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Non-lactate strong ion difference and cardiovascular, cancer and all-cause mortality

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Abstract

Objectives: Non-lactate strong ion difference (SID) has been shown to be associated with predictors of mortality in intensive care unit. However, the existence of any association between non-lactate SID (nlSID) and all cause, cardiovascular and cancer mortality has not been explored before in community dwelling US adults.

Methods: In a nationally representative cross-sectional survey of the US non-institutionalized population, all adult participants (≥ 20 years of age) using National Health and Nutrition Examination Survey data (1999–2010) combined with National Death Index for mortality status through December 2011. Cox proportional hazard models were built to estimate the hazard ratios for cardiovascular, cancer, and all-cause mortality for each unit increase in non-lactate SID. The models were adjusted for demographic and confounder variables

Results: In the study population the mean (SD) age was 49.6 (18.4) years. Of the study population, 31,475 (91.5%) were alive and 2,893 (8.4%) died during the mean (SD) follow-up period of 5.5 (3.5) years. In univariate regression model using nlSID as continuous variable, we found 2% (unadjusted hazard ratio, HR=1.02; 95% CI, 1.004–1.05) increase in all-cause but not in cardiovascular and cancer mortality (HR=1.03; 95% CI, 0.99–1.08, HR=1.01; 95% CI, 0.97–1.06). After adjusting for potential confounders, we found 7% (adjusted HR=1.07; 95% CI, 1.04–1.10), 5% (HR=1.05; 95% CI, 1.00–1.11) and 7% (HR=1.07; 95% CI, 1.02–1.12) increase in all-cause, cardiovascular, and cancer mortality.

Conclusions: A high nlSID is associated with an increase in cardiovascular, cancer and all-cause mortality and may

be a prognostic indicator of mortality in general adult population. These findings may provide a point of reference for further studies.

Keywords: acid-base; all-cause mortality; NHANES; non-lactate strong ion difference.

Introduction

According to the Stewart approach of acid-base status of body fluids, the three independent factors that control the acid-base status are partial pressure of CO_2 , the apparent strong ion difference (SID), and the total amount of weak acids [1]. Strong ions are ions that completely dissociate in solution. The apparent strong ion difference (SID)_a in plasma is the sum of strong cations minus strong anions. The strong cations are sodium, potassium, calcium and magnesium and the strong anions are lactate and chloride. The effective strong ion difference (SID)_e is the sum of serum bicarbonate and the concentration of weak non carbonic acids, principally albumin and phosphate [2]. In normal plasma, the (SID)_a is equivalent to (SID)_e [2]. The difference between the (SID)_a and (SID)_e called as strong ion gap (SIG) is an indicator of unmeasured anions [2]. As the concentration of potassium, calcium, and magnesium are low in plasma, the principal component of (SID)_a is the non-lactate SID (Na–Cl). The effect of strong ions, except lactate, on acid-base status can be calculated by subtracting chloride concentration from sodium concentration and is called non-lactate SID [3, 4]. The correlation between apparent SID and the difference between sodium and chloride is well-established in literature [5]. The relationship between bicarbonate and sodium–chloride difference exists, if anion gap remains constant [6]. A reduced non-lactate SID suggests metabolic acidosis, respiratory alkalosis and mixed acid base disorder, while increased non-lactate SID suggests metabolic alkalosis, respiratory acidosis, and mixed acid base disorder [7]. A change in non-lactate SID affects our acid-base milieu in the body. It is well-known known that acidosis and alkalosis have a negative impact on clinical outcomes and hence change in non-lactate SID is likely to affect the clinical outcomes adversely [1, 8–10].

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The association between electrolyte disturbances and mortality is well-established [11–14]. SID has been extensively investigated and has been shown to be associated with predictors of mortality, the length of hospital stays, and ventilator days in adult burn patients [9]. Non-lactate SID has not been investigated as thoroughly; one study found that lower non-lactate SID at ICU admission was a prognostic indicator of mortality in critically sick patients [8]. Specifically, the association of non-lactate SID with mortality has not been examined in non-hospitalized population. Based on the physicochemical effects of an acid-base disturbance on most physiological functions, it is conceivable that non-lactate SID will not only affect all-cause mortality but also cardiovascular and cancer mortality. Therefore, we examined the relationship between non-lactate SID and all-cause in a large cohort of community-dwelling adults.

