Associations of 24-Hour Urinary Sodium and Potassium Excretion with Cardiac Biomarkers

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Associations of 24-Hour Urinary Sodium and Potassium Excretion with Cardiac Biomarkers: The Maastricht Study

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ABSTRACT

Background: It is a matter of debate whether sodium and potassium intake are associated with heart disease. Further, the mechanisms underlying associations of sodium and potassium intake with cardiac events, if any, are not fully understood.

Objectives: We examined cross-sectional associations of 24-h urinary sodium excretion (UNaE) and potassium excretion (UKE), as estimates of their intakes, with high-sensitivity cardiac troponins T (hs-cTnT) and I (hs-cTnI), and N-terminal pro-B-type natriuretic peptide (NT-proBNP), which are markers of cardiomyocyte injury and cardiac dysfunction.

Methods: We included 2961 participants from the population-based Maastricht Study (mean ± SD age 59.8 ± 8.2 y, 51.9% men), who completed the baseline survey between November 2010 and September 2013. Associations were examined with restricted cubic spline linear regression analyses and ordinary linear regression analyses, adjusted for demographics, lifestyle, and cardiovascular disease (CVD) risk factors.

Results: Median [IQR] 24-h UNaE and UKE were 3.7 [2.8–4.7] g/24 h and 3.0 [2.4–3.6] g/24 h, respectively. After adjustment for potential confounders, 24-h UNaE was not associated with hs-cTnT, hs-cTnI, and NT-proBNP concentrations. In contrast, after adjustment for potential confounders, lower 24-h UKE was nonlinearly associated with higher hs-cTnT and NT-proBNP. For example, as compared with the third/median quintile of 24-h UKE (range: 2.8–3.2 g/24 h), participants in the first quintile (range: 0.5–2.3 g/24 h) had 1.05 (95% CI: 0.99, 1.11) times higher hs-cTnT and 1.14 (95% CI: 1.03, 1.26) times higher NT-proBNP. Associations were similar after further adjustment for estimated glomerular filtration rate, albuminuria, blood pressure, and serum potassium.

Conclusions: Twenty-four-hour UNaE was not associated with the studied cardiac biomarkers. In contrast, lower 24-h UKE was nonlinearly associated with higher hs-cTnT and NT-proBNP. This finding supports recommendations to increase potassium intake in the general population. In addition, it suggests that cardiac dysfunction and/or cardiomyocyte injury may underlie previously reported associations of lower potassium intake with CVD mortality. *J Nutr* 2020;150:1413–1424.

Keywords: sodium intake, potassium intake, sodium excretion, potassium excretion, cardiac biomarkers, troponin, natriuretic peptides, cardiovascular disease

Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide (1). This warrants public health efforts to reduce CVD risk. In this regard, both dietary sodium and potassium intake are advocated as modifiable targets for CVD prevention (2, 3).

However, results of studies on the association of sodium intake with CVD have been inconsistent and trial data are scarce. Indeed, observational studies have reported null, positive, negative, and J-shaped associations of sodium intake with total CVD and/or heart disease (4–9). This has led to vigorous debates on recommendations for population-wide

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reduction of sodium intake (10–12). Similarly, the association of potassium intake with total CVD and, in particular, heart disease is uncertain (9, 13–15), whereas lower potassium intake has been associated with higher risk of stroke in meta-analyses (13, 14).

In addition, mechanisms that underlie any associations of sodium and potassium intake with cardiac events are not fully understood. It may be hypothesized that these include cardiomyocyte injury from (micro)vascular disease and cardiac dysfunction from volume or pressure overload. In this regard, whether processes independent of blood pressure are involved is unknown.

Cardiac biomarkers, such as the high-sensitivity cardiac troponins (hs-cTn) T and I, and N-terminal pro-B-type natriuretic peptide (NT-proBNP), may shed more light on the direction of associations with CVD. Indeed, hs-cTnT, hs-cTnI, and NT-proBNP are associated with CVD morbidity and mortality in the general population (16–18). In addition, these biomarkers may provide data on the mechanisms of cardiac events related to sodium and potassium intake, if any.

Hs-cTnT and hs-cTnI, which are part of the thin filament of the sarcomere of cardiomyocytes, play an important role in excitation–contraction coupling, and are markers of cardiac injury (19). Further, NT-proBNP may indicate cardiac dysfunction, due to, for example, volume and pressure overload (20). NT-proBNP is the inactive amino-terminal fragment of the prohormone of B-type natriuretic peptide (BNP) and is co-released into the circulation when the biologically active BNP is cleaved from its prohormone. BNP has natriuretic, diuretic, and vasodilatory effects and is primarily released from the cardiac ventricles upon wall stress due to increased intracardiac pressure (21).

However, to the best of our knowledge, data on associations of estimates of sodium and potassium intake with hs-cTnT and hs-cTnI are lacking. In addition, data on associations with BNP or NT-proBNP are restricted to short-term intervention studies (22–24) and small studies in individuals with heart failure (25, 26). These studies provided mixed results for sodium intake (22, 23, 25, 26) and observed no difference in NT-proBNP with potassium supplementation (24).

In view of the foregoing, we examined cross-sectional associations of 24-h urinary sodium excretion (UNaE) and potassium excretion (UKE), as estimates of their intakes, with hs-cTnT, hs-cTnI, and NT-proBNP in a population-based cohort.

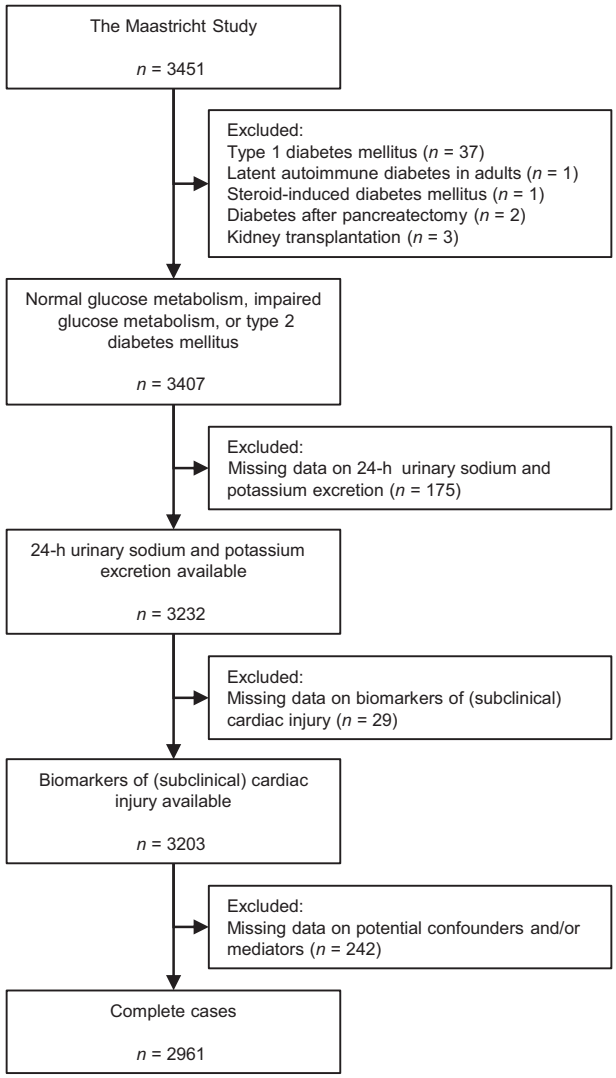

FIGURE 1 Flowchart showing the derivation of the present study population from the Maastricht Study participants.

Methods

The Maastricht Study population and design

We used data from the Maastricht Study, an observational, prospective, population-based cohort study. The rationale and methodology have been described previously (27). In brief, the study focuses on the etiology, pathophysiology, complications, and comorbidities of type 2 diabetes mellitus and is characterized by an extensive phenotyping approach. Eligible for participation were all individuals aged between 40 and 75 y and living in the southern part of the Netherlands. Participants were recruited through mass-media campaigns and from the municipal registries and the regional Diabetes Patient Registry via mailings. Recruitment was stratified according to known type 2 diabetes mellitus status, with an oversampling of individuals with type 2 diabetes mellitus, for reasons of efficiency. The present report includes

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Supplemental Methods, Supplemental Tables 1–7, and Supplemental Figures 1–5 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/jn/.
Data are available from the Maastricht Study for any interested researcher who meets the criteria for access to confidential data. The Maastricht Study management team (research.dms@mumc.nl) may be contacted to request data.
Address correspondence to JPK (e-mail: jeroen.kooman@mumc.nl).
Abbreviations used: BNP, B-type natriuretic peptide; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; hs-cTnI, high-sensitivity cardiac troponin I; hs-cTnT, high-sensitivity cardiac troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; UAE, urinary albumin excretion; UKE, urinary potassium excretion; UNaE, urinary sodium excretion.

