Plasma Bicarbonate and Odds of Incident Hypertension

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BACKGROUND
Several biomarkers of metabolic acidosis, including lower plasma bicarbonate, have been associated with prevalent hypertension in cross-sectional studies. We sought to examine prospectively whether lower plasma bicarbonate is associated with incident hypertension.

METHODS
We conducted a prospective case–control study nested within the Nurses' Health Study II. Plasma bicarbonate was measured in 695 nonobese women without hypertension at time of blood draw who subsequently developed hypertension during 6 years of follow-up. Control subjects were matched to case subjects according to age, race, time and day of blood draw, and day of menstrual cycle. We used unconditional logistic regression to generate odds ratios (ORs) for development of hypertension by quintile of baseline plasma bicarbonate.

RESULTS
After adjusting for matching factors, body mass index, family history of hypertension, plasma creatinine, and dietary and lifestyle factors, higher plasma bicarbonate was associated with lower odds of developing hypertension across quintiles (*P* for linear trend = 0.04). Those in the highest compared with the lowest quintile of plasma bicarbonate had 31% lower odds of developing hypertension (OR = 0.69; 95% confidence interval = 0.48–0.99). Further adjustment for diet-estimated net endogenous acid production, plasma insulin, 25-hydroxyvitamin D, and uric acid did not alter these findings.

CONCLUSIONS
Our case–control study is consistent with a modest association between higher plasma bicarbonate and reduced odds of developing hypertension among nonobese women, although our findings are of borderline statistical significance. Further research is required to confirm this finding as part of a larger prospective cohort study and to elucidate the mechanism for this relation.

Keywords: acidosis; bicarbonate; blood pressure; hypertension; risk factor; total CO_2.

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More than 60% of individuals aged 60 years or older have hypertension,[1] which is associated with increased risk of cardiovascular events, cardiovascular mortality, and all-cause mortality.[2,3] Hypertension therefore represents a key public health concern, and efforts to identify modifiable hypertension risk factors and new approaches to risk reduction are imperative.

Metabolic acidosis potentially represents one such novel, modifiable risk factor. Recent cross-sectional epidemiologic studies have demonstrated an association between markers of metabolic acidosis, such as lower serum bicarbonate, higher anion gap, and lower urinary citrate, and hypertension. In the National Health and Nutrition Examination Survey and other populations, both lower serum bicarbonate and higher anion gap, even within ranges considered normal, have been associated with higher blood pressure and increased prevalence of hypertension.[4,5] Further, lower urinary citrate excretion has been associated with prevalent hypertension in the Nurses' Health Studies I and II and the Health Professionals Follow-up Study.[6] However, it is unclear whether these associations represent a cause or consequence of hypertension.

To address this question, we examined the association between plasma bicarbonate and subsequent development of hypertension in a prospective case–control study nested within the Nurses' Health Study II.

METHODS

Source population

In 1989, 116,430 female registered nurses aged 25 to 42 years enrolled in the Nurses' Health Study II by completing and returning an initial questionnaire that provided detailed information on medical history, lifestyle, and medications. Participants have been followed using biennial mailed questionnaires. The follow-up for the cohort exceeds 90% of eligible person-time. From 1997 to 1999, 29,616 participants contributed blood samples that were stored in liquid nitrogen (−130 °C). Characteristics of

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those submitting blood samples were similar to the overall cohort population.

Study population

To conduct nested, prospective case–control studies of associations between plasma biomarkers and subsequent odds of incident hypertension, we previously identified 750 nonhypertensive and nonobese (body mass index (BMI) < 30 kg/m^2) participants who provided a blood sample and did not have diabetes, coronary heart disease, or cancer (except nonmelanoma skin cancer), had been fasting at least 8 hours at the time of blood draw, and who developed new-onset hypertension (i.e., case subjects) between blood draw and 2005.[7,8] Using risk set sampling, we matched control subjects 1:1 to hypertension case subjects according to age, race, time and day of blood draw, and day of menstrual cycle.[7,8] For this analysis, we excluded individuals whose samples were unable to be assayed (n = 10 case subjects and 15 control subjects) and those with processing delays (discussed below; n = 45 case subjects and 38 control subjects). Thus, our final study population consisted of 695 case subjects and 697 control subjects, of which 651 were matched pairs.