Materials and methods

Data source

We used data from six two-year cycles (1999–2010) of the continuous National Health and Nutrition Examination Survey (NHANES) to answer our research question. NHANES is a cross-sectional, complex, multistage, stratified, clustering sampling design survey, representative of the civilian, non-institutionalized population of the United States. NHANES was approved by the Centers for Disease Control and Prevention's Institutional Review Board and all participants gave written consent. Details of the sampling procedures and data collection technique are available online (http://www.cdc.gov/nchs/nhanes/about_nhanes.htm accessed on February 2018) [15]. National Death Index (NDI) was used to determine vital status of the participants using probabilistic matching. NDI provided follow-up from enrollment of participants until December 2011.

Participants younger than 20 years or those with missing laboratory data were excluded from the study. Non-lactate SID was calculated by subtracting serum chloride from serum sodium (in mmol/L). Participants self-reported their age, sex, and race. Diabetes was defined as self-reported history of diabetes, the use of oral hypoglycemic agents, or insulin or hemoglobin A1C > 7%. Body mass index (BMI) was calculated as weight in kilogram divided by the square of height in meters. Hypertension was defined as the systolic blood pressure >140 mm of Hg, diastolic blood pressure >90 mm of Hg, past or present history of hypertension or antihypertensive therapy. Participants were categorized into non-smokers if they had never smoked cigarettes in their life, past smokers, if smoked >100 cigarettes over their lifetime, and current smokers, if they were actively smoking.

Sodium, chloride, bicarbonate and albumin concentrations were measured utilizing Beckman Synchron LX20. Creatinine was measured using the Jaffe rate method to determine the concentration of creatinine in serum. Hemoglobin A_{1c} was measured on the fully automated glycohemoglobin analyzer. C-reactive protein (CRP) was measured by latex-enhanced nephelometry. The estimated glomerular filtration rate (eGFR) was determined using the Chronic Kidney

Disease Epidemiology Collaboration formula [16]. Chronic kidney disease (CKD) was defined as an eGFR of <60 mL/min/1.73 m².

Statistical analysis

All analyses were performed considering the complex survey sampling design of the NHANES. Survey weights were generated from the six two-year cycles so that the results were representative of the adult United States population. Continuous variables were summarized as mean and standard deviation or median and interquartile range, as appropriate, while categorical variables were presented as percentages. We examined the relationship between non-lactate SID and all-cause mortality as a continuous variable. The non-lactate SID quartiles were used to explore the relationship independent of the distribution of non-lactate SID. Kaplan-Meier survival curve analyses were performed to examine unadjusted survival difference between the uppermost and the lower-most quartiles of non-lactate SID. We used Cox proportional hazard models to estimate hazard ratios for all-cause mortality without and with adjustment for potential confounders; age, sex, race, hypertension, smoker, diabetes, CKD, CRP, bicarbonate, albumin, BMI, self-reported history of congestive heart failure and coronary artery disease. Variables for inclusion in the models were selected a priori based on biological plausibility. As sensitivity analysis, we used competing risk analysis for estimating hazard ratios for cardiovascular, cancer and other-cause mortality taking into account participants who did not remain in the cohort due to death from competing causes. Competing risk analysis calculates the sub hazard ratios using the Fine and Gray method [17]. All analyses were performed using Stata 14 (College Station, TX) and a p-value < 0.05 was considered significant.

Results

Baseline characteristics

Of the 34,370 participants, 51% were females, 48% were males, 50% were Caucasians, 21% were smokers, 12% had diabetes, and 36% had hypertension (Table 1). The mean (SD) age of participants was 49.6 (18.4) years, the mean (SD) concentrations of sodium and chloride were 139.1 (2.4) mmol/L, and 103.5 (2.97) mmol/L respectively. The calculated mean (SD) non-lactate SID was 35.61 (2.62) mmol/L. During the 190,000 person-year follow-up (median follow-up duration = 4.5 years, range = 0–12 years), 2,895 (8.4%) participants died. The mortality secondary to cardiovascular, cancer, and other cause was observed in 750 (25.9%), 651 (22.5%) and 1,492 (51.6%) participants. As expected, participants who were older or had diabetes, hypertension, or CKD were more likely to die during follow-up (Table 1). Individuals in the highest non-lactate SID quartiles had significantly lower survival than individuals in the lowest quartile (p < 0.001; Figure 1). The estimated incidence rate of mortality per 1,000 person-years in each quartile was 9.44, 13.34, 15.7, and 21.7% (p < 0.001; Figure 2). Table 2 illustrates the characteristics of the study population according to the quartiles.

