Relation of Dietary Sodium Intake With Subclinical Markers of Cardiovascular Disease (from MESA)

Karan Kapoor, MD[a,*], Oluwaseun Fashanu, MBBS, MPH[a], Wendy S. Post, MD, MS[a], Pamela L. Lutsey, PhD, MPH[a,b], Erin D. Michos, MD, MHS[a], Christopher R. deFilippi, MD[c], and J. William McEvoy, MBBCh, BAO, MEHP, MHS[a,d]

The associations between dietary sodium intake and markers of subclinical cardiovascular disease (CVD), such as high-sensitivity cardiac troponin T (hs-cTnT) and amino terminal pro b-type natriuretic peptide (NT-proBNP), may provide mechanistic insight into the relation between dietary sodium and cardiovascular events. We studied 6,131 participants of the Multi-Ethnic Study of Atherosclerosis, who were free of clinical CVD at baseline. Food frequency questionnaires were used to assess estimated sodium intake (ESI) at baseline. We tested the associations between 5 quintiles of ESI (quintile 1: 0.2 to 1.3 grams/day, quintile 2: 1.3 to 1.8 grams/day, quintile 3: 1.8 to 2.4 grams/day, quintile 4: 2.4 to 3.2 grams/day, and quintile 5: 3.2 to 9.9 grams/day) with cross-sectional and 5-year longitudinal change in hs-cTnT and NT-proBNP concentrations. Restricted cubic spline plots were utilized to explore the shape of the associations between ESI and biomarker outcomes. A cross-sectional association between baseline sodium intake and hs-cTnT (but not NT-proBNP) was observed, driven predominantly by a strong positive relation at an intake range of 0.2 to 2.4 g/day. Conversely, a longitudinal association between baseline sodium intake and NT-proBNP (but not hs-cTnT) was observed, driven predominantly by a strong positive relation at intake levels ≥2.4 g/day. In conclusion, temporal shifts in the association between increased ESI and markers of subclinical CVD, hs-cTnT in the short term and NT-proBNP in the longer term, point to the complex pathobiology of the association between sodium intake and CVD. There was also no consistent evidence supporting a J-curve (i.e., excess biomarker values at very low ESI). **(Am J Cardiol 2019;124:636−643)**

Sodium is a major component of our food supply, and excess dietary intake has an important role in the pathogenesis of hypertension.[1] Data from the National Health and Nutrition Examination Survey (NHANES) study estimate that average sodium intake in United States adults remains high, at approximately 3.6 g/day,[2,3] which vastly exceeds both the recommended upper limit of 2.3 g/day set by the 2015 United States Dietary Guidelines[4] and the more stringent limit of 1.5 g/day set by the American Heart Association.[5] By lowering blood pressure and reducing the risk for hypertension, sodium reduction should theoretically reduce cardiovascular disease (CVD).

One approach to further examine the relation of sodium intake with cardiovascular health is to study the associations between dietary sodium and markers of subclinical CVD. However, to our knowledge, the associations between dietary sodium intake and levels of high-sensitivity cardiac troponin T (hs-cTnT) and amino terminal pro b-type natriuretic peptide (NT-proBNP) have not yet been thoroughly examined. As such, we tested these associations in the Multi-Ethnic Study of Atherosclerosis (MESA).

Methods

Previous reports have described the MESA design in detail.[6] The MESA is a prospective observational cohort of 6,814 men and women who, at baseline (2000 to 2002), were free of clinical CVD and were between 45 and 84 years of age. Information on nutritional intake, predominantly by way of Food Frequency Questionnaires (FFQ), was available for 6,237 MESA participants (92%), consisting of a series of questions pertaining to the frequency and usual serving size for each of 120 food items.[7] The FFQ has been validated in relation to other metrics of dietary

[a]Department of Cardiology, Johns Hopkins Ciccarone Center for the Prevention of Cardiovascular Disease, Johns Hopkins Medical Institutions, Baltimore, Maryland; [b]Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, Minneapolis; [c]Inova Heart and Vascular Institute, Falls Church, Virginia; and [d]National Institute for Prevention and Cardiovascular Health, National University of Ireland, Galway, Ireland. Manuscript received March 24, 2019; revised manuscript received and accepted May 7, 2019.

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See page 642 for disclosure information.

*Corresponding author: Tel: 410-955-5999; fax: 410-367-2406

E-mail address: kkapoor5@jhmi.edu (K. Kapoor).

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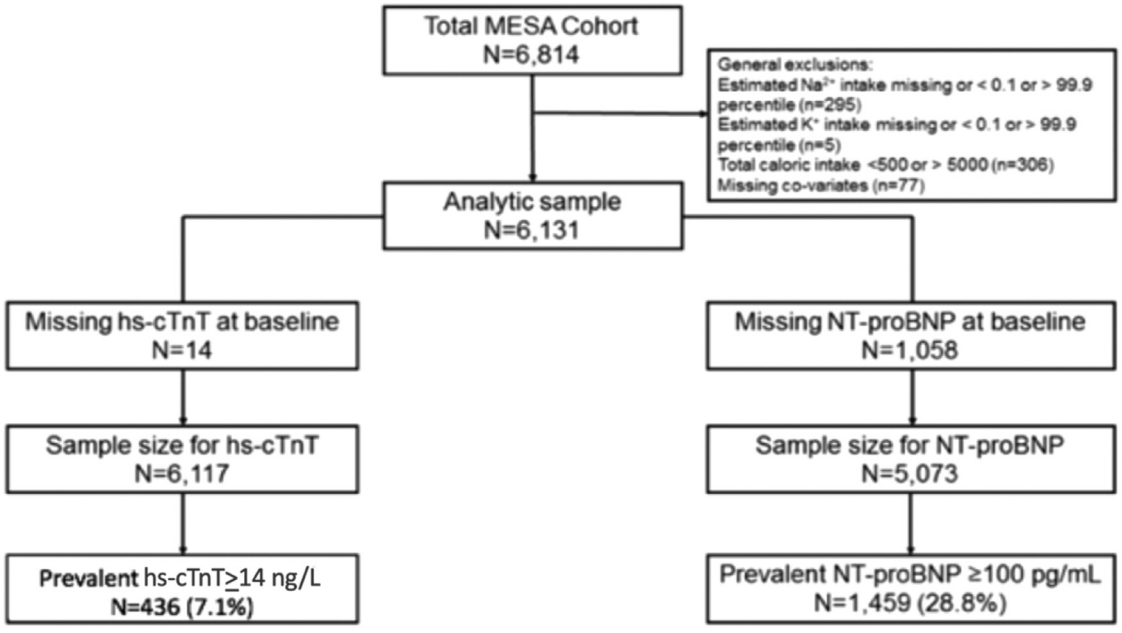