Ascertainment of hypertension

Clinician-diagnosed hypertension was self-reported by the participants on the biennial questionnaires. Self-reported hypertension was validated using medical record review in a similar cohort of nurses, with agreement nearly 100%.[9] Participants were considered to have prevalent hypertension if they reported hypertension on any questionnaire before blood draw or if they reported hypertension or use of antihypertensive medicines on the questionnaire immediately after blood draw.

Assessment of covariables

Baseline characteristics of case and control subjects were assessed at, or closest to, the time of blood draw. Age and weight were obtained from the supplemental questionnaire returned with the blood samples. BMI was computed as weight in kilograms divided by height in meters squared. Self-reported weights have been shown to correlate with measured weights (r = 0.97).[10] Other baseline exposures, including physical activity, smoking status, menopausal status, postmenopausal hormone use, and newly diagnosed medical conditions, were ascertained from the biennial questionnaire immediately after blood draw. Diet and alcohol consumption were assessed in 1991, 1995, and 1999 using semiquantitative food frequency questionnaires. Dietary factors and physical activity were calculated as updated cumulative average levels as of the baseline questionnaire. Diet-estimated net endogenous acid production (NEAP) was calculated according to the Frassetto equation.[11] The validity of self-reported physical activity and diet using our questionnaires has been described.[12–14]

Laboratory procedures

Between 1997 and 1999, women who agreed to provide a blood sample were sent a phlebotomy kit and returned the sample with a cold pack by overnight mail. Upon arrival, samples were processed and frozen in liquid nitrogen (−130 °C) until analysis; 97% arrived within 26 hours of phlebotomy. All assays were performed on aliquots from these stored samples.

Plasma total carbon dioxide ("bicarbonate") was measured using an enzymatic technique on the Hitachi 917 analyzer using reagents and calibrators from Roche Diagnostics (Indianapolis, IN). Study samples were analyzed in randomly ordered case–control pairs to reduce systematic bias and interassay variation. The intra-assay coefficient of variation (CV) was 4.5%. However, our previous pilot studies of plasma bicarbonate suggested greater variability with longer processing times (within-person correlation was 0.72 for samples processed at 0 compared with 24 hours compared with a correlation of 0.15 for samples processed at 0 compared with 48 hours). Thus, we excluded participants with processing times greater than 24 hours (n = 45 case subjects and 38 control subjects). Creatinine was measured using a modified Jaffe method and glomerular filtration rate (GFR) was estimated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[15] The CV for creatinine was 6.5%. Uric acid levels were determined by oxidation with the specific enzyme uricase to form allantoin and hydrogen peroxide (Roche Diagnostics). The CV for uric acid was 3.4%. Insulin levels were measured using a radio-immunoassay (Roche Diagnostics). The CV for insulin was 10.4%. Plasma concentration of 25-hydroxyvitamin D (25(OH)D) was determined by an enzyme immunoassay from Immunodiagnostic Systems (Fountain Hills, AZ). The CV for 25(OH)D was 3.2%.

Statistical analysis

Depending upon the distribution of each variable, we compared baseline characteristics of participants by case status using the Student t test, Wilcoxon rank-sum test, or χ^2 test. Spearman correlations were used to examine correlations between continuous plasma bicarbonate and considered covariables. We divided the distribution of plasma bicarbonate into quintiles according to the distribution in control subjects. For continuous variables, we evaluated trends of baseline characteristics across the quintiles of plasma bicarbonate using generalized linear models. For dichotomous and categorical variables, we evaluated trends of baseline characteristics across the quintiles of plasma bicarbonate using logistic regression. Application of our exclusion criteria led to 90 unmatched case and control subjects. To maximize the size of our study population, we used unconditional logistic regression to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for quintiles of plasma bicarbonate and development of hypertension. We adjusted all models for matching factors and considered potential confounders, including those possibly associated with our exposure of interest as well as factors associated with hypertension. These included BMI,