TABLE 1 Characteristics of the Maastricht Study participants: total population and stratified according to quintiles of 24-h UNaE[1]

Characteristic	Entire study population ($n = 2961$)	24-h UNaE				
		Q1 ($n = 592$)	Q2 ($n = 593$)	Q3 ($n = 592$)	Q4 ($n = 592$)	Q5 ($n = 592$)
Demographics						
Age, y	59.8 ± 8.2	59.5 ± 8.1	60.0 ± 8.5	59.8 ± 8.2	60.4 ± 8.1	59.2 ± 8.3
Men	1537 (51.9)	156 (26.3)	222 (37.5)	298 (50.3)	386 (65.2)	475 (80.2)
Educational level						
Low	491 (16.6)	81 (13.7)	89 (15.0)	98 (16.6)	96 (16.2)	127 (21.5)
Middle	1272 (43.0)	269 (45.4)	247 (41.7)	266 (44.9)	251 (42.4)	239 (40.4)
High	1198 (40.5)	243 (41.0)	256 (43.2)	228 (38.5)	245 (41.4)	226 (38.2)
Lifestyle variables						
Smoking behavior						
Never smoker	1035 (35.0)	224 (37.8)	215 (36.3)	212 (35.8)	202 (34.1)	182 (30.7)
Former smoker	1532 (51.7)	281 (47.4)	295 (49.8)	298 (50.3)	317 (53.5)	341 (57.6)
Current smoker	394 (13.3)	88 (14.8)	82 (13.9)	82 (13.9)	73 (12.3)	69 (11.7)
Alcohol consumption[2]						
None	538 (18.2)	135 (22.8)	102 (17.2)	101 (17.1)	97 (16.4)	103 (17.4)
Low	1642 (55.5)	297 (50.1)	307 (51.9)	335 (56.6)	335 (56.6)	368 (62.2)
High	781 (26.4)	161 (27.2)	183 (30.9)	156 (26.4)	160 (27.0)	121 (20.4)
Alcohol consumption,[3] g ethanol/24 h	8.6 [1.5–18.8]	6.7 [0.8–16.5]	8.6 [1.6–17.3]	9.0 [1.7–19.4]	9.6 [1.6–19.3]	9.3 [1.9–20.3]
Energy intake,[3] kcal/24 h	2181 ± 603	2055 ± 575	2114 ± 548	2192 ± 601	2278 ± 605	2282 ± 655
Greek Mediterranean diet score[3]	4 [3–6]	5 [3–6]	4 [3–6]	4 [3–6]	5 [3–6]	4 [3–5]
Total physical activity,[3] h/wk	13 [8–19]	14 [9–19]	14 [9–18]	14 [9–19]	14 [8–19]	11 [8–18]
Moderate-to-vigorous physical activity,[3] h/wk	5 [2–8]	5 [3–8]	5 [2–8]	5 [2–8]	5 [2–8]	4 [2–8]
Metabolic variables						
BMI categories,[4]						
Normal weight	1034 (34.9)	293 (49.4)	260 (43.9)	216 (36.5)	178 (30.1)	87 (14.7)
Overweight	1272 (43.0)	219 (36.9)	244 (41.2)	252 (42.6)	267 (45.1)	290 (49.0)
Obesity	655 (22.1)	81 (13.7)	88 (14.9)	124 (20.9)	147 (24.8)	215 (36.3)
Waist circumference, cm						
Men	101 ± 12	98 ± 11	98 ± 10	99 ± 11	102 ± 13	105 ± 12
Women	90 ± 13	87 ± 12	88 ± 12	91 ± 13	91 ± 13	99 ± 16
Office SBP, mm Hg	135 ± 18	132 ± 18	133 ± 19	135 ± 18	136 ± 18	139 ± 16
Office DBP, mm Hg	76 ± 10	75 ± 10	75 ± 10	76 ± 10	77 ± 10	79 ± 10
24-h average ambulatory SBP,[3] mm Hg	119 ± 12	116 ± 11	117 ± 12	119 ± 12	121 ± 12	123 ± 11
24-h average ambulatory DBP,[3] mm Hg	74 ± 7	72 ± 7	73 ± 7	73 ± 7	74 ± 8	75 ± 7
Hypertension	1663 (56.2)	292 (49.2)	305 (51.5)	329 (55.6)	350 (59.1)	387 (65.4)
Glucose metabolism status						
Normal glucose metabolism	1701 (57.4)	385 (64.9)	369 (62.3)	340 (57.4)	322 (54.4)	285 (48.1)
Impaired glucose metabolism	455 (15.4)	91 (15.3)	84 (14.2)	95 (16.0)	90 (15.2)	95 (16.0)
Type 2 diabetes mellitus	805 (27.2)	117 (19.7)	139 (23.5)	157 (26.5)	180 (30.4)	212 (35.8)
Fasting plasma glucose,[3] mmol/L						
Without type 2 diabetes mellitus	5.3 ± 0.5	5.2 ± 0.5	5.3 ± 0.5	5.3 ± 0.6	5.4 ± 0.5	5.5 ± 0.6
With type 2 diabetes mellitus	7.9 ± 2.0	7.6 ± 1.8	7.6 ± 1.4	7.7 ± 1.6	8.1 ± 2.5	8.2 ± 2.1
Whole-blood HbA1c,[3] mmol/mol						
Without type 2 diabetes mellitus	36.6 ± 4.1	36.3 ± 3.8	36.7 ± 3.7	36.7 ± 4.3	36.6 ± 4.1	37.1 ± 4.4
With type 2 diabetes mellitus	51.8 ± 11.0	49.7 ± 10.7	50.9 ± 8.9	50.6 ± 8.7	53.0 ± 13.0	53.5 ± 11.8
Serum total cholesterol, mmol/L	5.2 ± 1.2	5.4 ± 1.1	5.3 ± 1.2	5.2 ± 1.2	5.2 ± 1.1	5.0 ± 1.2
Serum HDL cholesterol, mmol/L						
Men	1.3 ± 0.4	1.4 ± 0.4	1.4 ± 0.4	1.4 ± 0.4	1.3 ± 0.4	1.3 ± 0.4
Women	1.7 ± 0.5	1.8 ± 0.5	1.8 ± 0.5	1.7 ± 0.5	1.7 ± 0.5	1.6 ± 0.4
Serum LDL cholesterol, mmol/L	3.1 ± 1.0	3.2 ± 1.0	3.1 ± 1.0	3.1 ± 1.1	3.1 ± 1.0	3.0 ± 1.1
Serum triglycerides, mmol/L	1.42 [0.88–1.71]	1.14 [0.85–1.61]	1.14 [0.86–1.59]	1.19 [0.86–1.72]	1.23 [0.89–1.74]	1.40 [1.00–1.90]
Serum ratio of total to HDL cholesterol	3.7 ± 1.2	3.5 ± 1.1	3.5 ± 1.1	3.7 ± 1.2	3.8 ± 1.2	4.0 ± 1.3
Prior CVD	483 (16.3)	97 (14.7)	95 (16.0)	92 (15.5)	104 (17.6)	105 (17.7)
Kidney function						
eGFR, mL · min^{-1} · 1.73m^{-2}	88.2 ± 14.7	88.2 ± 14.9	87.6 ± 14.4	87.7 ± 14.6	87.9 ± 14.6	89.9 ± 14.8
Urinary albumin excretion, mg/24 h	6.7 [4.0–11.7]	5.7 [3.5–10.1]	6.4 [4.0–11.0]	6.6 [4.0–11.2]	7.1 [4.3–14.6]	7.7 [4.4–14.4]
Urinary albumin excretion categories						
<15 mg/24 h	2413 (81.5)	512 (86.3)	501 (84.6)	499 (84.3)	449 (75.8)	452 (76.4)
15 to <30 mg/24 h	295 (10.0)	50 (8.4)	58 (9.8)	44 (7.4)	72 (12.2)	71 (12.0)
≥30 mg/24 h	253 (8.5)	31 (5.2)	33 (5.6)	49 (8.3)	71 (12.0)	69 (11.7)

(*Continued*)

TABLE 1 (*Continued*)