Figure 1. Figure 1 depicts the selection of final analytic cohort following application of aforementioned exclusion criterion.

sodium intake (namely, 24-hour urinary sodium excretion), with an area under the curve statistic for an excretion of >100 mmol sodium per day ranging from 0.57 to 0.76 in contemporary studies.[8,9] All FFQ responses were processed by the software package (DietSys Nutrient Analysis Program©), which subsequently assigned each participant an average estimated daily intake of sodium (ESI) based on their particular responses. Excluded from the analysis were (1) participants in whom ESI information was missing or those with implausible outlier values above or below the

Table 1
Baseline characteristics by estimated sodium intake quintile: The Multi-Ethnic Study of Atherosclerosis (MESA; 2000-2002)

Characteristic	Total	Estimated sodium intake (g/day)					p Value†
		Q1 (0.2-1.3 g/d)	Q2 (1.3-1.8 g/d)	Q3 (1.8-2.4 g/d)	Q4 (2.4-3.2 g/d)	Q5 (3.2-9.9 g/d)	-
N	6,131	1,227	1,226	1,226	1,226	1,226	
Age (years)	62.3 ± 10.2	63.9 ± 10.1	63.4 ± 10.3	62.0 ± 10.0	61.8 ± 10.1	60.3 ± 10.3	<0.001
Women	3,220 (52.5%)	823 (67.1%)	762 (62.2%)	639 (52.1%)	552 (45.0%)	444 (36.2%)	<0.001
White	2,427 (39.6%)	324 (26.4%)	477 (38.9%)	564 (46.0%)	555 (45.3%)	507 (41.4%)	<0.001
Black	1,614 (26.3%)	397 (32.4%)	296 (24.1%)	290 (23.7%)	283 (23.1%)	348 (28.4%)	<0.001
Hispanic	1,361 (22.2%)	279 (22.7%)	281 (22.9%)	229 (18.7%)	275 (22.4%)	297 (24.2%)	<0.001
Chinese	729 (11.9%)	227 (18.5%)	172 (14.0%)	143 (11.7%)	113 (9.2%)	74 (6.0%)	<0.001
Body mass index (kg/m^2)	28.3 ± 5.4	27.7 ± 5.4	27.8 ± 5.3	28.2 ± 5.4	28.5 ± 5.3	29.2 ± 5.5	<0.001
Current smoker	770 (12.6%)	133 (10.8%)	131 (10.7%)	152 (12.4%)	157 (12.8%)	197 (16.1%)	<0.001
Current alcohol	3,438 (56.1%)	598 (48.7%)	650 (53.0%)	722 (58.9%)	717 (58.5%)	751 (61.3%)	<0.001
Total cholesterol (mg/dl)	194.1 ± 35.4	197.3 ± 36.0	193.0 ± 33.7	194.7 ± 35.2	193.5 ± 35.8	191.9 ± 35.9	0.003
HDL cholesterol (mg/dl)	51.0 ± 14.9	53.7 ± 15.6	52.5 ± 15.4	51.3 ± 15.5	49.8 ± 14.1	47.9 ± 13.2	<0.001
Triglycerides (mg/dl)	131.5 ± 87.2	125.2 ± 77.9	130.7 ± 86.1	131.6 ± 77.5	133.1 ± 99.2	136.7 ± 93	0.02
eGFR (ml/min per 1.73 m^2)	77.6 ± 16.1	76.4 ± 16.1	76.2 ± 15.9	77.2 ± 16.4	78.2 ± 16.1	79.9 ± 15.9	<0.001
Hypertension medications	2,037 (33.2%)	469 (38.2%)	440 (35.9%)	380 (31%)	380 (31.0%)	368 (30.0%)	<0.001
Lipid lowering medications	1,005 (16.4%)	216 (17.6%)	230 (18.8%)	185 (15.1%)	204 (16.6%)	170 (13.9%)	0.009
Diabetes mellitus	755 (12.3%)	152 (12.4%)	160 (13.1%)	128 (10.4%)	155 (12.6%)	160 (13.1%)	0.25
SBP (mm Hg)	126.6 ± 21.3	128.0 ± 23.0	127.7 ± 21.7	125.7 ± 20.7	125.8 ± 20.3	125.7 ± 20.8	0.007
NT-proBNP*, (pg/ml)	55.2 (24.5 - 112.6)	61.5 (27.3 - 118.8)	64.1 (29.8 - 130.4)	58.7 (26.2 - 114.7)	51.6 (25.1 - 109.8)	42.0 (18.1 - 86.9)	<0.001
hs-cTnT*, (ng/L)	4.4 (3.0 - 7.5)	4.1 (3.0 - 6.9)	4.3 (3.0 - 7.0)	4.4 (3.0 - 7.5)	4.6 (3.0 - 7.9)	4.8 (3.0 - 8.2)	<0.001

eGFR = estimated glomerular filtration rate.

Results are mean ± SD and count (%) unless otherwise specified.

* Expressed as median (25th to 75th percentile).

† Derived for one-way ANOVA for normally distributed continuous variables and Kruskal-Wallis test for skewed continuous variables, chi-square test for categorical variables.

NB: P-for-trend was derived by using ESI categories as an ordinal variable and modeling this as a continuous variable in linear regression models using each baseline characteristic as the outcome.

99.9 and 0.1 percentile marks, respectively, (2) participants with unrealistic total caloric intake (≤500 g/day or ≥5,000 g/day), and (3) participants with missing covariate data. A flow chart is provided in Figure 1.