plasma creatinine, uric acid, insulin, 25(OH)D, physical activity, smoking, alcohol intake, caffeine intake, family history of hypertension, diet-estimated NEAP, and intakes of total fat, carbohydrates, animal protein, potassium, calcium, magnesium, sodium, folate, and dietary fiber. We explored effect modification by age and BMI, stratifying on age at the median (43.0 years) and BMI <25.0 or ≥25.0 kg/m^2. Further, because chronic kidney disease is associated with both low plasma bicarbonate[16] and hypertension,[17] we conducted an additional sensitivity analysis in which we excluded the 16 individuals with estimated GFR (eGFR) < 60 ml/min/1.73m^2. Moreover, because selection of control subjects via risk-set sampling was conducted as of the 2005 follow-up data, some control subjects were known to have subsequently developed hypertension. We addressed this in a secondary analysis in which we considered those control subjects that subsequently developed hypertension between 2005 and 2009 as both case subjects and control subjects. Finally, because higher diet-estimated NEAP,[18] higher plasma insulin,[7,19] higher uric acid,[7,20,21] and lower 25(OH)D[8,22] have been associated with development of hypertension and may underlie the association between low plasma bicarbonate and risk of developing hypertension, we added these factors to our final model to ascertain whether they attenuated the association between plasma bicarbonate and incident hypertension. The significance of linear trends across quintiles of plasma bicarbonate was tested by assigning the median value for the quintile to each participant and considering this value as a continuous variable. We used SAS (version 9.2; SAS Institute, Cary, NC) for all analyses. The study was approved by the institutional review board of Partners HealthCare System, Boston, Massachusetts.

RESULTS

At baseline, women who subsequently developed hypertension had higher BMI, less physical activity, and a greater prevalence of family history of hypertension than women who did not (Table 1). Further, they had lower intakes of dietary fiber and carbohydrates and higher intakes of animal protein and total fat. Plasma bicarbonate and 25(OH)D levels were significantly lower ($P = 0.03$ and $P < 0.001$, respectively) in those who subsequently developed hypertension, whereas plasma uric acid and insulin levels were higher among those who subsequently developed hypertension ($P < 0.001$).

Baseline characteristics of controls by quintile of plasma bicarbonate are shown in Table 2. Those in the higher quintiles of plasma bicarbonate tended to have higher dietary carbohydrate intake, lower total fat intake, lower sodium intake, and lower plasma insulin levels (P for linear trend across quintiles < 0.05), although in general the absolute differences were small. Plasma bicarbonate was positively correlated with dietary carbohydrate intake (rho = 0.11; $P < 0.01$) and negatively correlated with dietary total fat intake (rho = −0.10; $P = 0.01$). Correlation coefficients for plasma bicarbonate and all other considered covariables were all <0.10.

Higher plasma bicarbonate was associated with lower odds of incident hypertension across the quintiles after adjusting for matching factors (Table 3, model 1) (P for linear trend = 0.007). Individuals in the highest quintile of plasma bicarbonate had 35% lower odds of developing hypertension than those in the lowest quintile (OR = 0.65; 95% CI = 0.47–0.91). Additional adjustment for BMI attenuated the association (P for linear trend = 0.06), especially in the highest two quintiles (Table 3, model 2). Further adjustment for family history of hypertension, plasma creatinine, smoking, physical activity, alcohol intake, and intakes of animal protein, potassium, carbohydrate, total fat, calcium, magnesium, dietary fiber, folate, sodium, and caffeine yielded an OR of 0.69 (95% CI = 0.48–0.99) comparing individuals in the highest quintile with individuals in the lowest quintiles of plasma bicarbonate (P for linear trend = 0.04) (Table 3, model 3; Figure 1). Finally, conditional logistic regression in the subpopulation with matched case and control subjects (n = 651 pairs) yielded similar point estimates, although the P for linear trend in this smaller subset was not statistically significant.

Given the association of obesity with hypertension, we considered BMI linearly and with both a linear and squared term in 2 different models to ensure adequate control for confounding by BMI. The point estimates did not change regardless of method for controlling for BMI. Finally, to minimize confounding by obesity, we added waist circumference to continuous BMI in a secondary analysis and observed similar results.

We did not observe effect modification by age or BMI, as point estimates were similar for all stratified analyses. Further, exclusion of the 16 individuals with eGFR < 60 ml/min/1.73m^2, as well as consideration of control subjects that subsequently developed hypertension between 2005 and 2009 as both case subjects and control subjects, yielded similar results to the primary analysis. Finally, the ORs for development of hypertension by quintile of plasma bicarbonate were not materially different when diet-estimated NEAP, plasma insulin, uric acid, and 25(OH)D were included in the model.