Characteristic	Entire study population ($n = 2961$)	24-h UNaE				
		Q1 ($n = 592$)	Q2 ($n = 593$)	Q3 ($n = 592$)	Q4 ($n = 592$)	Q5 ($n = 592$)
Medication use						
Antihypertensive medication (total)	1171 (39.5)	198 (33.4)	221 (37.3)	232 (39.2)	252 (42.6)	268 (45.3)
Renin-angiotensin system inhibitor	884 (29.9)	127 (21.4)	173 (29.2)	184 (31.1)	194 (32.8)	206 (34.8)
Aldosterone antagonist	16 (0.5)	4 (0.7)	0 (0.0)	2 (0.3)	6 (1.0)	4 (0.7)
Diuretic	481 (16.2)	79 (13.3)	73 (12.3)	99 (16.7)	99 (16.7)	131 (22.1)
Lipid-modifying medication	1050 (35.5)	166 (28.0)	196 (33.1)	223 (37.7)	218 (36.8)	247 (41.7)
Electrolytes						
Serum sodium, mmol/L	140.4 ± 1.9	140.4 ± 2.0	140.6 ± 2.0	140.5 ± 1.8	140.4 ± 1.8	140.3 ± 1.8
Serum potassium, mmol/L	4.4 ± 0.7	4.5 ± 0.8	4.4 ± 0.7	4.4 ± 0.6	4.4 ± 0.7	4.4 ± 0.6
Cardiac biomarkers						
Serum hs-cTnT, ng/L	5.4 [3.9–7.9]	4.5 [3.3–6.5]	5.0 [3.6–7.4]	5.2 [3.7–7.8]	6.0 [4.2–8.5]	6.3 [4.6–9.0]
Serum hs-cTnI, ng/L	1.9 [1.3–3.1]	1.5 [1.1–2.4]	1.8 [1.2–2.9]	2.0 [1.2–3.0]	2.1 [1.5–3.5]	2.2 [1.5–3.5]
Serum NT-proBNP, ng/L	51.1 [29.2–90.2]	56.9 [35.4–95.8]	54.3 [31.7–97.1]	52.3 [31.2–89.8]	48.8 [25.6–88.9]	41.1 [21.2–79.2]
24-h urinary electrolyte excretion						
24-h UNaE, mmol/24 h	160 [123–206]	95 [80–106]	131 [123–138]	160 [152–167]	194 [184–206]	253 [231–286]
Range	12–530	12–114	114–145	145–175	175–217	217–530
24-h UNaE, g/24 h	3.7 [2.8–4.7]	2.2 [1.8–2.4]	3.0 [2.8–3.2]	3.7 [3.5–3.8]	4.4 [4.2–4.7]	5.8 [6.3–6.6]
Range	0.3–12.2	0.3–2.6	2.6–3.3	3.3–4.0	4.0–5.0	5.0–12.2
24-h UKE, mmol/24 h	76 [62–92]	61 [48–75]	70 [58–84]	76 [63–90]	84 [71–98]	90 [76–106]
Range	14–309	14–170	26–155	37–181	29–269	35–309
24-h UKE, g/24 h	3.0 [2.4–3.6]	2.4 [1.9–2.9]	2.7 [2.3–3.3]	3.0 [2.5–3.5]	3.3 [2.8–3.8]	3.5 [3.0–4.2]
Range	0.5–10.5	0.5–6.6	1.0–6.1	1.4–7.1	1.1–10.5	1.3–8.2

[1]Values are *n* (%), mean ± SD, or median [IQR]. CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; hs-cTnI, high-sensitivity cardiac troponin I; hs-cTnT, high-sensitivity cardiac troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; Q, quintile; SBP, systolic blood pressure; UKE, urinary potassium excretion; UNaE, urinary sodium excretion.
[2]Low: ≤7 glasses/wk for women, ≤14 glasses/wk for men; high: >7 glasses/wk for women, >14 glasses/wk for men.
[3]Data were available from $n = 2788$ for alcohol consumption expressed in g ethanol/24 h, $n = 2788$ for energy intake, $n = 2788$ for Greek Mediterranean diet score, $n = 2597$ for total physical activity, $n = 2596$ for moderate-to-vigorous physical activity, $n = 2633$ for 24-h average ambulatory blood pressure, $n = 2960$ for fasting glucose, and $n = 2956$ for HbA1c.
[4]Normal weight: <25 kg/m^2; overweight 25 to <30 kg/m^2; obesity: ≥30 kg/m^2.

cross-sectional data from the first 3451 participants, who completed the baseline survey between November 2010 and September 2013. The examinations of each participant were performed within a time window of 3 mo. The study has been approved by the institutional medical ethical committee (NL31329.068.10) and the Minister of Health, Welfare and Sports of the Netherlands (Permit 131088-105234-PG), and was conducted in accordance with the Declaration of Helsinki. All participants gave written informed consent.

For this study, participants with type 1 diabetes or other specific types of diabetes ($n = 41$) were excluded. After further successively excluding participants who had received a kidney transplant ($n = 3$), who had missing data on 24-h UNaE and UKE ($n = 175$), who had missing data on biomarkers of subclinical cardiac injury ($n = 29$), and who had missing data on other variables in the primary regression models (models 1–3d, except 3c, see further, $n = 242$), 2961 participants were included (for a flowchart, see **Figure 1**).

Twenty-four-hour UNaE and UKE

To assess 24-h UNaE and UKE, sodium and potassium concentrations were determined in a frozen sample from a single 24-h urine collection. Urine samples were stored at −80°C for 5–8 y. Urinary sodium and potassium concentrations were measured in millimoles per liter by indirect potentiometry on a Roche Cobas 6000 analyzer and multiplied by collection volume to obtain 24-h UNaE and UKE in millimoles per 24 h, respectively. Sodium and potassium concentrations outside the reporting range of the assay were assigned a value equal to half the lower reporting limit or equal to the upper reporting limit before multiplying by collection volume [sodium concentrations <20 mmol/L and >250 mmol/L were set at 10 mmol/L and 250 mmol/L, respectively ($n = 8$); potassium concentrations >100 mmol/L were set at 100 mmol/L ($n = 29$)]. Subsequently, 24-h UNaE and UKE in millimoles per 24 h were converted to grams per 24 h by multiplying by 22.99 and 39.10, respectively. Only urine collections with a collection time between 20 h and 28 h were considered valid. If collection time did not equal 24 h, UNaE and UKE were extrapolated to a 24-h excretion.

Biomarkers of subclinical cardiac injury

Concentrations of hs-cTnT, hs-cTnI, and NT-proBNP were determined in stored frozen serum samples, as described previously (28). Further details are described in the **Supplemental Methods**.

Potential confounders and/or mediators

We assessed fasting plasma glucose, whole-blood glycated hemoglobin (HbA1c), glucose metabolism status, serum total cholesterol, serum HDL cholesterol, serum LDL cholesterol, serum triglycerides, estimated glomerular filtration rate (eGFR), 24-h urinary albumin excretion (UAE), BMI, waist circumference, office blood pressure, 24-h average ambulatory blood pressure, medication use, smoking behavior, alcohol consumption (categorical and 24-h ethanol intake), educational level, prevalent CVD, energy intake, adherence to Mediterranean diet, and self-reported physical activity as described previously (27, 29–31).

Serum sodium and potassium concentrations were determined by indirect potentiometry on a Roche Cobas 6000 analyzer.

Further details on the definitions of the aforementioned potential confounders and/or mediators are provided in the Supplemental Methods.

Statistical analyses

Characteristics are presented for the entire study population and stratified according to quintiles of 24-h UNaE and UKE. Characteristics are presented numerically as *n* (%), mean ± SD, or median [IQR].

TABLE 2 Characteristics of the Maastricht Study participants: total population and stratified according to quintiles of 24-h UKE[1]