Primary outcomes

All-cause mortality

In unadjusted Cox proportional hazards model using non-lactate SID as a continuous variable, each one mmol/L SID increase was associated with a 2% increased risk of mortality (HR=1.02; 95% CI, 1.004–1.04; p=0.02). After adjusting for potential confounders, the association became stronger; each one mmol/L increase in non-lactate SID was associated with 7% increased risk of mortality (HR=1.07; 95% CI, 1.04–1.10, p<0.0001). When we examined the relationship between mortality and quartiles of non-lactate SID before adjusting for

Table 1: Baseline characteristics of the study population.

Characteristic	Alive	Dead
	n=31,475 (91.5%)	n=2,893 (8.4%)
Age, mean (SD), years	47.6(17.5)	71.1(13.5)
Elderly (>65 years), n (%)	6,043(19.2)	2,087(72.1)
Middle (40–65 years), n (%)	10,021(31.8)	632(21.8)
Young (20–40 years), n (%)	15,411(49)	176(6.1)
Female, n (%)	16,561(52.6)	1,233(42.6)
Serum creatinine, mean (SD), μmol/L	77.8(35.6)	104.3(85.7)
Estimated GFR, mean (SD), mL/min/1.73 m ²	95.49(23.32)	68.95(25.14)
BMI, mean (SD), kg/m ²	28.85(6.56)	27.78(6.44)
SBP, mean (SD), mmHg	123.2(18.7)	139(24.9)
DBP, mean (SD), mmHg	70.17(12.9)	66.8(25.1)
Follow up, mean (SD), years	5.63(3.6)	4.6(3.01)
Sodium, mean (SD), mmol/L	139.1(2.3)	139.07(3.03)
Chloride, mean (SD), mmol/L	103.6(2.8)	102.3(3.79)
Bicarbonate, mean (SD), mmol/L	24.7(2.3)	24.7(2.7)
nSID, mean (SD), mmol/L	35.5(2.6)	36.8(2.9)
Anion gap, mean (SD), mmol/L	10.7(2.4)	12.07(2.6)
CRP ^a , median (IQR)	0.2(0.4)	0.32(0.6)
HTN, n (%)	10,616(33.7)	1,937(66.9)
DM, n (%)	3,423(10.3)	724(25)
Ever smoker, n (%)	7,666(24.4)	1,155(39)
Current smoker, n (%)	6,946(22.1)	580(20)
Non-smoker, n (%)	16,838(53.5)	1,156(39.9)
Whites, n (%)	15,283(48.6)	1,753(60.5)
CKD, n (%)	2,243(67.8)	1,066(32.2)
Albumin, mean (SD), g/L	42.4(3.6)	41.1(3.8)
Hemoglobin, mean (SD), g/L	142(15)	135(12)

BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); Estimated GFR, Glomerular filtration rate (calculated using CKD-EPI equation); SBP, systolic blood pressure; DBP, diastolic blood pressure; nSID, non-lactate strong ion difference (difference between sodium and chloride concentrations); CRP, C-reactive protein; HTN, hypertension; DM, diabetes mellitus; CKD, chronic kidney disease. ^a Reported as median and interquartile range.

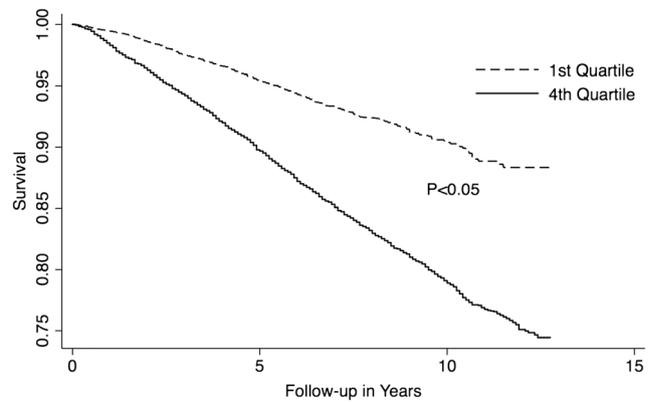


Figure 1: Kaplan-Meier Survival Curve illustrating survival difference between Quartile 1(14, 34) and Quartile 4(37, 53.1).

potential confounders, we found no significant difference between the lowest and the highest quartiles (HR=1.07; 95% CI, 0.93–1.23; p=0.29). However, after adjusting for potential confounders, we found a 50% higher risk of mortality for individuals in the highest quartile than those in the lowest quartile (HR=1.50; 95% CI, 1.25–1.79; p<0.0001) (Table 3).