Hs-cTnT was measured in ethylenediaminetetraacetic acid plasma collected at baseline (examination 1; July 2000 to August 2002) and at examination 3 (March 2004 to September 2005). Hs-cTnT was measured at a MESA collaborative site laboratory (University of Maryland Medical Center; Baltimore, Maryland) using the Cobas e601 Analyzer (Roche Diagnostics©; Indianapolis, Indiana). A previously unthawed 250 μl sample of ethylenediaminetetraacetic acid plasma was used for analysis. For hs-cTnT, the intra-assay coefficients of variation observed for the cohort measurements were 4% at 28 ng/L and 2% at 2,154 ng/L. The limit of detection was 3 ng/L.

Similarly, NT-proBNP was measured in plasma specimens collected at baseline (examination 1) and at examinations 2 (September 2002 to February 2004) and 3 (March 2004 to September 2005), and were stored at a temperature range of −70°C to −80°C before thawing for analysis. NT-proBNP measurements were made on the Elecsys 2010 Analyzer (Roche Diagnostics©; Indianapolis, Indiana). The analytical measurement range was 5 pg/mL to 35,000 pg/ml, with a coefficient of variation range of 2% to 5%.

Differences in baseline characteristics among study participants in various categories of ESI were compared using the chi-square test for categorical variables and analysis of variance for continuous variables. Consistent with previously reported data, ESI was analyzed continuously and as a categorical exposure through quintiles as follows: quintile 1 (ESI 0.2 to 1.3 g/day), quintile 2 (ESI 1.3 to 1.8 g/day), quintile 3 (ESI 1.8 to 2.4 g/day), quintile 4 (ESI 2.4-3.2 g/day), and quintile 5 (ESI 3.2 to 9.9 g/day).[10] Our main outcome measures were average adjusted differences in hs-cTnT and NT-proBNP concentrations at the first examination (cross-sectional linear analysis) as well as the 5-year change in these parameters at subsequent follow-up examinations (longitudinal linear analysis). Additional outcomes studied included the odds of prevalent and incident hs-cTnT ≥14 ng/L and NT-proBNP ≥100 pg/ml at examinations 1 and 3, as well the odds of a≥25% increase in these parameters from baseline. The rationale for utilizing these categorical cut points relates to their association with higher cardiovascular event rates.[11–13] Individuals meeting these cut points at the time of examination 1 were excluded from this portion of the analysis.

For cross-sectional analyses, we conducted multivariable-adjusted linear regression when assessing biomarker concentrations as continuous outcomes, and multivariable-adjusted logistic regression when assessing biomarker concentrations as prevalent categorical outcomes. For prospective longitudinal analyses, we conducted multivariable-adjusted linear regression with generalized estimating equation models in order to determine the continuous association between ESI and temporal change in biomarker level, as well as multivariable-adjusted logistic regression when assessing biomarker levels as incident categorical outcomes. For each of these analyses, we used 3 sequential adjustment models. Model 1 adjusted for age and sex. Model 2 also included race/ethnicity, body mass index (kg*m^{-2}), smoking status (current,

Table 2
Average adjusted* cross-sectional differences in hs-cTnT and NT-proBNP (both log transformed) according to estimated sodium intake quintile at MESA Exam 1

	Categorical analysis					Continuous analysis	
	Q1 (0.2-1.3 g/d)	Q2 (1.3-1.8 g/d)	Q3 (1.8-2.4 g/d)	Q4 (2.4-3.2 g/d)	Q5 (3.2-9.9 g/d)	Per 1 g/day increment in ESI (≤2.4 g/day)	Per 1 g/day increment in ESI (>2.4 g/day)
ln hs-cTnT, ng/L							
N	1,224	1,222	1,224	1,223	1,224	3,687	2,430
Model 1	−0.018 (−0.059, 0.022)	Ref=0	0.044 (0.004, 0.085)	0.033 (−0.007, 0.074)	0.071 (0.029, 0.112)	0.043 (0.016, 0.069)	0.015 (−0.003, 0.032)
Model 2	−0.011 (−0.049, 0.027)	Ref=0	0.042 (0.004, 0.080)	0.029 (−0.009, 0.067)	0.049 (0.010, 0.088)	0.034 (0.009, 0.060)	0.007 (−0.009, 0.024)
Model 3	−0.009 (−0.047, 0.029)	Ref=0	0.043 (0.005, 0.081)	0.030 (−0.008, 0.068)	0.049 (0.011, 0.088)	0.034 (0.009, 0.060)	0.006 (−0.010, 0.023)
ln NT-proBNP, pg/ml							
N	1,000	1,022	1,000	1,018	1,033	3,038	2,035
Model 1	−0.117 (−0.199, −0.036)	Ref=0	0.041 (−0.040, 0.123)	0.016 (−0.065, 0.098)	−0.069 (−0.151, 0.013)	0.093 (0.038, 0.147)	−0.044 (−0.079, −0.008)
Model 2	−0.065 (−0.143, 0.013)	Ref=0	0.030 (−0.048, 0.108)	0.005 (−0.073, 0.083)	−0.064 (−0.143, 0.015)	0.049 (−0.004, 0.102)	−0.028 (−0.062, 0.006)
Model 3	−0.057 (−0.134, 0.02)	Ref=0	0.032 (−0.045, 0.109)	0.009 (−0.068, 0.086)	−0.064 (−0.142, 0.014)	0.047 (−0.006, 0.099)	−0.030 (−0.064, 0.004)

* Estimates are β coefficients.
Model 1: age and sex.
Model 2: Model 1 plus race/ethnicity, body mass index, smoking status, alcohol consumption, total cholesterol, high-density lipoprotein cholesterol, triglycerides, estimated glomerular filtration rate, lipid-lowering medication use, blood pressure–lowering medication, and history of diagnosed diabetes.
Model 3: Model 2 plus systolic BP.
NB: Linear spline 1 measures the slope for ESI ≤2.4 g/day and Linear spline 2 measures the slope for ESI >2.4 g/day.

former, and never), alcohol consumption (current, former, and never), total cholesterol (mg/dl), high-density lipoprotein cholesterol (mg/dl), triglycerides (mg/dl), estimated glomerular filtration rate (ml*min^{-1}*1.73 m^{-2}; as estimated by the Chronic Kidney Disease Epidemiology Collaboration equation; CKD-EPI), lipid-lowering medication use (yes or no), antihypertensive therapy (yes or no), and history of diagnosed diabetes (yes or no). In addition to the variables included in models 1 and 2, model 3 also adjusted for systolic blood pressure (in mmHg), a parameter which might mediate any association between ESI and biomarker levels. The measurement of the aforementioned covariates has been previously described.[6] In addition, in order to address the potential confounder of sodium reduction in patients with established hypertension, we performed sensitivity analyses excluding individuals with a history of hypertension and those on antihypertensive therapies at the baseline MESA visit.