Characteristic	Entire study population ($n = 2961$)	24-h UKE				
		Q1 ($n = 593$)	Q2 ($n = 592$)	Q3 ($n = 592$)	Q4 ($n = 592$)	Q5 ($n = 592$)
Demographics						
Age, y	59.8 ± 8.2	59.5 ± 8.7	59.7 ± 8.4	59.8 ± 8.3	60.2 ± 8.1	59.6 ± 7.7
Men	1537 (51.9)	186 (31.4)	258 (43.6)	293 (49.5)	361 (61.0)	439 (74.2)
Educational level						
Low	491 (16.6)	116 (19.6)	106 (17.9)	106 (17.9)	81 (13.7)	82 (13.9)
Middle	1272 (43.0)	288 (48.6)	274 (46.3)	248 (41.9)	233 (39.4)	229 (38.7)
High	1198 (40.5)	189 (31.9)	212 (35.8)	238 (40.2)	278 (47.0)	281 (47.5)
Lifestyle variables						
Smoking behavior						
Never smoker	1035 (35.0)	225 (37.9)	201 (34.0)	216 (36.5)	206 (34.8)	187 (31.6)
Former smoker	1532 (51.7)	264 (44.5)	309 (52.2)	298 (50.3)	329 (55.6)	332 (56.1)
Current smoker	394 (13.3)	104 (17.5)	82 (13.9)	78 (13.2)	57 (9.6)	73 (12.3)
Alcohol consumption[2]						
None	538 (18.2)	158 (26.6)	112 (18.9)	102 (17.2)	86 (14.5)	80 (13.5)
Low	1642 (55.5)	302 (50.9)	330 (55.7)	340 (57.4)	340 (57.4)	330 (55.7)
High	781 (26.4)	133 (22.4)	150 (25.3)	150 (25.3)	166 (28.0)	182 (30.7)
Alcohol consumption,[3] g ethanol/24 h	8.6 [1.5–18.8]	4.8 [0.4–14.2]	8.0 [1.2–16.8]	8.8 [1.8–17.4]	9.8 [2.7–19.8]	11.1 [3.0–23.0]
Energy intake,[3] kcal/24 h	2181 ± 603	2039 ± 560	2091 ± 585	2167 ± 566	2242 ± 598	2380 ± 648
Greek Mediterranean diet score[3]	4 [3–6]	4 [3–5]	4 [3–5]	4 [3–6]	5 [3–6]	5 [4–6]
Total physical activity,[3] h/wk	13 [8–19]	13 [8–18]	13 [8–18]	13 [8–18]	14 [8–19]	14 [8–20]
Moderate-to-vigorous physical activity,[3] h/wk	5 [2–8]	5 [2–7]	5 [2–7]	5 [2–8]	5 [2–8]	5 [3–9]
Metabolic variables						
BMI categories,[4]						
Normal weight	1034 (34.9)	240 (40.5)	215 (36.3)	215 (36.3)	186 (31.4)	178 (30.1)
Overweight	1272 (43.0)	237 (40.0)	246 (41.6)	246 (41.6)	269 (45.4)	274 (46.3)
Obesity	655 (22.1)	116 (19.6)	131 (22.1)	131 (22.1)	137 (23.1)	140 (23.6)
Waist circumference, cm						
Men	101 ± 12	101 ± 11	102 ± 12	101 ± 11	100 ± 11	102 ± 13
Women	90 ± 13	90 ± 13	89 ± 13	89 ± 13	91 ± 14	91 ± 14
Office SBP, mm Hg	135 ± 18	134 ± 16	134 ± 18	134 ± 18	136 ± 18	137 ± 16
Office DBP, mm Hg	76 ± 10	76 ± 10	76 ± 10	76 ± 10	77 ± 10	78 ± 10
24-h average ambulatory SBP,[3] mm Hg	119 ± 12	117 ± 12	117 ± 12	119 ± 12	120 ± 12	121 ± 11
24-h average ambulatory DBP,[3] mm Hg	74 ± 7	73 ± 7	73 ± 7	73 ± 7	74 ± 7	75 ± 7
Hypertension	1663 (56.2)	323 (54.5)	329 (55.6)	332 (56.1)	332 (56.1)	347 (58.6)
Glucose metabolism status						
Normal glucose metabolism	1701 (57.4)	342 (57.7)	337 (56.9)	339 (57.3)	338 (57.1)	345 (58.3)
Impaired glucose metabolism	455 (15.4)	90 (15.2)	87 (14.7)	94 (15.9)	101 (17.1)	83 (14.0)
Type 2 diabetes mellitus	805 (27.2)	161 (27.2)	168 (28.4)	159 (26.9)	153 (25.8)	164 (27.7)
Fasting plasma glucose,[3] mmol/L						
Without type 2 diabetes mellitus	5.3 ± 0.5	5.2 ± 0.5	5.3 ± 0.5	5.3 ± 0.5	5.4 ± 0.6	5.4 ± 0.5
With type 2 diabetes mellitus	7.9 ± 2.0	7.7 ± 1.8	7.5 ± 1.5	8.0 ± 2.2	7.9 ± 1.9	8.3 ± 2.4
Whole-blood HbA1c,[3] mmol/mol						
Without type 2 diabetes mellitus	36.6 ± 4.1	36.4 ± 4.1	36.7 ± 4.2	36.5 ± 4.0	36.8 ± 4.1	36.8 ± 4.0
With type 2 diabetes mellitus	51.8 ± 11.0	51.5 ± 10.3	50.9 ± 9.8	51.9 ± 11.8	52.5 ± 11.0	52.2 ± 12.1
Serum total cholesterol, mmol/L	5.2 ± 1.2	5.3 ± 1.2	5.1 ± 1.1	5.3 ± 1.1	5.2 ± 1.2	5.2 ± 1.1
Serum HDL cholesterol, mmol/L						
Men	1.3 ± 0.4	1.3 ± 0.4	1.3 ± 0.3	1.3 ± 0.4	1.3 ± 0.4	1.4 ± 0.4
Women	1.7 ± 0.5	1.7 ± 0.5	1.7 ± 0.5	1.8 ± 0.5	1.7 ± 0.5	1.7 ± 0.5
Serum LDL cholesterol, mmol/L	3.1 ± 1.0	3.1 ± 1.1	3.0 ± 1.0	3.1 ± 1.0	3.1 ± 1.1	3.1 ± 1.0
Serum triglycerides, mmol/L	1.42 [0.88–1.71]	1.23 [0.93–1.76]	1.21 [0.90–1.75]	1.18 [0.87–1.60]	1.21 [0.88–1.66]	1.22 [0.85–1.79]
Serum ratio of total to HDL cholesterol	3.7 ± 1.2	3.6 ± 1.2	3.6 ± 1.1	3.6 ± 1.2	3.8 ± 1.2	3.8 ± 1.2
Prior CVD	483 (16.3)	99 (16.7)	95 (16.0)	108 (18.2)	96 (16.2)	85 (14.4)
Kidney function						
eGFR, mL · min^{-1} · 1.73m^{-2}	88.2 ± 14.7	86.5 ± 15.6	87.3 ± 15.0	88.3 ± 14.6	88.4 ± 14.0	90.7 ± 13.9
Urinary albumin excretion, mg/24 h	6.7 [4.0–11.7]	5.7 [3.5–10.3]	6.7 [3.9–11.6]	6.5 [4.0–11.4]	7.1 [4.4–12.3]	7.8 [4.3–13.5]
Urinary albumin excretion categories						
<15 mg/24 h	2413 (81.5)	500 (84.3)	484 (81.8)	493 (83.3)	475 (80.2)	461 (77.9)
15 to <30 mg/24 h	295 (10.0)	45 (7.6)	63 (10.6)	50 (8.5)	68 (11.5)	69 (11.7)
≥30 mg/24 h	253 (8.5)	48 (8.1)	45 (7.6)	49 (8.3)	49 (8.3)	62 (10.5)

(*Continued*)

TABLE 2 (*Continued*)

Characteristic	Entire study population ($n = 2961$)	24-h UKE				
		Q1 ($n = 593$)	Q2 ($n = 592$)	Q3 ($n = 592$)	Q4 ($n = 592$)	Q5 ($n = 592$)
Medication use						
Antihypertensive medication (total)	1171 (39.5)	246 (41.5)	239 (40.4)	226 (38.2)	226 (38.2)	234 (39.5)
Renin-angiotensin system inhibitor	884 (29.9)	176 (29.7)	180 (30.4)	170 (28.7)	178 (30.1)	180 (30.4)
Aldosterone antagonist	16 (0.5)	4 (0.7)	1 (0.2)	6 (1.0)	3 (0.5)	2 (0.3)
Diuretic	481 (16.2)	104 (17.5)	94 (15.9)	90 (15.2)	107 (18.1)	86 (14.5)
Lipid-modifying medication	1050 (35.5)	197 (33.2)	230 (38.9)	212 (35.8)	221 (37.3)	190 (32.1)
Electrolytes						
Serum sodium, mmol/L	140.4 ± 1.9	140.4 ± 2.1	140.5 ± 1.9	140.4 ± 1.8	140.6 ± 1.8	140.3 ± 1.9
Serum potassium, mmol/L	4.4 ± 0.7	4.5 ± 0.8	4.4 ± 0.7	4.5 ± 0.8	4.4 ± 0.6	4.4 ± 0.6
Cardiac biomarkers						
Serum hs-cTnT, ng/L	5.4 [3.9–7.9]	4.9 [3.5–7.3]	5.2 [3.5–7.7]	5.4 [3.7–8.3]	5.7 [4.0–8.1]	5.8 [4.4–8.0]
Serum hs-cTnI, ng/L	1.9 [1.3–3.1]	1.7 [1.2–2.9]	1.8 [1.2–2.9]	1.9 [1.2–3.2]	2.1 [1.3–3.2]	2.1 [1.5–3.2]
Serum NT-proBNP, ng/L	51.1 [29.2–90.2]	60.0 [34.4–103.4]	53.4 [31.8–98.2]	48.8 [28.6–89.7]	47.9 [25.6–82.3]	44.2 [25.1–78.7]
24-h urinary electrolyte excretion						
24-h UNaE, mmol/24 h	160 [123–206]	121 [94–148]	149 [118–186]	160 [127–200]	178 [143–218]	201 [159–247]
Range	12–530	12–342	29–358	20–447	58–421	49–530
24-h UNaE, g/24 h	3.7 [2.8–4.7]	2.8 [2.2–3.4]	3.4 [2.7–4.3]	3.7 [2.9–4.6]	4.1 [3.3–5.0]	4.6 [3.7–5.7]
Range	0.3–12.2	0.3–7.9	0.7–8.2	0.5–10.3	1.3–9.7	1.1–12.2
24-h UKE, mmol/24 h	76 [62–92]	50 [44–55]	65 [62–68]	76 [73–79]	89 [85–92]	108 [101–121]
Range	14–269	14–59	59–71	71–82	82–96	96–269
24-h UKE, g/24 h	3.0 [2.4–3.6]	2.0 [1.7–2.1]	2.5 [2.4–2.7]	3.0 [2.9–3.1]	3.5 [3.3–3.6]	4.2 [4.0–4.7]
Range	0.5–10.5	0.5–2.3	2.3–2.8	2.8–3.2	3.2–3.8	3.8–10.5