Cardiovascular mortality

Using non-lactate SID as a continuous variable, we did not find significant association between nSID and

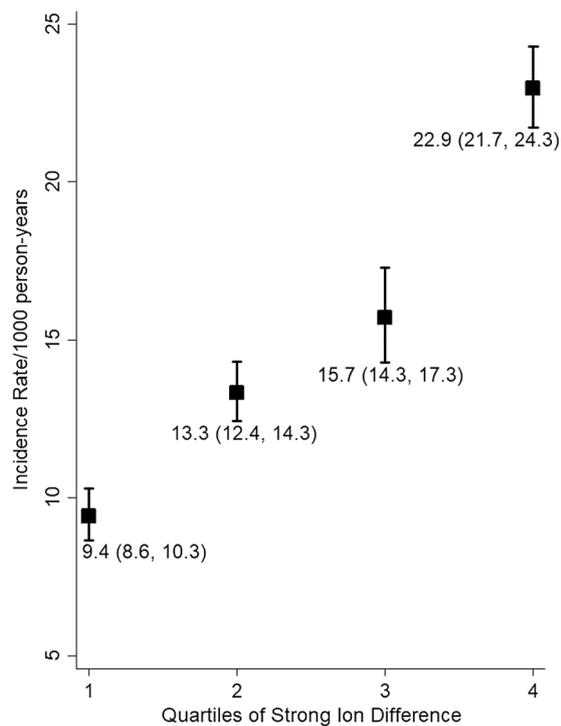


Figure 2: Estimated incidence rate of mortality per 1,000 in each quartile.

Table 2: Baseline characteristics of the study population according to quartiles of non-lactate strong ion difference.

Characteristic	Q1 ^a	Q2 ^b	Q3 ^c	Q4 ^d
	n=11,086 ^e	n=10,713 ^e	n=4,568 ^e	n=8,000 ^e
Age, mean (SD), years	44.6 ± 17.2	49.7 ± 18.04	51.6 ± 18.4	55.04 ± 18.6
Elderly (>65 years), n (%)	1,667(15.03)	2,446(22.8)	1,251(27.4)	2,764(34.5)
Middle-aged (40–65 years), n (%)	2,945(26.6)	3,546(33.1)	1,511(33.08)	2,651(33.1)
Young (20–40 years), n (%)	6,474(58.4)	4,721(44.07)	1,806(39.5)	2,585(39.3)
Creatinine, mean (SD), μmol/L	75.1 ± 30.9	78.6 ± 23.8	81.3 ± 38.02	88.4 ± 65.4
eGFR, mean (SD), mL/min/1.73 m ²	99.15 ± 25.17	93.25 ± 22.9	91.3 ± 22.8	86.24 ± 24.07
Albumin, mean (SD), g/L	40.8 ± 3.8	42.5 ± 3.2	43.1 ± 3.2	43.6 ± 3.5
Hemoglobin, mean (SD), g/L	137 ± 16	142 ± 15	144 ± 14	146 ± 15
BMI, mean (SD), kg/m ²	29.5 ± 6.6	28.6 ± 6.5	28.3 ± 6.4	28.2 ± 6.4
SBP, mean (SD), mmHg	119.8 ± 18.04	124.5 ± 19.3	126.6 ± 19.9	129.5 ± 20.9
DBP, mean (SD), mmHg	68.5(13.2)	70.3(12.5)	70.9(13.3)	70.8(14.4)
Follow up, mean (SD), years	4.97 ± 3.14	5.32 ± 3.4	5.73 ± 3.6	6.54 ± 3.9
Sodium, mean (SD), mmol/L	138.3 ± 2.3	139.1 ± 2.2	139.5 ± 2.3	139.9 ± 2.5
Chloride, mean (SD), mmol/L	105.6 ± 2.4	103.6 ± 2.2	102.6 ± 2.3	100.9 ± 2.7
Bicarbonate, mean (SD), mmol/L	23.3 ± 2.03	24.8 ± 1.9	25.4 ± 2.06	26.2 ± 2.4
nSID, mean (SD), mmol/L	32.7 ± 1.4	35.5 ± 0.51	36.9 ± 0.18	39.01 ± 1.5
CRP ^f , median (IQR)	0.23(0.44)	0.2(0.38)	0.2(0.38)	0.22(0.44)
Anion gap, mean (SD), mmol/L	9.47 ± 1.92	10.6 ± 1.9	11.5 ± 2.01	12.8 ± 2.4
HTN, n (%)	2,996(27.03)	3,755(35.05)	1,879(41.13)	3,922(49.02)
DM, n (%)	1,049(9.46)	1,211(11.3)	620(13.6)	1,266(15.8)
Non-smoker, n (%)	5,929(53.5)	5,699(53.2)	2,372(51.9)	3,994(49.9)
Current smoker, n (%)	2,603(23.5)	2,337(21.8)	972(20.2)	1,613(20.2)
Ever smoker, n (%)	2,544(22.9)	2,673(24.9)	1,220(26.7)	2,382(29.7)
Black, n (%)	2,088(18.8)	1,873(17.5)	883(19.3)	1,544(19.3)
White, n (%)	5,040(45.5)	5,366(50.09)	2,341(51.2)	4,288(53.6)
Hispanic, n (%)	3,451(31.1)	3,005(28.05)	1,130(24.7)	1,872(34.5)
CKD, n (%)	3,580(32.3)	3,342(31.2)	607(13.3)	1,864(23.3)