DISCUSSION

Among nonobese adult women, higher plasma bicarbonate was modestly associated with lower odds of developing hypertension after adjusting for matching factors. After controlling for potential confounders, including dietary, lifestyle, and medical factors, the point estimates were similar, although the P for trend was of borderline statistical significance. Our study is therefore consistent with a modest inverse association between plasma bicarbonate and risk of incident hypertension, although our results need to be interpreted cautiously. Nonetheless, to our knowledge, this is the first prospective study to demonstrate a possible association between lower plasma bicarbonate, a marker of metabolic acidosis, and development of hypertension.

We found that BMI was the strongest confounder of the association between plasma bicarbonate and odds of incident hypertension, as demonstrated in Table 3, model 2. Given that higher BMI has been associated with both hypertension[23] and other markers of metabolic acidosis, including higher NEAP,[18] impaired ammonia production,[24] and lower

Table 1. Baseline characteristics of the study population by case subject status

Characteristic	Case subjects (n = 695)	Control subjects (n = 697)	*P* value
Age at blood draw, years	42.9 (4.0)	42.9 (4.0)	0.61
White, %	93	95	0.07
Body mass index, kg/m^2	25.1 (22.9–27.5)	23.1 (21.0–25.4)	<0.001
Activity, METs/wk	13.1 (5.2–24.6)	14.7 (6.6–27.9))	0.008
Smoking status, %			0.43
Never smoked, %	71	73	
Past smoker, %	24	22	
Current smoker, %	5	5	
Alcohol intake, g/d	1.2 (0–4.4)	1.6 (0–4.3)	0.58
Animal protein intake, g/d	61 (52–68)	59 (51–66)	0.003
Total fat intake, g/d	62 (55–69)	61 (55–66)	0.02
Carbohydrate intake, g/d	229 (211–245)	234 (216–251)	<0.001
Potassium intake, mg/d	3,006 (2,708–3,356)	3,026 (2,728–3,376)	0.34
Magnesium intake, mg/d	304 (275–339)	313 (281–346)	0.005
Total calcium intake, mg/d	1,025 (827–1,317)	1,085 (871–1,329)	0.22
Dietary fiber intake, g/d	18.1 (15.6–20.9)	18.7 (16.1–22.0)	0.008
Folate intake, μg/d	268 (124–485)	278 (138–495)	0.10
Sodium intake, mg/d	2,097 (1,917–2,269)	2,116 (1,929–2,294)	0.23
Caffeine intake, mg/d	185 (86–332)	174 (70–334)	0.19
Estimated net endogenous acid production, meq/d	49 (43–56)	48 (42–54)	0.004
Family history of hypertension, %	64	50	<0.001
Creatinine, mg/dl	0.78 (0.71–0.86)	0.79 (0.72–0.86)	0.23
eGFR, ml/min/1.73m^2	94 (83–104)	92 (83–102)	0.32
25-hydroxyvitamin D, nmol/L	64 (51–78)	68 (54–83)	<0.001
Uric acid, mg/dl	4.1 (3.5–4.8)	3.7 (3.2–4.4)	<0.001
Insulin, μU/ml	5.4 (3.4–8.1)	4.1 (2.6–6.0)	<0.001
Plasma bicarbonate, mmol/L	22.0 (20.5–23.2)	22.1 (20.9–23.5)	0.03

Values are means (SD), median (IQR), or percentages. *P* values are from the Student *t* test for characteristics reported as means, Wilcoxon rank sum test for those reported as medians, and χ^2 test for those reported as percentages.

Abbreviations: eGFR, estimated glomerular filtration rate according to Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation; METs, metabolic equivalents.

urine pH,[25] this was not surprising. However, the association was borderline statistically significant after multivariable adjustment, suggesting that plasma bicarbonate may be associated with odds of incident hypertension independent of BMI.