[1]Values are *n* (%), mean ± SD, or median [IQR]. CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin A1c; hs-cTnI, high-sensitivity cardiac troponin I; hs-cTnT, high-sensitivity cardiac troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; Q, quintile; SBP, systolic blood pressure; UKE, urinary potassium excretion; UNaE, urinary sodium excretion.
[2]Low: ≤7 glasses/wk for women, ≤14 glasses/wk for men; high: >7 glasses/wk for women, >14 glasses/wk for men.
[3]Data were available from $n = 2788$ for alcohol consumption expressed in g ethanol/24 h, $n = 2788$ for energy intake, $n = 2788$ for Greek Mediterranean diet score, $n = 2597$ for total physical activity, $n = 2596$ for moderate-to-vigorous physical activity, $n = 2633$ for 24-h average ambulatory blood pressure, $n = 2960$ for fasting glucose, and $n = 2956$ for HbA1c.
[4]Normal weight: <25 kg/m^2; overweight: 25 to <30 kg/m^2; obesity: ≥30 kg/m^2.

The correlation between 24-h UNaE and 24-h UKE was tested with Spearman correlation analysis.

The cardiac biomarkers were positively skewed and ln transformed for all regression analyses described below. This allowed calculation of relative concentration differences by taking the exponent of the regression coefficients.

First, restricted cubic spline functions were plotted to examine (the shapes of) associations of 24-h UNaE with the cardiac biomarkers. These functions included all variables of model 2 (see below), with 4 knots for continuous variables (located at the 5th, 35th, 65th, and 95th percentiles) (32). Median 24-h UNaE and UKE served as references.

Second, relative differences in concentrations of the cardiac biomarkers according to 24-h UNaE and UKE were evaluated with linear regression analyses. Twenty-four-hour UNaE and UKE were expressed as continuous and categorical variables (quintiles, with the third/median quintile as reference). Regression coefficients indicate relative differences in concentrations of the cardiac biomarkers per 1-g higher 24-h UNaE or UKE and as compared with the third quintile of 24-h UNaE or UKE, respectively.

Adjustments were made for potential confounders in sequential models. Model 1 adjusted for age, sex, and glucose metabolism status; and model 2: model 1 + educational level, BMI, ratio of total to HDL cholesterol, triglycerides, use of lipid-modifying medication, smoking behavior, categorical alcohol consumption, and history of CVD. In models 3a–3d, variables which may confound and/or mediate (i.e., may be in the causal pathway of) associations of 24-h UNaE and UKE with the cardiac biomarkers were added to model 2. To be specific, model 3a: model 2 + eGFR and 24-h UAE; model 3b: model 2 + office systolic blood pressure and use of antihypertensive medication; model 3c: model 2 + 24-h average ambulatory blood pressure and use of antihypertensive medication; and model 3d: model 2 + serum sodium/serum potassium concentrations.

Several analyses were performed to explore the robustness of results. First, in model 2, we tested for statistical interaction of 24-h UNaE and UKE with type 2 diabetes mellitus, systolic blood pressure, and presence of hypertension in restricted cubic spline linear regression analyses to explore reverse causality (33) and given previously reported stronger associations of sodium intake with CVD in individuals with hypertension (8, 34). In addition, we tested for statistical interaction with sex and for interaction between 24-h UNaE and UKE because potassium intake modifies the salt-sensitivity of blood pressure (35). We did not explore statistical interaction with ethnicity because almost all participants were Caucasians of European descent. Second, analyses were repeated after exclusion of 24-h urine collections with a measured 24-h urinary creatinine excretion not within 30% of expected values (36) to explore bias related to misclassification due to inaccurate collection. Third, individuals with known CVD or evident CVD risk factors may have changed sodium and/or potassium intake following medical advice (i.e., reverse causality). To reduce the possibility of reverse causality, analyses were repeated in a "healthy" subpopulation of participants that excluded participants with a self-reported history of CVD and participants with prediabetes, type 2 diabetes mellitus, hypertension, use of antihypertensive medication, chronic kidney disease, obesity, and/or use of lipid-modifying medication (definitions are provided in the Supplemental Methods) (33). Fourth, analyses were repeated with mutual adjustment for 24-h UNaE and UKE [mutual adjustment is performed as an additional analysis because errors of 24-h UNaE and UKE are correlated (37, 38)]; additional adjustment for energy intake and adherence to Mediterranean diet (as a measure of healthy dietary habits); adjustment for alcohol consumption in grams of ethanol per 24 h instead of categorical alcohol consumption; additional adjustment for total and moderate-to-vigorous physical activity; with alternative blood pressure measurements; and with individual classes

of antihypertensive medication. Fifth, analyses were repeated with participants categorized into groups based on 1 g/24 h increments in 24-h UNaE and UKE, respectively. Categories of 24-h UNaE were truncated at <2 g/24 h and ≥7 g/24 h, and categories of 24-h UKE were truncated at <2 g/24 h and ≥5 g/24 h to avoid small numbers of participants in the most extreme categories.

A 2-tailed P value < 0.05 was considered statistically significant.

All analyses were performed in R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) (39) with RStudio version 1.1.456 (RStudio Inc., Boston, MA, USA) (40) combined with the packages haven, tidyverse, rms, Hmisc, and ggpubr.

Results

Population characteristics

In the entire study population, median [IQR] 24-h UNaE was 3.7 [2.8–4.7] g/24 h (160 [123–206] mmol/24 h) (**Table 1**). In men, median [IQR] 24-h UNaE was 4.2 [3.4–5.2] g/24 h (184 [146–227] mmol/24 h), and in women it was 3.2 [2.5–3.9] g/24 h (137 [108–171] mmol/24 h). Participants with higher 24-h UNaE were more often men, were less educated, had higher energy intake, more often had type 2 diabetes mellitus, and, in general, had a worse CVD risk profile (Table 1).

In the entire study population, median [IQR] 24-h UKE was 3.0 [2.4–3.6] g/24 h (76 [62–92] mmol/24 h) (**Table 2**). In men, median [IQR] 24-h UKE was 3.2 [2.6–3.9] g/24 h (83 [68–99] mmol/24 h), and in women it was 2.7 [2.2–3.3] g/24 h (70 [57–84] mmol/24 h). Participants with lower 24-h UKE were more often women, were less educated, more often smoked, and had lower energy intake. Differences in CVD risk profile across the quintiles of 24-h UKE were small (Table 2).

In general, participants with higher 24-h UNaE had higher 24-h UKE, and vice versa (Spearman's $\rho = 0.45$, $P < 0.001$).

Associations of 24-h UNaE with cardiac biomarkers

Restricted cubic spline linear regression analyses showed no evidence of an association of 24-h UNaE with hs-cTnT, hs-cTnI, or NT-proBNP after adjustment for the potential confounders of model 2 (**Figure 2**).

Similar results were obtained in ordinary linear regression analyses with 24-h UNaE expressed as a continuous variable and with quintiles of 24-h UNaE (**Table 3**). For example, after adjustment for the potential confounders of model 2, relative concentration differences in the cardiac biomarkers per 1-g higher 24-h UNaE and as compared with the third quintile of 24-h UNaE were in general close to 1 (i.e., 0%) and not statistically significant. Results were not materially altered after additional adjustment for eGFR and 24-h UAE (model 3a), office systolic blood pressure and use of antihypertensive medication (model 3b), 24-h average ambulatory systolic blood pressure and use of antihypertensive medication (model 3c), and serum sodium (model 3d).

