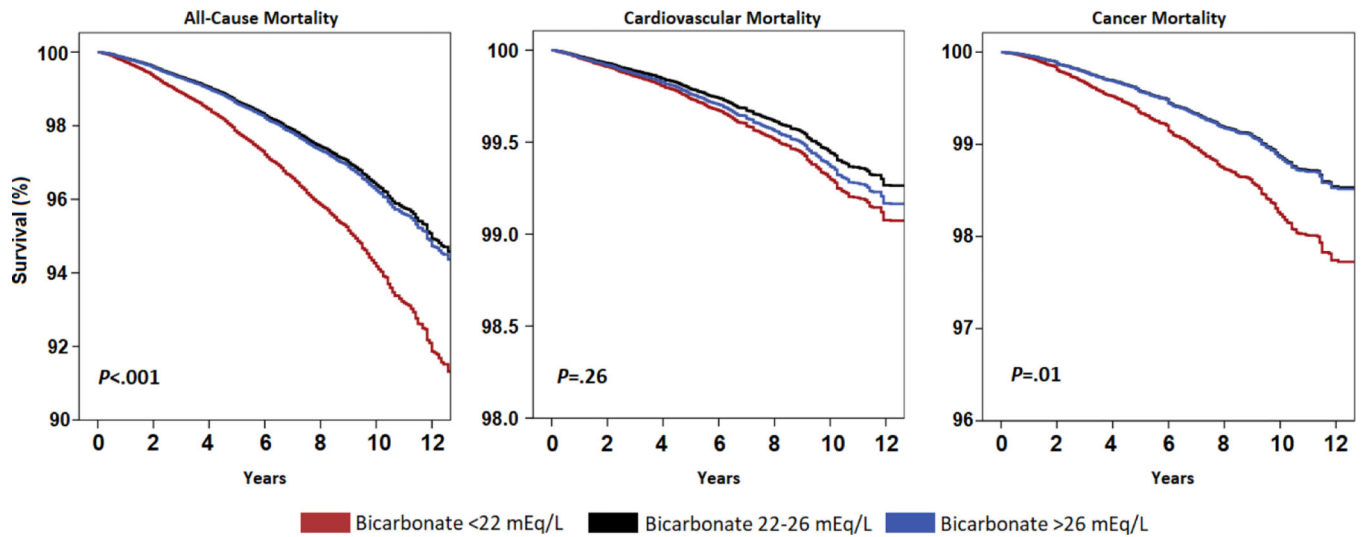Consort diagram.

FIGURE 2. Demographic adjusted curves for cause-specific mortality by baseline serum bicarbonate strata (< 22 mEq/L, 22 – 26 mEq/L and > 26 mEq/L). (A) All-cause mortality (B) Cardiovascular mortality (C) Cancer mortality.

Analysis was done using Kaplan-Meier method accounting for complex survey design.

P-values are of Log-Rank (Mantel-Cox) test.
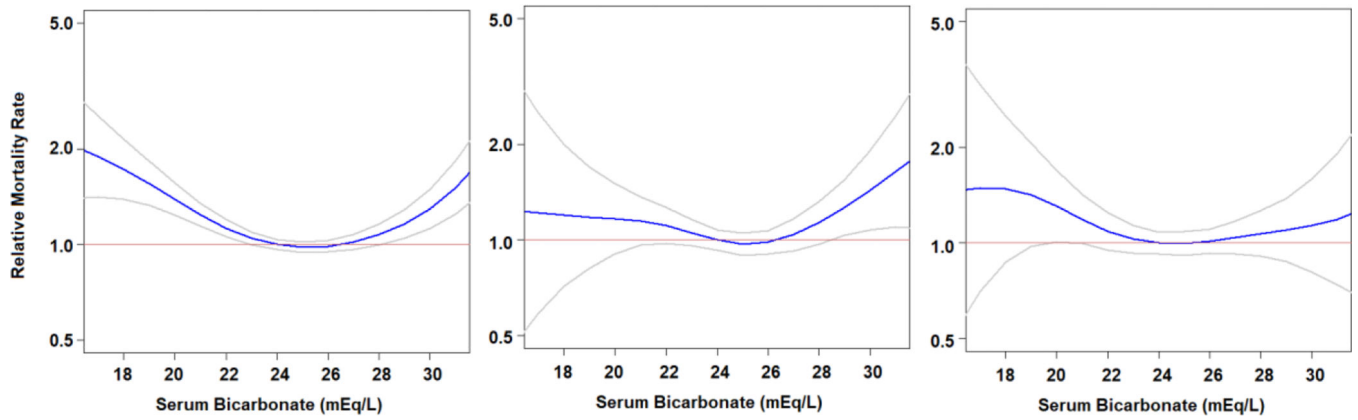
FIGURE 3.
Adjusted (model 3) penalized smoothing splines for all-cause, cardiovascular- and cancer-mortality (unweighted data). Gray lines represent 95% confidence interval. Red line represents HR of 1.