BMI, body mass index(calculated as weight in kilograms divided by height in meters squared); Estimated GFR, Glomerular filtration rate (calculated using CKD-EPI equation); SBP, systolic blood pressure; DBP, diastolic blood pressure; nSID, non-lactate strong ion difference (difference between sodium and chloride concentrations); CRP, C-reactive protein; HTN, hypertension; DM, diabetes mellitus; CKD, chronic kidney disease. ^a Q1 is defined as first quartile ranges from value of nSID from 14 to 34. ^b Q2 is defined as second quartile ranges from value of nSID from 34 to 36. ^c Q3 is defined as third quartile ranges from value of nSID from 36 to 37. ^d Q4 is defined as fourth quartile ranges from value of nSID from 37 to 53.1. ^e Reported as non-survey weighted does not add to make total number of observations used in analysis. ^f Reported as median and interquartile range.

cardiovascular mortality. Like all-cause mortality, after adjusting for potential confounders, the association became stronger; cardiovascular mortality risk increased by 5% for each one mmol/L increase in non-lactate SID (HR=1.05; 95% CI, 1.00–1.11; p=0.026). When we examined the relationship between cardiovascular mortality and quartiles of non-lactate SID, we found no significant difference between the lowest and the highest quartiles in unadjusted analysis (HR=1.17; 95% CI, 0.90–1.52, p=0.23). However, after adjusting for potential confounders, individuals in the highest quartile had 46% higher risk of mortality than those in the lowest quartile (HR=1.48; 95% CI, 1.01–2.10; p=0.04). The sensitivity analysis using the competing risk regression model confirmed the results of the Cox proportional hazards model. There was significant relationship in the unadjusted analysis(HR 1.03; 95% CI,

1.002–1.06; p=0.031), and after adjustment for potential confounders, we found 6% higher risk for cardiovascular mortality with each mmol/L increase in non-lactate SID (HR=1.06; 95% CI, 1.02–1.10; p<0.001). Similarly, the difference between the highest and lowest quartile in the adjusted competing risk analysis was statistically significant (HR=1.53; 95% CI, 1.16–2.00; p=0.02; Table 3).

Cancer mortality

Although unadjusted Cox proportional hazard model did not find an association between non-lactate SID and cancer mortality (HR=1.01; 95% CI, 0.97–1.06; p=0.49), after adjusting for potential confounders, we found 7% increased risk of cancer mortality with each unit increase in non-lactate SID (HR=1.07; 95% CI, 1.02–1.12; p=0.007).

Table 3: Cox proportional hazard models used to estimate hazard ratio (HR) and 95% confidence intervals for all-cause mortality.