Associations of 24-h UKE with cardiac biomarkers

Restricted cubic spline linear regression analyses showed a nonlinear association of 24-h UKE with hs-cTnT and NT-proBNP. That is, lower 24-h UKE was associated with higher hs-cTnT and NT-proBNP after adjustment for the potential confounders of model 2 (**Figure 3**).

Similarly, analyses with quintiles of 24-h UKE showed that lower 24-h UKE was associated with higher hs-cTnT and NT-proBNP (**Table 4**). For example, as compared with the third quintile of 24-h UKE (range: 2.8–3.2 g/24 h) and after adjustment for the potential confounders of model 2, participants in the first quintile (range: 0.5–2.3 g/24 h) had 1.05 (95% CI: 0.99, 1.11) times higher hs-cTnT concentrations and 1.14 (95% CI: 1.03, 1.26) times higher NT-proBNP concentrations. Results were similar after additional adjustment

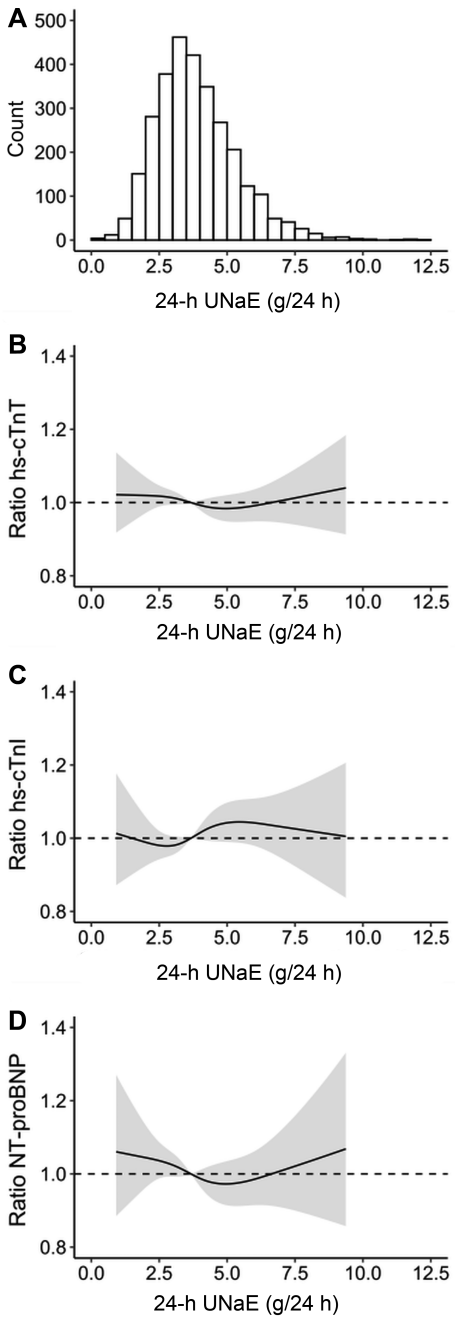

FIGURE 2 Associations of 24-h UNaE with cardiac biomarkers among the Maastricht Study participants. (A) Histogram of 24-h UNaE in the entire study population ($n = 2961$). (B–D) Plots of restricted cubic spline linear regression analyses adjusted for the variables in model 2. Ratios represent the ratio of concentrations of hs-cTnT, hs-cTnI, and NT-proBNP, respectively, relative to levels at median 24-h UNaE. Gray areas indicate 95% CIs. Spline curves are truncated at the 10th smallest and 10th largest values of the distribution of 24-h UNaE. ANOVA P values of 24-h UNaE and P values of the nonlinear part are 0.591 and 0.464 for hs-cTnT, 0.426 and 0.469 for hs-cTnI, and 0.487 and 0.402 for NT-proBNP, respectively. hs-cTnI, high-sensitivity cardiac troponin I; hs-cTnT, high-sensitivity cardiac troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; UNaE, urinary sodium excretion.

TABLE 3 Associations of 24-h UNaE with cardiac biomarkers among the Maastricht Study participants[1]

			24-h UNaE				
Biomarker	Model	Continuous 24-h UNaE, g/24 h ($n = 2961$)	Q1 (0.3–2.6 g/24 h) ($n = 592$)	Q2 (2.6–3.3 g/24 h) ($n = 593$)	Q3 (3.3–4.0 g/24 h) ($n = 592$)	Q4 (4.0–5.0 g/24 h) ($n = 592$)	Q5 (5.0–12.2 g/24 h) ($n = 592$)
hs-cTnT	1	1.01 (0.99, 1.02)	1.00 (0.95, 1.07)	1.05 (0.99, 1.12)	Reference	1.03 (0.98, 1.10)	1.03 (0.97, 1.10)
	2	1.00 (0.99, 1.01)	1.01 (0.96, 1.08)	1.06 (1.00, 1.13)	Reference	1.03 (0.97, 1.09)	1.01 (0.95, 1.07)
	3a	1.00 (0.99, 1.02)	1.02 (0.96, 1.07)	1.06 (1.00, 1.12)	Reference	1.03 (0.97, 1.09)	1.03 (0.97, 1.09)
	3b	1.00 (0.99, 1.01)	1.01 (0.96, 1.07)	1.06 (1.00, 1.12)	Reference	1.03 (0.97, 1.09)	1.01 (0.95, 1.07)
	3c	1.00 (0.99, 1.01)	1.01 (0.94, 1.07)	1.06 (0.99, 1.12)	Reference	1.03 (0.97, 1.09)	1.01 (0.95, 1.07)
	3d	1.00 (0.99, 1.01)	1.01 (0.96, 1.08)	1.06 (1.00, 1.13)	Reference	1.03 (0.97, 1.09)	1.01 (0.95, 1.07)
hs-cTnI	1	1.03 (1.01, 1.05)	0.97 (0.89, 1.05)	1.01 (0.93, 1.10)	Reference	1.08 (0.99, 1.17)	1.07 (0.98, 1.16)
	2	1.02 (1.00, 1.04)	0.98 (0.90, 1.07)	1.02 (0.94, 1.10)	Reference	1.07 (0.98, 1.16)	1.03 (0.95, 1.12)
	3a	1.02 (1.00, 1.04)	0.98 (0.91, 1.07)	1.02 (0.94, 1.10)	Reference	1.06 (0.98, 1.15)	1.04 (0.96, 1.13)
	3b	1.01 (1.00, 1.03)	0.99 (0.91, 1.07)	1.02 (0.93, 1.10)	Reference	1.07 (0.99, 1.16)	1.03 (0.95, 1.12)
	3c	1.01 (1.00, 1.03)	0.97 (0.89, 1.05)	1.01 (0.93, 1.10)	Reference	1.07 (0.98, 1.16)	1.01 (0.93, 1.11)
	3d	1.02 (1.00, 1.04)	0.98 (0.91, 1.07)	1.02 (0.94, 1.10)	Reference	1.07 (0.99, 1.16)	1.03 (0.95, 1.12)
NT-proBNP	1	0.98 (0.96, 1.01)	1.07 (0.97, 1.19)	1.03 (0.93, 1.14)	Reference	1.02 (0.92, 1.13)	0.94 (0.85, 1.05)
	2	0.99 (0.96, 1.01)	1.06 (0.96, 1.18)	1.02 (0.93, 1.13)	Reference	1.02 (0.93, 1.13)	0.96 (0.86, 1.06)
	3a	0.99 (0.97, 1.01)	1.07 (0.97, 1.18)	1.03 (0.93, 1.13)	Reference	1.02 (0.92, 1.12)	0.97 (0.88, 1.08)
	3b	0.99 (0.96, 1.01)	1.06 (0.96, 1.18)	1.02 (0.93, 1.13)	Reference	1.02 (0.93, 1.13)	0.96 (0.87, 1.06)
	3c	0.98 (0.96, 1.01)	1.07 (0.96, 1.19)	1.05 (0.94, 1.16)	Reference	1.01 (0.91, 1.12)	0.95 (0.85, 1.06)
	3d	0.99 (0.96, 1.01)	1.07 (0.97, 1.18)	1.02 (0.93, 1.13)	Reference	1.02 (0.93, 1.13)	0.96 (0.86, 1.06)

[1]Values are ratios (95% CIs). Ratios represent relative differences in concentrations of the cardiac biomarkers per 1-g higher 24-h UNaE and as compared with Q3 of 24-h UNaE, respectively. For example, a ratio of 1.03 for hs-cTnT in Q4 indicates that the concentration of hs-cTnT in Q4 is on average 1.03 (i.e., 3%) times higher than in Q3. Model 1 adjusted for age, sex, and glucose metabolism status; model 2: model 1 + educational level, BMI, ratio of total to HDL cholesterol, triglycerides, use of lipid-modifying medication, smoking behavior, alcohol consumption, and history of cardiovascular disease; model 3a: model 2 + estimated glomerular filtration rate and 24-h urinary albumin excretion; model 3b: model 2 + office systolic blood pressure and use of antihypertensive medication; model 3c: model 2 + 24-h average ambulatory systolic blood pressure and use of antihypertensive medication (available in $n = 2633$); and model 3d: model 2 + serum sodium. hs-cTnI, high-sensitivity cardiac troponin I; hs-cTnT, high-sensitivity cardiac troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; Q, quintile; UNaE, urinary sodium excretion.

for eGFR and 24-h UAE (model 3a), office systolic blood pressure and use of antihypertensive medication (model 3b), 24-h average ambulatory systolic blood pressure and use of antihypertensive medication (model 3c), and serum potassium (model 3d).