We also used restricted cubic spline plots to explore the shape of the association between ESI (as a continuous exposure) and the biomarker outcomes, fitted with 4 knots (at the 5th, 35th, 65th, and 95th percentiles of the ESI distribution). On the basis of our restricted cubic spline plots for the primary outcome and the results of previous analyses, we also added a spline terms to our logistic regressions, evaluating associations between ESI and outcomes below and above a threshold of 2.40 g/day (22). All statistical analyses were performed using the Statistical Analysis Software (SAS) (Version 9.4; The SAS Institute©; Cary, North Carolina).

Results

Baseline characteristics of the study population are outlined in Table 1. The study included 6,814 participants, of whom 683 were excluded according to aforementioned criteria (see Figure 1). In the study sample of 6,131 participants, 14 were missing hs-cTnT and 1,058 were missing NT-proBNP at baseline. Accordingly, the sample sizes were 6,117 participants and 5,073 participants in the hs-cTnT and NT-proBNP outcome groups, respectively. In all studied participants, mean age was 62 years and 53% were female. Antihypertensive therapy was prescribed to 33% of participants at baseline and the mean systolic blood pressure was 126.6 mm Hg. There were inverse crude associations observed between ESI quintile and both systolic blood pressure and use of antihypertensive medications. Overall, hs-cTnT ≥14 ng/L was present in 436 (7%) whereas NT-proBNP ≥100 pg/ml was present in 1,459 (29%) of participants. The median baseline values of NT-proBNP and hs-cTnT were 55.2 pg/ml and 4.4 ng/L, respectively. It is noteworthy that baseline NT-proBNP values were highest in the reference quintile (ESI 1.3 to 1.8 g/day), an observation that was not seen in terms of hs-cTnT.

The average adjusted baseline cross-sectional differences in hs-cTnT and NT-proBNP, according to ESI quintile, are shown in Table 2. Compared with the reference quintile (i.e., quintile 2), significantly higher hs-cTnT levels were seen in quintiles 3 and 5, albeit in a nongraded fashion given the lack of a significant difference in quintile 4. Continuous analyses through linear (Table 2) and restricted cubic splines (Figure 2, Panel A) demonstrated similar cross-sectional trends, with the strongest association between ESI and hs-cTnT seen in an ESI range of 0.2 to 2.4 g/day. In contrast, there was no cross-sectional relation between ESI and NT-proBNP (Table 2 and Figure 2, Panel B).

The average adjusted 5-year differences in hs-cTnT and NT-proBNP, according to ESI, between MESA examinations 1 and 3 are shown in Table 3 and Figure 3. There was no consistent association between baseline ESI quintile and temporal change in hs-cTnT, although there appeared to be excess troponin increases at very low ESI values (quintile 1). Compared with the reference quintile, a statistically significant increase in NT-proBNP was evident between quintiles 4 and 5, a trend which was further manifest in both the linear (Table 3) and restricted cubic (Figure 3, Panel B) spline analyses. Unlike the cross-sectional relation with hs-cTnT, the longitudinal association of ESI with NT-proBNP was driven predominantly by a strong relation at ESI levels ≥2.4 g/day.

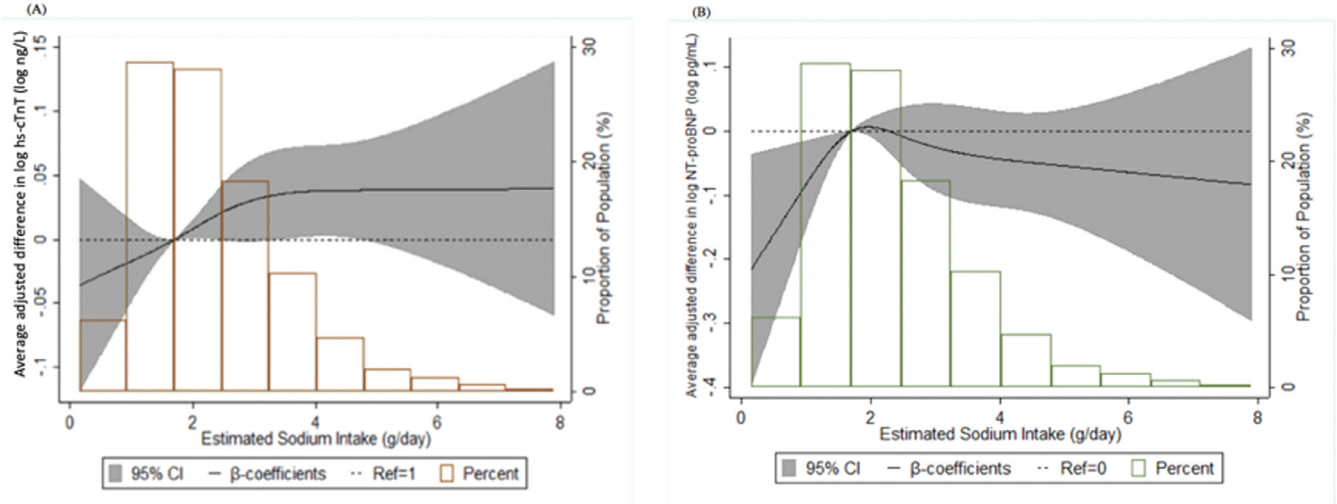

Figure 2. (*A-B*) Panel A shows a restricted cubic spline plot of the association between estimated sodium intake and hs-cTnT (log transformed) at MESA Exam 1. Panel B shows a restricted cubic spline plot of the association between estimated sodium intake and NT-proBNP (log-transformed) at MESA Exam 1. 95% confidence intervals are depicted within the span of the gray bars. All results are presented following multivariable adjustment.