Characteristic	Model 1 ^a	Model 2 ^b	Model 3 ^c	Model 4 ^d
All-cause mortality				
nSID (continuous)	1.02(1.00–1.04)	1.07(1.04–1.10)		
nSID (quartiles)	REF	REF		
Q1				
Q2	0.88(0.78–0.99)	1.08 (0.93–1.25)		
Q3	0.99(0.86–1.15)	1.33(1.13–1.55)		
Q4	1.07(0.93–1.23)	1.53(1.25–1.79)		
Cardiovascular mortality				
nSID (continuous)	1.03(0.99–1.08)	1.05 (1.00–1.11)	1.04(1.0–1.07)	1.06(1.04–1.10)
nSID (quartiles)	REF	REF	REF	REF
Q1				
Q2	1.04(0.85–1.35)	1.29 (0.97–1.73)	1.12(0.89–1.41)	1.33(1.03–1.72)
Q3	1.19(0.88–1.60)	1.42 (1.00–2.02)	1.04(0.80–1.37)	1.30(0.96–1.77)
Q4	1.17(0.90–1.47)	1.46 (1.01–2.10)	1.18(0.95–1.47)	1.53(1.16–2.00)
Cancer mortality				
nSID (continuous)	1.01(0.97–1.06)	1.07(1.02–1.12)	1.02(0.99–1.05)	1.05(1.01–1.09)
nSID (quartiles)	REF	REF	REF	REF
Q1				
Q2	0.83(0.64–1.08)	1.01(0.77–1.33)	0.91(0.71–1.15)	1.02(0.79–1.33)
Q3	1.28(0.94–1.74)	1.70(1.23–2.33)	1.10(0.84–1.44)	1.34(1.00–1.81)
Q4	1.05(0.81–1.37)	1.46(1.08–1.97)	1.05(0.84–1.32)	1.36(1.04–1.78)
Other cause mortality				
nSID (continuous)	1.02(0.99–1.05)	1.08(1.04–1.12)	1.03(1.0–1.05)	1.10(1.07–1.13)
nSID (quartiles)	REF	REF	REF	REF
Q1				
Q2	0.84(0.69–1.01)	1.04(0.82–1.32)	0.88(0.75–1.03)	1.19(0.95–1.35)
Q3	0.80(0.65–1.00)	1.12(0.88–1.44)	0.93(0.77–1.12)	1.39(1.13–1.71)
Q4	1.04(0.85–1.27)	1.54(1.17–2.01)	1.14(0.98–1.32)	1.85(1.55–2.21)

nSID, non-lactate strong ion difference (difference between sodium and chloride concentration in mmol/L); HR, Hazard ratio; CI, confidence interval. Covariates adjusted in multivariable model: sex, age, white race, hypertension, Diabetes mellitus, C-reactive protein, CKD, serum bicarbonate, smoking status, serum albumin, body mass index, history of congestive heart failure and coronary artery disease. ^a Model 1 depicts nSID and quartiles in unadjusted regression. ^b Model 2 depicts nSID and quartiles in adjusted regression. ^c Model 3 depicts nSID and quartiles in unadjusted competing risk regression. ^d Model 4 depicts nSID and quartiles in adjusted competing risk regression.

Similarly, there was no difference in cancer mortality between the lowest and highest quartiles in unadjusted analysis (HR=1.05; 95% CI, 0.81–1.37; $p=0.67$); after adjustment for potential confounders we found 46% higher risk of mortality in the highest quartile than those in the lowest quartile of non-lactate SID (HR=1.46; 95% CI, 1.08–1.97; $p=0.013$). In the sensitivity analysis, unadjusted competing risk regression found no statistically significant difference but, in adjusted analysis, there was 5% higher risk for cancer mortality for each mmol/L increase in non-lactate SID (HR=1.05, 95% CI, 1.01–1.09; $p<0.005$). Similarly, unadjusted analysis found no difference in mortality between the quartiles of non-lactate SID but, after adjustment, individuals in the highest quartile had 36% higher risk of cancer death than those in the lowest quartile (HR=1.36; 95% CI, 1.04–1.78; $p=0.021$; Table 3).