Several potential mechanisms may underlie the association between metabolic acidosis and hypertension, including increased endothelial dysfunction,[26] activation of the renin-angiotensin system,[27,28] and increased salt sensitivity.[29,30] Alternatively, markers of acid–base balance may be regulated by factors that are associated with hypertension, such as low plasma 25(OH)D, high plasma insulin, and high plasma uric acid. Although our study did not directly address mechanisms, our findings were unchanged after further adjustment for plasma 25(OH)D, uric acid, and insulin, suggesting that the association may be independent of these factors. It is also possible that dietary acid load accounts for our findings. NEAP estimated from the dietary intakes of protein and potassium has previously been shown to be associated with incident hypertension.[18] However, adjustment for intakes of animal protein and potassium, as well as diet-estimated NEAP, did not alter the associations in our study. Chronic kidney disease is known to be associated with both hypertension[17] and lower plasma bicarbonate.[16] However, we adjusted for plasma creatinine, and our population consisted largely of individuals with eGFR ≥ 60 ml/min/1.73m^2, a level at which plasma bicarbonate is largely unaffected.[31] Moreover, exclusion of those individuals with eGFR < 60 ml/min/1.73m^2 yielded similar results. Finally, we speculate that metabolic acidosis may play a role in the metabolic syndrome. In a different population, we previously reported associations between higher plasma bicarbonate

Table 2. Baseline characteristics of control subjects by quintile of plasma bicarbonate

	Quintile of plasma bicarbonate (mmol/L)					
	Quintile 1 <20.7 (n=147)	Quintile 2 20.7–21.7 (n=141)	Quintile 3 21.8–22.6 (n=134)	Quintile 4 22.7–23.8 (n=141)	Quintile 5 >23.8 (n=134)	*P* value
Age at blood draw, years	42.9 (3.8)	42.9 (4.0)	42.9 (3.9)	42.9 (3.9)	42.8 (3.9)	0.98
White, %	94	96	94	95	97	0.30
Body mass index, kg/m^2	23.7 (21.4–25.6)	22.8 (21.0–25.4)	23.4 (21.5–25.7)	22.9 (20.5–25.0)	23.0 (21.3–25.4)	0.09
Activity, METs/wk	13.1 (6.9–26.2)	16.0 (7.7–27.5)	15.0 (5.6–28.3)	14.3 (6.9–25.4)	15.9 (7.0–32.9)	0.85
Smoking Status, %						
Never smoked, %	66	73	82	71	74	0.21
Past smoker, %	29	22	13	25	22	
Current smoker, %	5	5	5	4	4	
Alcohol intake, g/d	1.8 (0.3–5.2)	1.3 (0–3.7)	1.4 (0–3.6)	1.7 (0–4.1)	1.6 (0–4.5)	0.29
Animal protein intake, g/d	60 (50–68)	59 (51–64)	59 (52–66)	56 (51–65)	58 (48–67)	0.21
Total fat intake, g/d	63 (56–71)	61 (55–66)	61 (57–66)	60 (53–64)	61 (54–66)	0.006
Carbohydrate intake, g/d	228 (206–247)	235 (217–251)	235 (217–248)	239 (221–258)	235 (216–251)	0.002
Potassium intake, mg/d	2,967 (2,744–3,358)	3,073 (2,720–3,379)	3,050 (2,771–3,376)	3,026 (2,727–3,413)	3,019 (2,707–3,366)	0.81
Magnesium intake, mg/d	304 (280–339)	320 (282–348)	311 (294–343)	315 (279–350)	318 (278–356)	0.50
Total calcium intake, mg/d	1,076 (828–1,308)	1,100 (883–1,294)	1,162 (915–1,403)	1,048 (859–1,372)	1,053 (853–1,342)	0.86
Dietary fiber intake, g/d	17.7 (15.6–21.4)	19.3 (16.4–22.3)	18.5 (16.2–21.0)	19.5 (15.7–22.9)	18.8 (16.4–22.5)	0.16
Folate intake, µg/d	203 (118–480)	269 (134–472)	297 (144–477)	293 (140–561)	318 (150–527)	0.11
Caffeine intake, mg/d	204 (87–398)	174 (63–293)	174 (52–313)	155 (89–334)	159 (70–333)	0.08
Sodium intake, mg/d	2,127 (1,963–2,356)	2,116 (1,899–2,294)	2,126 (1,910–2,290)	2,085 (1,916–2,258)	2,109 (1,903–2,293)	0.04
Net endogenous acid production, meq/d	49 (43–55)	48 (42–53)	49 (43–53)	47 (43–52)	49 (42–55)	0.42
Family history of hypertension, %	50	48	49	48	57	0.33
Creatinine, mg/dl	0.79 (0.72–0.86)	0.79 (0.72–0.86)	0.79 (0.73–0.87)	0.79 (0.72–0.85)	0.79 (0.72–0.86)	0.26
eGFR, ml/min/1.73m^2	93 (82–103)	92 (83–101)	92 (83–102)	93 (84–102)	93 (82–103)	0.33
25-hydroxyvitamin D, nmol/L	67 (54–83)	70 (54–83)	68 (51–81)	68 (55–83)	70 (55–88)	0.25
Uric acid, mg/dl	3.8 (3.2–4.5)	3.6 (3.2–4.3)	3.9 (3.3–4.5)	3.7 (3.3–4.2)	3.8 (3.2–4.4)	0.57
Insulin, µU/ml	4.5 (2.7–6.9)	4.2 (2.6–5.8)	4.1 (2.7–6.3)	3.7 (2.6–5.8)	4.0 (2.7–5.8)	0.03
Plasma bicarbonate, mmol/L	19.7 (18.8–20.3)	21.2 (21.0–21.4)	22.2 (21.9–22.4)	23.2 (22.9–23.5)	24.8 (24.2–25.8)	<0.001