Table 3
Estimated sodium intake and average adjusted* 5-year change in hs-cTnT and NT-proBNP (both log transformed) at MESA Exam 3

	Categorical analysis					Continuous analysis	
	Q1 (0.2-1.3 g/d)	Q2 (1.3-1.8 g/d)	Q3 (1.8-2.4 g/d)	Q4 (2.4-3.2 g/d)	Q5 (3.2-9.9 g/d)	Per 1 g/day increment in ESI (≤2.4 g/day)	Per 1 g/day increment in ESI (>2.4 g/day)
ln hs-cTnT, ng/L							
N	663	692	667	706	686	3,687	2,430
Model 1	0.069 (0.005, 0.133)	Ref=0	0.018 (−0.046, 0.082)	0.041 (−0.022, 0.104)	0.031 (−0.033, 0.094)	−0.020 (−0.063, 0.022)	0.011 (−0.019, 0.041)
Model 2	0.067 (0.004, 0.131)	Ref=0	0.018 (−0.046, 0.082)	0.043 (−0.020, 0.106)	0.034 (−0.029, 0.097)	−0.018 (−0.060, 0.025)	0.011 (−0.018, 0.041)
Model 3	0.067 (0.003, 0.131)	Ref=0	0.018 (−0.045, 0.082)	0.043 (−0.020, 0.106)	0.034 (−0.029, 0.097)	−0.017 (−0.060, 0.025)	0.011 (−0.019, 0.041)
ln NT-proBNP, pg/ml							
N	849	890	883	896	914	3,038	2,035
Model 1	0.025 (−0.023, 0.073)	Ref=0	0.007 (−0.040, 0.054)	0.058 (0.011, 0.105)	0.113 (0.066, 0.160)	0.021 (−0.011, 0.052)	0.030 (0.009, 0.051)
Model 2	0.023 (−0.025, 0.071)	Ref=0	0.005 (−0.042, 0.052)	0.056 (0.009, 0.103)	0.110 (0.063, 0.157)	0.021 (−0.011, 0.053)	0.029 (0.008, 0.051)
Model 3	0.023 (−0.025, 0.071)	Ref=0	0.006 (−0.042, 0.053)	0.055 (0.008, 0.103)	0.110 (0.063, 0.157)	0.020 (−0.011, 0.052)	0.029 (0.008, 0.050)

* Estimates are β coefficients.
Model 1: age and sex.
Model 2: Model 1 plus race/ ethnicity, body mass index, smoking status, alcohol consumption, total cholesterol, high-density lipoprotein cholesterol, triglycerides, estimated glomerular filtration rate, lipid-lowering medication use, blood pressure−lowering medication, and history of diagnosed diabetes.
Model 3: Model 2 plus systolic BP.
NB: Linear spline 1 measures the slope for ESI ≤2.4 g/day and Linear spline 2 measures the slope for ESI >2.4 g/day.

The odds of prevalent and incident hs-cTnT ≥14 ng/L and NT-proBNP ≥100 pg/ml at MESA examinations 1 and 3 are shown in Tables 4 and 5 (restricted cubic splines are show in Supplemental Figure 1). Although the point estimates for the odds ratios in these tables were generally consistent with the results in Tables 2 and 3 (i.e., evidence of higher odds for prevalent hs-cTnT ≥14 ng/L and incident NT-proBNP ≥100 pg/ml according to higher baseline ESI quintile), these categorical results were not consistently statistically significant. Precision was, however, limited. Also consistent with the above results, analysis of linear (Supplemental Table 1) and restricted cubic (Supplemental Figure 2) splines demonstrated a strong association between an ESI ≥2.4 g/day and the odds of a ≥25% temporal increase in NT-proBNP, but not hs-cTnT. Sensitivity analyses performed following the exclusion of individuals with either baseline hypertension or on antihypertensive therapy corroborated similar cross-sectional (Supplemental Table 2) and longitudinal (Supplemental Table 3) associations with hs-cTnT and NT-proBNP, respectively.

Discussion

Our study demonstrates that ESI is associated with hs-cTnT predominantly in a cross-sectional manner. In particular, ESI appears positively associated with hs-cTnT when ESI was within a range of 0.2 to 2.4 g/day, whereas beyond an ESI of 2.4 g/day, the association plateaued. In contrast, ESI is only associated with NT-proBNP in a longitudinal manner, with significant increases in NT-proBNP occurring over the 5 years of follow-up. Unlike the association with hs-cTnT, this association appears to be driven primarily by a strong correlation at an ESI ≥2.4 g/day. Indeed, ESI in this range was also linked to increased odds of ≥25% increase in NT-proBNP from baseline at the 5-year examination. Furthermore, in longitudinal (but not cross-sectional analyses) there appeared to be a possible J-curve phenomenon for elevated hs-cTnT and NT-proBNP at low ESI, though this may have been due to chance given there were no consistent significant findings for a J-curve with either hs-cTnT or NT-proBNP in any of the other analyses performed. To the best of our knowledge, the temporal differences in the impact of sodium excess on these important markers of CVD have not been previously described.