Other-cause mortality

We found 2 and 8% increase risk of other-cause mortality with each mmol/L increase in non-lactate SID in unadjusted and adjusted Cox proportional hazards models respectively (HR=1.02; 95% CI, 0.99–1.05; $p=0.147$ and HR=1.08; 95% CI, 1.04–1.12; $p<0.001$ respectively). In contrast to unadjusted, adjusted analysis found a significant difference between the lowest and the highest quartiles of non-lactate SID (HR=1.56; 95% CI, 1.19–2.04; $p=0.001$ and HR=1.04; 95% CI, 0.85–1.27; $p=0.66$ respectively). Sensitivity analysis was consistent with Cox proportional model results; unadjusted and adjusted competing risk regression found 3 and 10% higher risk of other-cause mortality with each mmol/L increase in non-lactate SID (HR=1.03; 95% CI, 1.008–1.05; $p=0.008$ and

HR=1.10; 95% CI, 1.07–1.13; $p < 0.001$). The difference in other-cause mortality between the highest and the lowest quartiles of non-lactate SID was present only with adjustment for potential confounders (unadjusted HR=1.14; 95% CI, 0.98–1.32; $p = 0.071$ and adjusted HR=1.85; 95% CI, 1.55–2.21; $p < 0.001$; Table 3).

Discussion

From this large community-based nationally representative cohort of the adult population of the United States, we report a linear association between non-lactate SID and all-cause mortality. This association not only persists but gets stronger after adjusting for confounding variables. The association also persists when non-lactate SID is examined in quartiles suggesting that the association is independent of the underlying distribution of the non-lactate SID.

Non-lactate SID has been an area of research in critical care research as it has been studied only in critically ill patients [8, 9, 18]. It is well known that non-lactate SID correlates strongly with bicarbonate especially in a patient with hyperchloremic acidosis [18]. Depending on the study, the normal SID was considered to be 38 ± 1 , 40 ± 3.8 , 40 , 40 – 42 , and 42 mmol/L, as these values were present in patients with lower mortality and normal acid base milieu [14, 19–22]. Even when the sodium and chloride concentrations are normal, non-lactate SID ranges from 33.5 ± 1.8 to 54.5 ± 1.8 mmol/L [22]. Thus, the relationship between sodium and chloride concentrations is more important than their individual values as high and low non-lactate SID may occur independent of sodium and chloride concentrations [8]. We did not include other cations, such as calcium or magnesium or anions, such as urate, in our model due to their small molar concentrations in plasma.

To our knowledge, this is the first study that has examined the relationship between non-lactate SID and all-cause mortality. Previous studies have examined the effect of non-lactate SID on mortality among patients admitted to intensive care units and found that low non-lactate SID were associated with higher risk of mortality [8]. In contrast, we found that higher non-lactate SID was associated with higher risk of all-cause mortality. While the mechanisms underlying these disparate results are unclear, and were not the subject of this study, several differences between our study and other studies are obvious. Patients in intensive care units are critically ill and the acid-base milieu is deranged secondary to multiple factors such as infection, sepsis, renal failure, lactic acidosis and hyperchloremia. On the other hand, there is a scarcity of data examining the role of acid-base status in predicting

mortality in community-dwelling adults. In fact, it is known that patients in intensive care units have higher levels of unexplained anions that may result in lower SID than healthy control [23]. High non-lactate SID can be due to multiple factors such chloride loss, sodium gain, mineralocorticoid excess, Barter syndrome, Liddle syndrome, Cushing syndrome and severe deficiency of intracellular cations [24]. These causes usually result in metabolic alkalosis. In critically ill patients, metabolic alkalosis contributes to mortality by causing cardiovascular, respiratory, metabolic and cerebral adverse events [25].

Our study has important implications for clinical practice and future research. We demonstrate that acid-base disorders, such as non-lactate SID, are important for non-hospitalized individuals. Chronic diseases and medications that result in acid-base disorders in non-hospitalized patients may increase the risk of mortality through alteration of acid-base milieu of the body. Further research may focus on examining the effect of strategies and therapies that optimize the acid-base milieu on all-cause mortality.

Strength and limitations

The strength of our study is its large sample size representative of the community-dwelling individuals in the United States. We considered important potential confounders of the association between non-lactate SID and all-cause mortality. Despite its strengths, there are a few limitations. We did not calculate non-lactate SID including strong ions calcium, potassium and magnesium because of the non-availability of magnesium values in the data sets. We did not adjust for diuretics and dietary intake due to lack of data.

Conclusions

In cross sectional data of US adults, increase in non-lactate SID is associated with high all-cause mortality and our results are robust to statistical modeling assumptions. Future research is needed to validate our findings and discovery of therapies that can optimize the non-lactate SID. These findings provide a point of reference for future studies.

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