FIGURE 4. Bicarbonate levels and cause-specific mortality in subgroups
CKD=chronic kidney disease, DM=Diabetes Mellitus. P values are for interaction between subgroup and bicarbonate levels. Analysis was done using Cox regression accounting for complex survey design

TABLE 1.

Characteristics of NHANES Participants by Baseline Serum Bicarbonate[a,b]
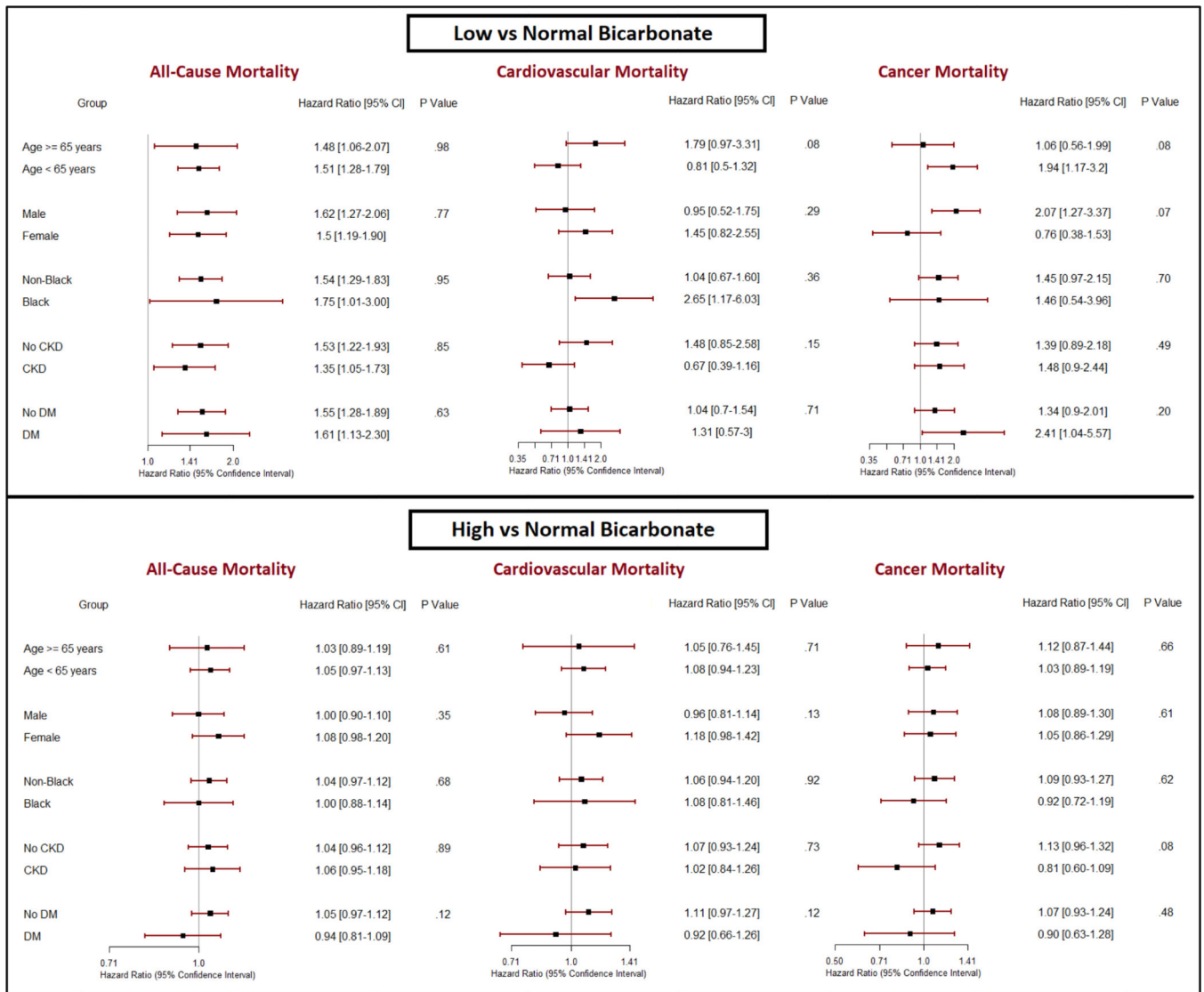
Characteristics	Total (N=31,195)	Serum Bicarbonate (mEq/L)			P value[c]
		<22 (n=3143)	22–26 (n=21,801)	> 26 (n=6251)	
Serum bicarbonate, mEq/L	24.5 (24.4–24.6)	20.2 (20.1–20.3)	24.2 (24.1–24.3)	27.7 (27.6–27.8)	
Demographics and Clinical Characteristics					
Age, years	45.3 (45.1–45.5)	40.4 (39.7–41.0)	44.5 (44.3–44.8)	50.4 (49.9–50.9)	<.001
Women	51.6 (50.9–52.3)	65.5 (63.2–67.8)	52.5 (51.6–53.3)	42.0 (40.4–43.5)	<.001
Black	10.7 (10.4–11.0)	9.8 (8.9–10.7)	10.5 (10.2–10.8)	12.0 (11.3–12.7)	<.001
Ever-smoker[d]	48.3 (47.6–49.1)	51.1 (48.7–53.6)	48.8 (47.9–49.7)	45.3 (43.7–46.9)	<.001
Diabetes	7.3 (7.0–7.7)	6.9 (5.8–8.0)	7.1 (6.7–7.5)	8.3 (7.6–9.1)	.01
Hypertension	27.6 (27.0–28.2)	26.4 (24.4–28.5)	26.0 (25.3–26.7)	34.1 (32.6–35.5)	<.001
Alcohol[e]	16.3 (15.7–16.9)	18.6 (16.5–20.8)	16.3 (15.6–17.0)	15.0 (13.8–16.3)	.01
History of coronary disease	3.4 (3.1–3.6)	2.7 (2.0–3.4)	3.1 (2.9–3.4)	4.4 (3.8–5.0)	<.001
History of heart failure	2.2 (2.1–2.4)	2.2 (1.6–2.9)	2.0 (1.8–2.3)	2.9 (2.5–3.4)	.001
