Association of rheumatoid arthritis and high sodium intake with major adverse cardiovascular events: a cross-sectional study from the seventh Korean National Health and Nutrition Examination Survey

Jeong-Hyeon Bae, 1 Min-Young Shin, 1 Eun Ha Kang, 2 Yun Jong Lee 2, 2 You-Jung Ha 2

ABSTRACT

Objectives High salt intake has a harmful effect on hypertension; however, the association between major adverse cardiovascular events (MACE) and salt intake is still controversial. Rheumatoid arthritis (RA) is also characterised by excess cardiovascular risk. However, few studies have investigated the combined role of salt intake and RA in MACE in the general Korean population. Here, we evaluated this relationship among the Korean adult population.

Design Retrospective, cross-sectional.

Setting Population-based survey in Korea.

Methods This study was based on the data of the seventh Korean National Health and Nutrition Examination Survey (2016–2018). The estimated 24-hour urinary sodium excretion (24HUNa), a surrogate marker for daily sodium intake, was calculated using the Tanaka equation and was stratified into five groups (<3, 3–3.999, 4–4.999, 5–5.999 and ≥6 g/day). Finally, data from 13,464 adult participants (weighted n=90,425,888) were analysed; all analyses considered a complex sampling design. Multivariable logistic regression for MACE as primary dependent variable was performed and adjusted for potential covariates.

Results Participants with MACE had higher 24HUNa levels and RA proportion than those without MACE (p<0.001). The association of MACE with 24HUNa was J-shaped with a gradual increase from about 3 g/day. The highest 24HUNa (≥6 g/day) group was significantly associated with increased prevalence of MACE compared with the reference group (3–3.999 g/day) after adjusting for all associated covariates (OR 6.75, 95% CI 1.421 to 32.039). In the multivariate logistic regression analysis, RA (OR 2.05, 95% CI 1.283 to 3.264) and the highest 24HUNa group (OR 6.35, 95% CI 1.337 to 30.147) were significantly associated with MACE even after adjusting for baseline covariates.

Conclusions These nationally representative data suggest that RA and extremely high sodium intake are associated with MACE in the general adult Korean population. Avoiding extremely high salt intake and considering RA as an important risk factor for MACE might help promote public cardiovascular health.

INTRODUCTION

The global burden of cardiovascular diseases (CVD) has risen steadily over the last three decades, and CVD has been the second leading cause of death, accounting for approximately 20% of all deaths, in Korea. 1, 2 Therefore, it is important to monitor and manage risk factors for CVD. High salt intake is a well-known risk factor for hypertension. A positive association has been shown between salt intake and blood pressure and decreased dietary salt intake can reduce blood pressure.3 4 The PURE study, a large-scaled global study on the relationship between dietary sodium intake and human health, has reported that positive relationship between sodium intake and blood pressure was steeper at a level of urinary sodium excretion of >5 g/day.5 However, the association...
between sodium intake and major adverse cardiovascular events (MACE) remains controversial, because the previous studies have reported heterogeneous (linear, J-shaped or U-shaped) associations.6-10 The association between salt intake and MACE may vary depending on the characteristics of the study population, such as ethnicity, age distribution and dietary pattern. A recent meta-analysis showed that the effect of reducing sodium intake on blood pressure might be greater in Black and Asian populations.11 Mente et al showed that the impact of high urinary sodium excretion on cardiovascular events differed between the populations with and without hypertension.12 Therefore, whether high sodium intake is an independent risk factor for MACE requires further investigation.