Additional analyses

First, restricted cubic spline analyses suggested that lower 24-h UKE was associated with higher hs-cTnI in men but not in women (**Supplemental Figure 1**; $P_{interaction} = 0.039$), although this was less evident in analyses with quintiles of 24-h UKE (**Supplemental Table 1**; $P_{interaction} = 0.050$ for Q2). There was no statistical interaction with diabetes mellitus, hypertension, and office systolic blood pressure, or between 24-h UNaE and 24-h UKE ($P_{interaction} > 0.05$).

Second, results were similar in participants with 24-h urine collections with measured 24-h urinary creatinine excretion within 30% of expected values ($n = 2323$; **Supplemental Figures 2**, **3** and **Supplemental Tables 2**, **3**).

Third, in the "healthy" subpopulation ($n = 770$), results of 24-h UNaE were similar (**Supplemental Figure 4**, **Supplemental Table 4**). Associations of 24-h UKE with hs-cTnT and NT-proBNP were no longer statistically significant, although their strengths and shapes were similar (**Supplemental Figure 5**, **Supplemental Table 5**).

Fourth, results were similar after mutual adjustment for 24-h UNaE and 24-h UKE; additional adjustment for energy intake and adherence to a Greek Mediterranean diet ($n = 2788$); adjustment for alcohol consumption in grams of ethanol per 24 h ($n = 2788$); additional adjustment for total and moderate-to-vigorous physical activity ($n = 2596$ and $n = 2595$, respectively); and adjustment for alternative blood pressure measurements and individual classes of antihypertensive medication ($n = 2961$) (data not shown).

Fifth, when participants were categorized into groups based on 1 g/24 h increments of 24-h UNaE and UKE, respectively, results of 24-h UNaE were similar (**Supplemental Table 6**). Associations of lower 24-h UKE excretion with higher hs-cTnT and NT-proBNP became more evident (**Supplemental Table 7**).

Discussion

In this population-based cohort study on cross-sectional associations of 24-h UNaE and UKE, as estimates of sodium and potassium intakes, with cardiac biomarkers, 24-h UNaE was not independently associated with hs-cTnT, hs-cTnI, or NT-proBNP. In contrast, lower 24-h UKE was nonlinearly associated with higher hs-cTnT and NT-proBNP after adjustment for potential confounders.

Differences in methods to estimate sodium intake (e.g., 24-h UNaE, spot urine samples, and dietary surveys), distributions of estimated sodium intake, and methods to assess CVD (clinical outcomes compared with biomarkers) are relevant when interpreting the lack of associations of 24-h UNaE with cardiac biomarkers in light of the inconsistent literature on sodium intake and CVD (4–9). For example, in this study, median 24-h UNaE was relatively low as compared with estimates of sodium intake in previous studies, and few participants had extremes of 24-h UNaE ($n = 216$ with <2 g/24 h and $n = 257$ with ≥6 g/24 h). In this regard, another Dutch cohort study with a similar distribution of 24-h UNaE did not find an association with coronary artery disease (41), and a meta-analysis did not

TABLE 4 Associations of 24-h UKE with cardiac biomarkers among the Maastricht Study participants[1]

			24-h UKE				
Biomarker	Model	Continuous 24-h UKE, g/24 h ($n = 2961$)	Q1 (0.5–2.3 g/24 h) ($n = 593$)	Q2 (2.3–2.8 g/24 h) ($n = 592$)	Q3 (2.8–3.2 g/24 h) ($n = 592$)	Q4 (3.2–3.8 g/24 h) ($n = 592$)	Q5 (3.8–10.5 g/24 h) ($n = 592$)
hs-cTnT	1	0.99 (0.97, 1.01)	1.04 (0.98, 1.10)	0.97 (0.92, 1.03)	Reference	1.02 (0.96, 1.08)	0.99 (0.94, 1.05)
	2	0.99 (0.97, 1.01)	1.05 (0.99, 1.11)	0.97 (0.92, 1.10)	Reference	1.01 (0.96, 1.08)	0.99 (0.94, 1.05)
	3a	1.00 (0.98, 1.02)	1.03 (0.97, 1.09)	0.97 (0.91, 1.02)	Reference	1.02 (0.96, 1.08)	1.01 (0.96, 1.07)
	3b	0.99 (0.97, 1.01)	1.04 (0.98, 1.10)	0.97 (0.92, 1.03)	Reference	1.02 (0.96, 1.08)	0.99 (0.93, 1.05)
	3c	0.99 (0.97, 1.01)	1.04 (0.97, 1.10)	1.00 (0.94, 1.06)	Reference	1.01 (0.95, 1.07)	0.99 (0.93, 1.05)
	3d	0.99 (0.97, 1.01)	1.04 (0.99, 1.11)	0.97 (0.92, 1.03)	Reference	1.01 (0.95, 1.07)	0.99 (0.93, 1.05)
hs-cTnI	1	1.00 (0.97, 1.03)	1.01 (0.93, 1.10)	0.97 (0.89, 1.05)	Reference	1.00 (0.92, 1.09)	0.99 (0.91, 1.07)
	2	1.00 (0.97, 1.03)	1.02 (0.94, 1.11)	0.97 (0.90, 1.06)	Reference	0.99 (0.91, 1.08)	0.99 (0.91, 1.07)
	3a	1.00 (0.97, 1.03)	1.01 (0.93, 1.09)	0.97 (0.89, 1.05)	Reference	0.99 (0.92, 1.08)	0.99 (0.92, 1.08)
	3b	1.00 (0.97, 1.03)	1.01 (0.93, 1.09)	0.97 (0.90, 1.05)	Reference	0.99 (0.92, 1.07)	0.98 (0.90, 1.06)
	3c	1.00 (0.97, 1.03)	1.01 (0.93, 1.11)	0.99 (0.91, 1.08)	Reference	0.98 (0.90, 1.07)	0.99 (0.91, 1.07)
	3d	1.00 (0.97, 1.03)	1.02 (0.93, 1.11)	0.97 (0.90, 1.06)	Reference	0.99 (0.91, 1.08)	0.99 (0.91, 1.07)
NT-proBNP	1	0.94 (0.91, 0.98)	1.12 (1.02, 1.24)	1.06 (0.96, 1.17)	Reference	0.95 (0.86, 1.06)	0.96 (0.87, 1.07)
	2	0.95 (0.91, 0.98)	1.14 (1.03, 1.26)	1.07 (0.97, 1.18)	Reference	0.97 (0.88, 1.07)	0.99 (0.89, 1.09)
	3a	0.95 (0.92, 0.99)	1.12 (1.02, 1.24)	1.06 (0.97, 1.17)	Reference	0.97 (0.88, 1.07)	1.00 (0.91, 1.10)
	3b	0.95 (0.92, 0.98)	1.12 (1.02, 1.24)	1.07 (0.97, 1.18)	Reference	0.97 (0.88, 1.07)	0.98 (0.89, 1.08)
	3c	0.94 (0.91, 0.98)	1.14 (1.03, 1.27)	1.08 (0.97, 1.20)	Reference	0.98 (0.88, 1.09)	0.98 (0.88, 1.09)
	3d	0.95 (0.91, 0.98)	1.13 (1.03, 1.26)	1.07 (0.97, 1.18)	Reference	0.97 (0.88, 1.07)	0.99 (0.89, 1.09)

[1] Values are ratios (95% CIs). Ratios represent relative differences in concentrations of the cardiac biomarkers per 1-g higher 24-h UKE and as compared with Q3 of 24-h UKE, respectively. For example, a ratio of 1.05 for hs-cTnT in Q2 indicates that the concentration of hs-cTnT in Q2 is on average 1.05 times (i.e., 5%) higher than in Q3. Model 1 adjusted for age, sex, and glucose metabolism status; model 2: model 1 + educational level, BMI, ratio of total to HDL cholesterol, triglycerides, use of lipid-modifying medication, smoking behavior, alcohol consumption, and history of cardiovascular disease; model 3a: model 2 + estimated glomerular filtration rate and 24-h urinary albumin excretion; model 3b: model 2 + office systolic blood pressure and use of antihypertensive medication; model 3c: model 2 + 24-h average ambulatory systolic blood pressure and use of antihypertensive medication (available in $n = 2633$); and model 3d: model 2 + serum potassium. hs-cTnI, high-sensitivity cardiac troponin I; hs-cTnT, high-sensitivity cardiac troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; Q, quintile; UKE, urinary potassium excretion.

show differences in a composite CVD outcome between "low-normal" and "high-normal" sodium intake (7). In addition, the performance of biomarkers as surrogates for CVD depends on their signal-to-noise ratio, which is reduced by, for example, biological variability (42).