History of malignancy	8.3 (7.9–8.7)	7.1 (5.9–8.3)	8.0 (7.3–8.2)	10.9 (9.9–11.8)	<.001
eGFR <60 mL/min per 1.73 m²	6.2 (5.9–6.5)	7.3 (6.3–8.4)	5.6 (5.3–5.9)	7.8 (7.1–8.5)	<.001
History of asthma	13.2 (12.7–13.7)	15.1 (13.4–16.8)	13.0 (12.4–13.6)	12.8 (11.8–13.9)	.03
BMI, kg/m²	28.2 (28.1–28.3)	29.7 (29.4–30.0)	28.3 (28.2–28.4)	27.4 (27.2–27.6)	<.001
Heart rate, beats/min	72.7 (72.6–72.9)	76.8 (76.2–77.4)	72.8 (72.6–73.0)	70.5 (70.1–70.9)	<.001
Systolic blood pressure, mm Hg	122.0 (121.7–122.2)	119.5 (118.7–120.3)	121.6 (121.3–121.9)	124.5 (123.9–125.0)	<.001
Diastolic blood pressure, mm Hg	70.6 (70.5–70.8)	70.4 (69.8–71.0)	70.8 (70.6–71.0)	70.3 (69.9–70.6)	.01
Laboratory data					
eGFR, mL/min per 1.73 m²	97.0 (96.7–97.3)	102.3 (101.2–103.4)	97.9 (97.6–98.2)	91.4 (90.8–92.0)	<.001
Urine albumin/creatinine, median (IQR), mg/g	0.06 (0.04–0.1)	0.06 (0.04–0.1)	0.06 (0.04–0.1)	0.06 (0.04–0.1)	<.001
Hemoglobin, g/dL	14.4 (14.3–14.5)	14.2 (14.1–14.3)	14.4 (14.3–14.5)	14.5 (14.50–14.59)	<.001
Albumin, g/dL	4.3 (4.2–4.4)	4.19 (4.18–4.21)	4.3 (4.2–4.4)	4.33 (4.32–4.34)	<.001
Serum cholesterol, mg/dL	198.1 (197.5–198.6)	196.6 (194.5–198.8)	198.0 (197.3–198.7)	198.9 (197.7–200.2)	.05
High-density liprotein, mg/dL	52.6 (52.4–52.9)	50.7 (49.9–51.4)	52.4 (52.1–52.7)	54.4 (53.9–54.9)	<.001
Serum potassium, mEq/L	4.0 (4.01–4.03)	4.01 (3.99–4.02)	4.017 (4.012–4.022)	4.01 (4.007–4.03)	.57