Values are mean (SD), median (IQR), or percentages. *P* values are from generalized linear models for continuous variables and logistic regression for dichotomous and categorical variables.

Abbreviations: eGFR, estimated glomerular filtration rate according to Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation; METs, metabolic equivalents.

Table 3. Odds ratios of incident hypertension by baseline level of plasma bicarbonate

Model		OR (95% CI)					*P* for linear trend
		Plasma bicarbonate quintile 1	Plasma bicarbonate quintile 2	Plasma bicarbonate quintile 3	Plasma bicarbonate quintile 4	Plasma bicarbonate quintile 5	
		<20.7 mmol/L	20.7–21.7 mmol/L	21.8–22.6 mmol/L	22.7–23.8 mmol/L	>23.8 mmol/L	
	Case subjects, No.	192	132	131	122	118	
	Control subjects, No.	147	141	134	141	134	
Model 1[a]		Referent	0.71 (0.52–0.99)	0.75 (0.54–1.04)	0.64 (0.46–0.89)	0.65 (0.47–0.91)	0.007
Model 2[b]		Referent	0.79 (0.57–1.11)	0.79 (0.57–1.11)	0.75 (0.53–1.06)	0.73 (0.52–1.03)	0.06
Model 3[c]		Referent	0.82 (0.57–1.17)	0.83 (0.58–1.19)	0.75 (0.52–1.08)	0.69 (0.48–0.99)	0.04

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]Model 1 adjusted for matching factors: age at blood draw (continuous), race (white vs. nonwhite and Hispanic vs. non-Hispanic), time of blood draw (in 2-hour increments), day of blood draw (in months), and luteal day. N = 695 case subjects and 697 control subjects.

[b]Model 2 adjusted for matching factors and body mass index (continuous).

[c]Model 3 adjusted for matching factors, body mass index (continuous), family history of hypertension (binary), plasma creatinine (continuous), smoking (never, past, current), physical activity (quintiles of metabolic equivalents/week), alcohol intake (0 g/d, 0.1–5.0 g/d, 5.1–10.0 m/d, >10 m/d), intakes of animal protein, potassium, carbohydrate, total fat, calcium, magnesium, dietary fiber, folate, sodium, and caffeine (all in quintiles).