The pathobiological basis upon which incremental increases in ESI result in elevations in hs-cTnT in the short term and NT-proBNP in the long term is not clear, but are likely to be multifactorial. Clearly established as the gold standard diagnostic and prognostic instrument in acute coronary syndrome patients, by enabling the detection of significantly lower concentrations of troponin than conventional assays, the advent of hs-cTnT has extended the application of this test to prognostication in otherwise stable disease states.[15] In addition to detecting minute levels of myocyte necrosis, other proposed pathophysiologic phenomena unrelated to necrosis − including increased cell wall permeability, production of troponin-containing membranous blebs, cellular release of proteolytic degradation products and apoptosis − may now be detectable with the increasingly sensitive assays.[16,17] In animal models, salt

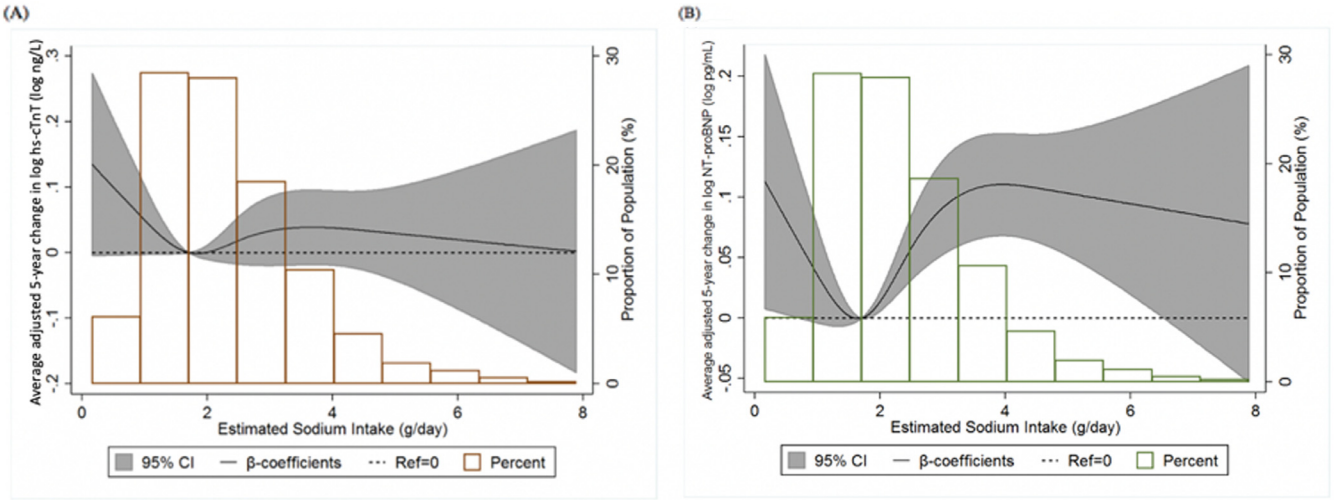

Figure 3. (*A-B*) Panel A shows a restricted cubic spline plot of the association between baseline estimated sodium intake and 5-year change in hs-cTnT (log-transformed) at MESA Exam 3. Panel B shows a restricted cubic spline plot of the association between baseline estimated sodium intake and 5-year change in NT-proBNP (log-transformed) at MESA Exam 3. 95% confidence intervals are depicted within the span of the gray bars. All results are presented following multivariable adjustment.

Table 4
Odds ratios (95% CI) of prevalent hs-cTnT ≥14 ng/L and NT-proBNP ≥100 pg/ml at MESA Exam 1 according to estimated sodium intake quintile

	Q1 (0.2-1.3 g/d)	Q2 (1.3-1.8 g/d)	Q3 (1.8-2.4 g/d)	Q4 (2.4-3.2 g/d)	Q5 (3.2-9.9 g/d)
hs-cTnT ≥14 ng/L	68 (5.6%)	72 (5.9%)	101 (8.3%)	93 (7.6%)	102 (8.3%)
Model 1	1.03 (0.72, 1.46)	Ref=1	1.47 (1.06, 2.05)	1.22 (0.87, 1.70)	1.40 (1.00, 1.95)
Model 2	1.06 (0.72, 1.54)	Ref=1	1.52 (1.07, 2.16)	1.26 (0.89, 1.80)	1.37 (0.96, 1.95)
Model 3	1.07 (0.73, 1.56)	Ref=1	1.54 (1.08, 2.19)	1.27 (0.89, 1.82)	1.38 (0.97, 1.96)
NT-proBNP ≥100 pg/ml	315 (31.5%)	351 (34.3%)	290 (29%)	279 (27.4%)	224 (21.7%)
Model 1	0.76 (0.62, 0.93)	Ref=1	0.95 (0.77, 1.17)	0.95 (0.77, 1.17)	0.83 (0.66, 1.03)
Model 2	0.81 (0.66, 1.01)	Ref=1	0.93 (0.75, 1.15)	0.93 (0.75, 1.15)	0.83 (0.66, 1.05)
Model 3	0.83 (0.67, 1.03)	Ref=1	0.93 (0.75, 1.15)	0.94 (0.75, 1.16)	0.82 (0.66, 1.04)

Model 1: age and sex.

Model 2: Model 1 plus race/ ethnicity, body mass index, smoking status, alcohol consumption, total cholesterol, high-density lipoprotein cholesterol, triglycerides, estimated glomerular filtration rate, lipid-lowering medication use, blood pressure−lowering medication, and history of diagnosed diabetes.

Model 3: Model 2 plus systolic BP.

Table 5
Odds ratios (95% CI) of incident hs-cTnT ≥14 ng/L and NT-proBNP ≥100 pg/ml at MESA Exam 3 according to estimated sodium intake quintile

	Q1 (0.2-1.3 g/d)	Q2 (1.3-1.8 g/d)	Q3 (1.8-2.4 g/d)	Q4 (2.4-3.2 g/d)	Q5 (3.2-9.9 g/d)
hs-cTnT ≥14 ng/L	43 (7%)	44 (7%)	40 (6.8%)	56 (8.9%)	54 (8.9%)
N	611	630	593	631	607
Model 1	1.11 (0.71, 1.73)	Ref=1	0.96 (0.61, 1.52)	1.20 (0.79, 1.84)	1.31 (0.85, 2.02)
Model 2	1.14 (0.72, 1.80)	Ref=1	0.98 (0.61, 1.55)	1.17 (0.76, 1.80)	1.25 (0.81, 1.95)
Model 3	1.15 (0.73, 1.81)	Ref=1	0.98 (0.62, 1.57)	1.16 (0.75, 1.80)	1.24 (0.79, 1.93)
NT-proBNP ≥100 pg/ml	103 (18.3%)	112 (19.7%)	119 (19.8%)	112 (17.9%)	105 (15.6%)
N	563	569	601	627	675
Model 1	0.86 (0.63, 1.17)	Ref=1	1.20 (0.89, 1.63)	1.01 (0.75, 1.38)	1.02 (0.75, 1.39)
Model 2	0.89 (0.65, 1.23)	Ref=1	1.23 (0.90, 1.67)	1.05 (0.77, 1.44)	1.10 (0.80, 1.51)
Model 3	0.90 (0.65, 1.23)	Ref=1	1.22 (0.89, 1.66)	1.04 (0.76, 1.42)	1.10 (0.80, 1.52)

Model 1: age and sex.