Characteristics	Total (N=31,195)	Serum Bicarbonate (mEq/L)			P value[c]
		<22 (n=3143)	22–26 (n=21,801)	> 26 (n=6251)	
C-reactive protein, mg/dL, median (IQR)	0.2 (0.1–0.4)	0.3 (0.1–0.6)	0.2 (0.07–0.4)	0.1 (0.05–0.3)	<.001
Medications					
Diuretics	10.3 (9.9–10.7)	6.6 (5.5–7.6)	8.7 (8.3–9.2)	17.8 (16.6–18.9)	<.001
ACEi/ARB	13.2 (12.8–13.7)	10.6 (9.3–12.0)	12.5 (12.0–13.0)	17.2 (16.1–18.3)	<.001
Beta blockers	7.9 (7.6–8.3)	6.2 (5.2–7.2)	7.2 (6.8–7.6)	11.5 (10.5–12.4)	<.001
Statins	11.7 (11.3–12.1)	7.8 (6.6–9.0)	10.8 (10.3–11.3)	16.8 (15.8–17.9)	<.001

[a] ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; eGFR = estimated glomerular filtration rate; IQR = interquartile range.

[b] Numbers at the top represent the unweighted number of participants. Numbers represent n (%) or mean ± SD unless otherwise specified.

[c] One-way analysis of variance (normal data continuous), Kruskal-Wallis (non-normal continuous), χ^2 test (categorical).

[d] Smoking: at least 100 cigarettes/lifetime.

[e] Alcohol: ever had more than 5 drinks per day.

TABLE 2.

Causes of Death and Mortality Rates per 1000 Person-Years Across Serum Bicarbonate Strata

Cause of death	Serum Bicarbonate (mEq/L)		
	<22	22–26	>26
	Mortality rate per 1000 person-years (95% CI)	Mortality rate per 1000 person-years (95% CI)	Mortality rate per 1000 person-years (95% CI)
All cause deaths	9.59 (9.58–9.61)	8.72 (8.64–8.80)	13.48 (13.47–13.49)
Cardiovascular diseases	1.65 (1.64–1.66)	2.02 (2.02–2.02)	3.6 (3.59–3.61)
Malignancy	2.29 (2.28–2.29)	2.11 (2.10–2.12)	3.04 (3.02–3.05)
Chronic lower respiratory diseases	0.41 (0.40–0.42)	0.47 (0.46–0.48)	1.13 (1.12–1.14)
Alzheimer disease	0.05 (0.04–0.06)	0.27 (0.26–0.28)	0.38 (0.37–0.38)
Diabetes mellitus	0.47 (0.46–0.48)	0.25 (0.24–0.26)	0.37 (0.36–0.38)
Influenza and pneumonia	0.16 (0.15–0.17)	0.21 (0.20–0.21)	0.31 (0.30–0.33)
Kidney disease	0.42 (0.41–0.43)	0.17 (0.16–0.18)	0.14 (0.13–0.15)
Accidents (unintentional injuries)	0.83 (0.82–0.84)	0.39 (0.38–0.40)	0.62 (0.61–0.63)

TABLE 3.

Cox Regression Models for the Association Between Serum Bicarbonate Groups and Clinical Outcomes Accounting for Complex Survey Design[a,b]

	Serum Bicarbonate (mEq/L)		
	<22	[22–26]	>26
All-cause mortality			
Model 1	1.63 (1.42–1.88); <.001	Ref	1.02 (0.96–1.07); .51
Model 2	1.62 (1.37–1.92); <.001	Ref	1.03 (0.97–1.10); .31
Model 3	1.54 (1.30–1.83); <.001	Ref	1.04 (0.97–1.11); .26
CVD mortality			
Model 1	Ref	1.26 (0.89–1.77); .19	1.06 (0.96–1.17); .23
Model 2	1.26 (0.89–1.79); .20	Ref	1.04 (0.93–1.16); .54
Model 3	1.12 (0.77–1.62); .56	Ref	1.06 (0.94–1.19); .33
Cancer mortality			
Model 1	Ref	1.57 (1.16–2.11); .003	1.01 (0.89–1.14); .88
Model 2	1.47 (1.01–2.15); .05	Ref	1.07 (0.93–1.22); .37
Model 3	1.46 (1.00–2.13); .05	Ref	1.07 (0.93–1.23); .34

[a]CVD = cardiovascular disease; HR = hazard ratio; Ref = reference.

[b]Values shown are HR (95% CI); *P* value.

Model 1 is adjusted for age, sex, race (n=31,195).

Model 2 is adjusted for variables in Model 1+ tobacco use, coronary artery disease, heart failure, cholesterol, systolic blood pressure, chronic obstructive pulmonary disease, liver disease, body mass index, high-density lipoprotein, malignancy, diuretics, angiotensin converting enzyme inhibitors, or angiotensin receptor blockers (n=26,652).

Model 3 is adjusted for variables in Model 2 + estimated glomerular filtration rate, and log transformed spot urine albumin/creatinine (n=26,404).