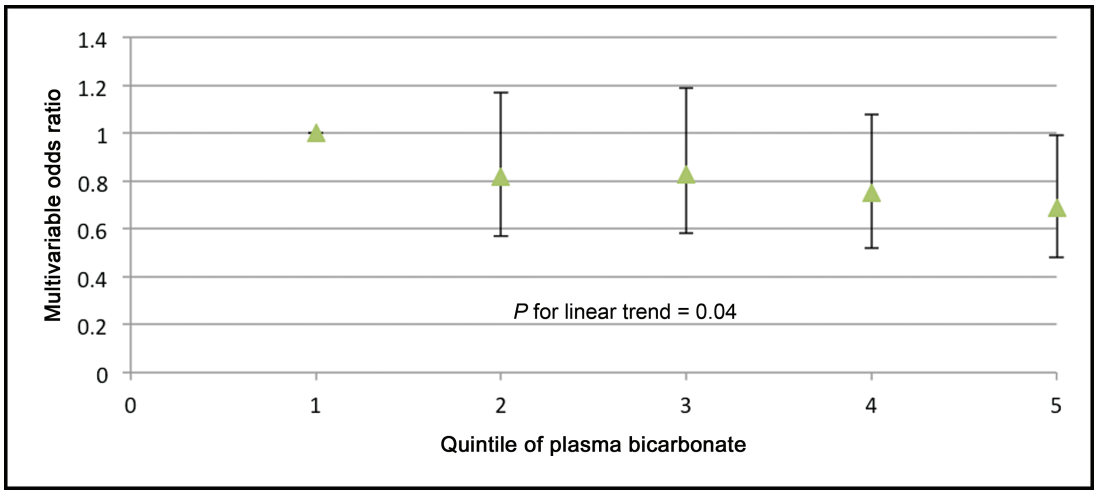

Figure 1. Multivariable odds ratios for incident hypertension by quintile of plasma bicarbonate. Multivariable odds ratio adjusted for matching factors—body mass index (continuous), family history of hypertension (binary), plasma creatinine (continuous), smoking (never, past, current), physical activity (quintiles of metabolic equivalents/week), alcohol intake (0 g/d, 0.1–5.0 g/d, 5.1–10.0 g/d, >10 g/d), and intakes of animal protein, potassium, carbohydrate, total fat, calcium, magnesium, dietary fiber, folate, sodium, and caffeine (all in quintiles).

and lower odds of developing type 2 diabetes mellitus, independent of hypertension.[32] In this study, we report an association between higher plasma bicarbonate and incident hypertension that is independent of plasma insulin. Taken together, these studies suggest a common underlying mechanism related to the metabolic syndrome that requires further exploration.

Whether alkali supplementation with citrate or bicarbonate salts to raise plasma bicarbonate will reduce risk of hypertension is uncertain. Past studies of potassium supplementation in hypertension have yielded mixed results and generally used potassium chloride, rather than citrate or bicarbonate as the conjugate base.[33,34] A small cross-over trial of 14 individuals treated first with potassium chloride and then potassium citrate for 1 week each showed a statistically significant decline in blood pressure from both potassium formulations but no statistically significant difference between formulations.[35] Further, among patients with chronic kidney disease (eGFR< 60 ml/min/1.73m^2), bicarbonate supplementation with sodium bicarbonate did not appreciably change blood pressure.[36] However, the small enrollments and short durations of these studies, as well as the heterogeneity in design, necessitate further exploration of the effects of alkali supplementation on blood pressure.

Our study has limitations. First, diagnosis of hypertension was ascertained by self-report, and data on covariables were obtained from questionnaires, which may result in misclassification. However, as noted above, both self-reported hypertension and questionnaire-derived data have

been validated. Second, the range of mean plasma bicarbonate among our participants was lower than that commonly encountered clinically, likely reflecting systematic measurement error related to storage or other laboratory techniques. Because samples were handled identically and the vials of case–control pairs were contiguous, such error would be expected to apply equally to both case and control subjects. Therefore, although the exact values of plasma bicarbonate may not lend themselves to direct clinical interpretation and application, the observed trends remain valid. Third, we did not have data on serum pH or renal net acid excretion for participants, limiting the ability to characterize precisely their acid–base status. Fourth, we had only 1 measurement of plasma bicarbonate so cannot draw conclusions as to how changes in bicarbonate over time may impact risk of hypertension. However, previous studies have reported a within-person coefficient of variation of 4.2% for repeated bicarbonate measurements,[37] suggesting that within-person variation in plasma bicarbonate levels over time is low. Fifth, although we used extensive data on potential confounders, confounding by other unmeasured or unknown factors may still exist. Finally, our results may not be generalizable to nonobese individuals, men, or racial or ethnic minorities.

Our study found a modest inverse association between higher plasma bicarbonate and odds of incident hypertension among nonobese women in the Nurses' Health Study II. However, because of the borderline statistical significance and case–control design, these findings will need to be confirmed in a larger prospective cohort study. Moreover, given the inclusion and exclusion criteria of our study, the association between plasma bicarbonate and incident hypertension needs to be examined in obese, older, and male populations. Finally, further research is required to elucidate the mechanism for this relation and to explore the role for increased dietary or supplementary alkali intake as a novel strategy for prevention of hypertension.

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DISCLOSURE

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