Model 2: Model 1 plus race/ethnicity, body mass index, smoking status, alcohol consumption, total cholesterol, high-density lipoprotein cholesterol, triglycerides, estimated glomerular filtration rate, lipid-lowering medication use, blood pressure−lowering medication, and history of diagnosed diabetes.

Model 3: Model 2 plus systolic BP.

loading even in the short term has been linked to several such derangements, and as such, could explain our observed cross-sectional relation between ESI and hs-cTnT.[18−20]

In contrast, BNP (as well as its n-terminal fragment) is a natriuretic hormone released from myocardial cells in a graded fashion following transcriptional activation in response to *chronic* increases in either atrial or ventricular

wall tension.[21,22] Given that the predominant downstream consequence of prolonged excessive dietary sodium intake is systemic hypertension, it is possible that in the short term, the accrued burden of left ventricular remodeling is insufficient to yield significant increases in plasma NT-proBNP levels. Indeed, various animal models have shown that left ventricular hypertrophy and fibrosis only manifest following prolonged exposure to elevated systemic blood pressures.[23–25]

Complicating the aforementioned association between excess dietary sodium and cardiovascular events is controversial evidence supporting a J-curve relation.[14,26–29] Indeed, in the largest study of its kind, the Prospective Urban Rural Epidemiology (PURE) research team reported that an ESI between 3 to 6 g/day was associated with a lower risk of cardiovascular events and mortality than either higher or lower estimated levels of intake.[14] However, our findings from MESA do not appear to corroborate the PURE findings in that we only found inconsistent evidence for elevated biomarkers at ESI levels well below those reported as harmful in PURE (ESI 0.2 to 1.3 g/day) in the longitudinal hs-cTnT analysis and not in any other analysis (a finding which could therefore have been due to chance). Thus, while we cannot definitely rule out a J-curve, our findings are more consistent with those reported by Cook and others, who analyzed both phases of the Trials of Hypertension Prevention (TOHP) program and demonstrated a direct linear relation of average sodium excretion down to the lowest intake level with all-cause mortality.[27] Mechanistically, the subclinical myocardial damage rendered by hs-cTnT in the short term and by NT-proBNP in the longer term may account for the linearity of this relation.

There were several limitations to our study. First, although validated in a variety of nutritional intake studies, the inherent biases of FFQs (e.g., recall bias) as well as their other limitations (e.g., inability to account for within-person variability in intake when a single FFQ is used) must be acknowledged. Second, only baseline ESI data was available, and as such, change in ESI patterns over time was not studied. Third, we recognize that despite consistency between the point estimates for the odds ratios in both the categorical and continuous analyses, the former are inherently underpowered relative to continuous analyses and as such, may be more likely to miss true associations. Furthermore, we recognize the limitations of contextualizing the impact of incremental increases in ESI on biomarkers in absolute terms. Finally, as with any observational study, residual confounding may persist even beyond multivariate adjustment.

In summary, our results demonstrate a relation between dietary sodium intake and hs-cTnT and NT-proBNP in cross-sectional and longitudinal fashions, respectively. Further study is needed to better define this relation, and in particular, to further examine the possibility of a salt intake J-curve phenomenon from the perspective of these and other novel biomarkers. Doing so will enhance understanding of the mechanisms through which sodium intake influences cardiovascular risk.

Disclosures

The authors have nothing to disclose.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2019.05.014.