Nonlinear associations of lower 24-h UKE with higher hs-cTnT and NT-proBNP fit the hypothesis that lower potassium intake increases the risk of heart disease. These findings may clarify the inconclusive results from 2 meta-analyses, which suggested inverse associations of potassium intake with total CVD and heart disease (13, 14), and agree with a more recent study, which observed inverse associations of potassium intake with total CVD and myocardial infarction (9). In this regard, the use of cardiac biomarkers as surrogates for CVD may have increased statistical power. In addition, in several previous studies, the use of dietary surveys may have increased misclassification of potassium intake.

The only interventional study found no difference in NT-proBNP between the potassium supplementation and placebo groups (24). This may be explained by a lack of statistical power related to sample size. In addition, 24-h UKE in the placebo group was higher than the inflection point on the spline curve of NT-proBNP in the present study.

The associations of 24-h UKE with NT-proBNP and hs-cTnT suggest that heart disease related to lower potassium intake may involve cardiac dysfunction and/or cardiomyocyte injury. However, the association of lower 24-h UKE with higher hs-cTnT should be interpreted with caution because it seemed to be rather weak and was not paralleled by a similar association with hs-cTnI.

Associations of 24-h UKE were not explained by eGFR, albuminuria, blood pressure, serum potassium, or 24-h UNaE. This suggests that other mechanisms are involved, although their nature remains speculative. For example, it has been hypothesized that low potassium intake increases production of reactive oxygen species, subsequently leading to degradation of nitric oxide and endothelial dysfunction (43, 44). In the heart, endothelial dysfunction of the microcirculation may lead to (subclinical) ischemia (45) and cardiac dysfunction (46). Alternatively, lower potassium intake may be a proxy for lifestyle factors not fully captured by our models (i.e., residual confounding).

The statistical interaction of 24-h UKE with sex for hs-cTnI in additional spline analyses was less evident in analyses with quintiles of 24-h UKE, and may be the result of the play of chance, given the large number of statistical interactions tested.

From a public health perspective, this study supports previous notions that the greatest health benefit of dietary sodium restriction is to be expected when populations with high sodium intake are specifically targeted (12). In addition, it endorses the WHO's recommendation to increase potassium intake in adults to reduce CVD risk (3), although high variability in the fraction of potassium intake that is excreted in urine [i.e., 0.50–0.90 (47, 48)] hampers setting specific targets. For example, a 24-h UKE of 2.5 g/24 h, which is close to the inflection points on the spline curves, may correspond to a potassium intake of 2.8–5.0 g/24 h. The variability in the fraction of potassium intake excreted in urine has not been fully explained but may depend on ethnicity, dietary composition, and fecal and sweat potassium loss (47, 48).

An important strength of this study is the evaluation of cardiac injury and cardiac dysfunction with biomarkers with a proven association with hard clinical CVD endpoints in the general population (16–18). In addition, the detailed characterization of the study participants allowed extensive

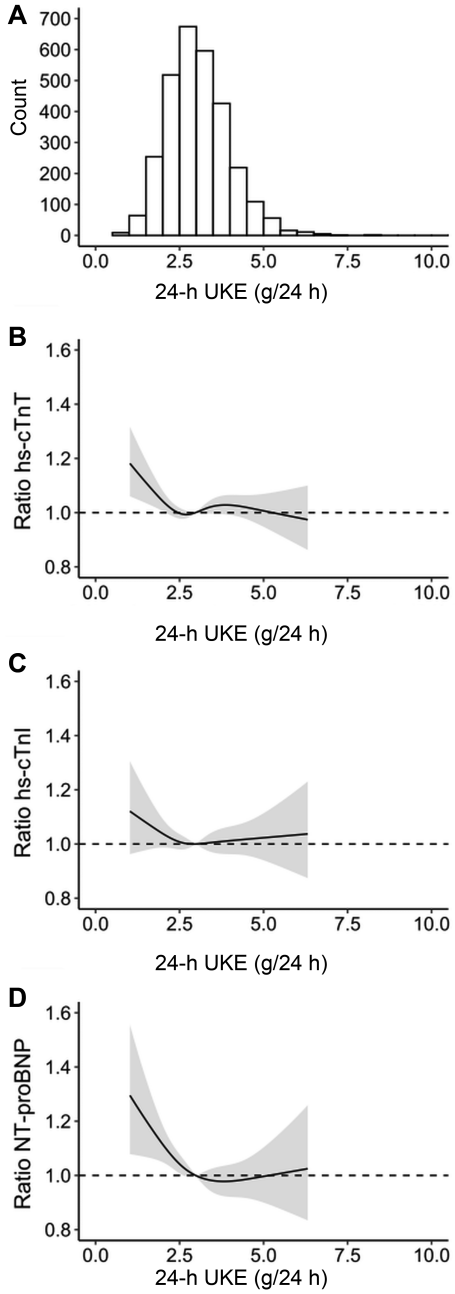

FIGURE 3 Associations of 24-h UKE with cardiac biomarkers among the Maastricht Study participants. (A) Histogram of 24-h UKE in the entire study population (n = 2961). (B–D) Plots of restricted cubic spline linear regression analyses adjusted for the variables in model 2. Ratios represent the ratio of concentrations of hs-cTnT, hs-cTnI, and NT-proBNP, respectively, relative to levels at median 24-h UKE. Gray areas indicate 95% CIs. Spline curves are truncated at the 10th smallest and 10th largest values of the distribution of 24-h UKE. ANOVA P values of 24-h UKE and P values of the nonlinear part are 0.023 and 0.018 for hs-cTnT, 0.498 and 0.357 for hs-cTnI, and 0.005 and 0.049 for NT-proBNP, respectively. hs-cTnI, high-sensitivity cardiac troponin I; hs-cTnT, high-sensitivity cardiac troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; UKE, urinary potassium excretion.

adjustment for potential confounders and exploration of the roles of possible mediators of the associations reported, including 24-h average ambulatory blood pressure. Further, several additional analyses, including examination of the consequences of inaccurately sampled urine collections, strengthened the robustness of our results.

However, some limitations of this study also deserve attention. First, the cross-sectional design limited causal inferences and reverse causality cannot be excluded. Nevertheless, the finding that the strengths and shapes of associations of 24-h UKE with hs-cTnT and NT-proBNP were similar in the small "healthy" subpopulation, supports our results. Second, usual sodium and potassium intake were estimated with a single 24-h urine collection, which reduces the reliability of the estimates. Although 24-h urine collections provide more valid estimates than dietary surveys, to take the biological variability of 24-h UNaE into account, the use of >4 urine collections, preferably sampled over a longer period of time (49), is recommended (33). Random error due to biological variability causes nondifferential misclassification of usual sodium and potassium intake and will, in general, have biased associations with cardiac biomarkers toward the null (50). Third, estimated sodium intake in the present study was relatively low as compared with previous studies and its results may, therefore, not be generalizable to populations with higher sodium intake. Fourth, generalizability to populations which are not from European descent may be limited owing to the lack of ethnic diversity in the present study population.

In conclusion, in this cross-sectional population-based cohort study, 24-h UNaE was not associated with hs-cTnT, hs-cTnI, and NT-proBNP after adjustment for potential confounders. In contrast, lower 24-h UKE was nonlinearly associated with higher hs-cTnT and NT-proBNP after adjustment for potential confounders. This finding supports recommendations to increase potassium intake in the general population. In addition, it suggests that cardiac dysfunction and/or cardiomyocyte injury may underlie previously reported associations of lower potassium intake with CVD mortality.

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