1. Appel LJ, Brands MW, Daniels SR, Karanja N, Elmer PJ, Sacks FM. Dietary approaches to prevent and treat hypertension: a scientific statement from the American Heart Association. *Hypertension* 2006;47:296–308.
2. Cogswell ME, Loria CM, Terry AL, Zhao L, Wang C-Y, Chen T-C, Wright JD, Pfeiffer CM, Merritt R, Moy CS, Appel LJ. Estimated 24-hour urinary sodium and potassium excretion in US adults. *JAMA* 2018;319:1209–1220.
3. Elijovich F, Weinberger MH, Anderson CAM, Appel LJ, Bursztyn M, Cook NR, Dart RA, Newton-Cheh CH, Sacks FM, Laffer CL. Salt sensitivity of blood pressure: a scientific statement from the American Heart Association. *Hypertension* 2016;68:e7–e46.
4. McGuire S. Scientific Report of the 2015 dietary guidelines advisory committee. Washington, DC: US departments of agriculture and health and human services, 2015. *Adv Nutr* 2016;7:202–204.
5. Lloyd-Jones DM, Hong Y, Labarthe D, Mozaffarian D, Appel LJ, Van Horn L, Greenlund K, Daniels S, Nichol G, Tomaselli GF, Arnett DK, Fonarow GC, Ho PM, Lauer MS, Masoudi FA, Robertson RM, Roger V, Schwamm LH, Sorlie P, Yancy CW, Rosamond WD. Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. *Circulation* 2010;121:586–613.
6. Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR, Greenland P, Jacob DRJ, Kronmal R, Liu K, Nelson JC, O'Leary D, Saad MF, Shea S, Szklo M, Tracy RP. Multi-ethnic study of atherosclerosis: objectives and design. *Am J Epidemiol* 2002;156:871–881.
7. Steinemann N, Grize L, Ziesemer K, Kauf P, Probst-Hensch N, Brombach C. Relative validation of a food frequency questionnaire to estimate food intake in an adult population. *Food Nutr Res* 2017;61:1305193.
8. Kelly C, Geaney F, Fitzgerald AP, Browne GM, Perry IJ. Validation of diet and urinary excretion derived estimates of sodium excretion against 24-h urine excretion in a worksite sample. *Nutr Metab Cardiovasc Dis* 2015;25:771–779.
9. McLean RM, Farmer VL, Nettleton A, Cameron CM, Cook NR, Campbell NRC. Assessment of dietary sodium intake using a food frequency questionnaire and. *J Clin Hypertens (Greenwich)* 2017;19:1214–1230.
10. Selvaraj S, Djousse L, Aguilar FG, Martinez EE, Polsinelli VB, Irvin MR, Arnett DK, Shah SJ. Association of estimated sodium intake with adverse cardiac structure and function: from the HyperGEN study. *J Am Coll Cardiol* 2017;70:715–724.
11. McEvoy JW, Chen Y, Ndumele CE, Solomon SD, Nambi V, Ballantyne CM, Blumenthal RS, Coresh J, Selvin E. Six-year change in high-sensitivity cardiac troponin T and risk of subsequent coronary heart disease, heart failure, and death. *JAMA Cardiol* 2016;1:519–528.
12. Daniels LB, Clopton P, deFilippi CR, Sanchez OA, Bahrami H, Lima JAC, Tracy RP, Siscovick D, Bertoni AG, Greenland P, Cushman M, Maisel AS, Criqui MH. Serial measurement of N-terminal pro-B-type natriuretic peptide and cardiac troponin T for cardiovascular disease risk assessment in the Multi-Ethnic Study of Atherosclerosis (MESA). *Am Heart J* 2015;170:1170–1183.
13. Blaha MJ, Cainzos-Achirica M, Greenland P, McEvoy JW, Blankstein R, Budoff MJ, Dardari Z, Sibley CT, Burke GL, Kronmal RA, Szklo M, Blumenthal RS, Nasir K. Role of coronary artery calcium score of zero and other negative risk markers for cardiovascular disease: the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation* 2016;133:849–858.
14. O'Donnell M, Mente A, Rangarajan S, McQueen MJ, Wang X, Liu L, Yan H, Lee SF, Mony P, Devanath A, Rosengren A, Lopez-Jaramillo P, Diaz R, Avezum A, Lanas F, Yusoff K, Iqbal R, Ilow R, Mohammadifard N, Gulec S, Yusufali AH, Kruger L, Yusuf R, Chifamba J, Kabali C, Dagenais G, Lear SA, Teo K, Yusuf S. Urinary sodium and potassium excretion, mortality, and cardiovascular events. *N Engl J Med* 2014;371:612–623.

15. Sherwood MW, Kristin Newby L. High-sensitivity troponin assays: evidence, indications, and reasonable use. *J Am Heart Assoc* 2014;3: e000403.
16. White HD. Pathobiology of troponin elevations: do elevations occur with myocardial ischemia as well as necrosis? *J Am Coll Cardiol* 2011;57:2406–2408.
17. Hickman PE, Potter JM, Aroney C, Koerbin G, Southcott E, Wu AHB, Roberts MS. Cardiac troponin may be released by ischemia alone, without necrosis. *Clin Chim Acta* 2010;411:318–323.
18. Tsukamoto Y, Mano T, Sakata Y, Ohtani T, Takeda Y, Tamaki S, Omori Y, Ikeya Y, Saito Y, Ishii R, Higashimori M, Kaneko M, Miwa T, Yamamoto K, Komuro I. A novel heart failure mice model of hypertensive heart disease by angiotensin II infusion, nephrectomy, and salt loading. *Am J Physiol Heart Circ Physiol* 2013;305:H1658–H1667.
19. Nishimoto M, Fujita T. Renal mechanisms of salt-sensitive hypertension: contribution of two steroid receptor-associated pathways. *Am J Physiol Renal Physiol* 2015;308:F377–F387.
20. Weil BR, Suzuki G, Young RF, Iyer V, Canty JMJ. Troponin release and reversible left ventricular dysfunction after transient pressure overload. *J Am Coll Cardiol* 2018;71:2906–2916.
21. Globits S, Frank H, Pacher B, Huelsmann M, Ogris E, Pacher R. Atrial natriuretic peptide release is more dependent on atrial filling volume than on filling pressure in chronic congestive heart failure. *Am Heart J* 1998;135:592–597.
22. Iwanaga Y, Nishi I, Furuichi S, Noguchi T, Sase K, Kihara Y, Goto Y, Nonogi H. B-type natriuretic peptide strongly reflects diastolic wall stress in patients with chronic heart failure: comparison between systolic and diastolic heart failure. *J Am Coll Cardiol* 2006;47:742–748.
23. Santos M, Shah AM. Alterations in cardiac structure and function in hypertension. *Curr Hypertens Rep* 2014;16:428.
24. Tomek J, Bub G. Hypertension-induced remodelling: on the interactions of cardiac risk factors. *J Physiol* 2017;595:4027–4036.
25. Petriz BA, Franco OL. Effects of hypertension and exercise on cardiac proteome remodelling. *Biomed Res Int* 2014;2014:634132.
26. Mente A, O'Donnell MJ, Yusuf S. How robust is the evidence for recommending very low salt intake in entire populations? *J Am Coll Cardiol* 2016;68:1618–1621.
27. Cook NR, Appel LJ, Whelton PK. Sodium intake and all-cause mortality over 20 years in the trials of hypertension prevention. *J Am Coll Cardiol* 2016;68:1609–1617.
28. Mancia G, Oparil S, Whelton PK, McKee M, Dominiczak A, Luft FC, AlHabib K, Lanas F, Damasceno A, Prabhakaran D, La Torre G, Weber M, O'Donnell M, Smith SC, Narula J. The technical report on sodium intake and cardiovascular disease in low- and middle-income countries by the joint working group of the World Heart Federation, the European Society of Hypertension and the European Public Health Association. *Eur Heart J* 2017;38:712–719.
29. Graudal N, Jurgens G, Baslund B, Alderman MH. Compared with usual sodium intake, low- and excessive-sodium diets are associated with increased mortality: a meta-analysis. *Am J Hypertens* 2014;27: 1129–1137.