Rheumatoid arthritis (RA), which is one of the most common inflammatory arthropitides in adults, is reportedly associated with an increased cardiovascular risk, to a similar extent as type 2 diabetes mellitus (DM).13 14 The increased cardiovascular risk in RA has been largely attributed to the systemic inflammation of RA disease activity and premature atherosclerosis.15-17 Several studies in Western populations reported a 1.5- to 2-fold increased risk of cardiovascular morbidity and mortality in patients with RA compared with individuals without RA.18-20 A similar association was found in a Chinese study, showing approximately twice the risk of MACE in patients with RA than in those with osteoarthritis.21 A few studies evaluated the association between RA and CVD among the Korean population. Rhew reported that RA was associated with ischaemic heart disease (OR 1.75, 95% CI 1.73 to 1.77) and cerebral infarction (OR 1.28, 95% CI 1.26 to 1.30) from the data of the Korean Health Insurance Review and Assessment Service.22 Jeong et al showed that RA was associated with an increased prevalence of myocardial infarction or angina (OR 1.86, 95% CI 1.17 to 2.96) using data from the Korean National Health and Nutrition Examination Survey (KNHANES) 2010-2012.23 So far, several studies have evaluated the relationship between certain risk factors and MACE from the KNHANES dataset; however most did not include RA as a potential risk factor.23 24

Hence, it is necessary to evaluate the association of these potential risk factors—sodium intake and RA—with MACE in addition to the traditional risk factors in the Korean population. The purpose of this study was to evaluate the relationship of MACE with 24-hour urinary sodium excretion (24HUNa), as a surrogate marker of dietary sodium intake, and RA in the Korean adult population using data from the KNHANES.

MATERIALS AND METHODS
Study design and population
The KNHANES is an annual nationwide survey of the Korean population, conducted by the Korea Centers for Disease Control and Prevention (CDC) with the approval of the Institutional Review Board of the Korean CDG. Participants were selected using the proportional allocation-systemic sampling method with multistage stratification to derive a representative Korean population. Voluntary participants, who provided written informed consents, were included in the KNHANES. The survey was conducted by special research teams that completed 1 month of education and practices and whose research ability was verified through regular education and onsite quality management. The KNHANES data were anonymised and released to researchers and are publicly available (http://knhanes.cdc.go.kr).

This study used data from the KNHANES VII (2016-2018) survey. Among a total of 24 269 participants, we included adults aged 20 years or older. We excluded participants with implausible data on daily energy intake (<500 kcal or >5000 kcal), as in previous studies.25 26 Participants diagnosed with liver cirrhosis, cancer and renal insufficiency and those with a serum creatine concentration ≥2.0 mg/dL or missing urinary sodium data were excluded. After applying the exclusion criteria, 13 464 participants (weighted n=90 425 889) were finally included in our analyses (figure 1).

Covariates and definition of variables
The data on participants’ age, sex, region of residence, income, education and smoking status were collected. Body mass index (BMI) was calculated as weight (kg) divided by the height squared (m). Income status was categorised into four groups (low/mid-low/mid-high/high) according to the quartiles of the average individual monthly income. Regions of residence were classified by the administrative district. Alcohol consumption was categorised into the following four groups based on the frequency of alcohol consumption during the past year: (1) never, (2) ≤1 time/month, (3) 2-4 times/month and (4) ≥1/ week. Information on comorbidities, family history, blood and urine laboratory test results, and variables from nutritional questionnaires were also collected. We defined MACE as a composite of self-reported physician-diagnosed myocardial infarction, angina pectoris, stroke, or a combination of these. Other disease conditions including RA, depression, hypertension, dyslipidaemia and DM were also defined based on self-reported physician diagnosis.

Estimating the 24HUNa
The KNHANES dataset provided sodium intake, which was estimated using the 24-hour diet recall questionnaire and morning spot urine sodium. The 24-hour diet recall method was reported to inaccurately reflect and underestimate the 24HUNa.27 28 The formula for estimating the 24HUNa using a single morning fasting urine, as suggested by Tanaka,29 strongly correlates with the measured 24HUNa from 24-hour urine collection sample.30 It is also suggested as a valid and simple tool to estimate sodium intakes in a large population study as a better alternative to the 24-hour urine collection method.31 32 Hence, we used the estimated 24HUNa as...
a surrogate marker of dietary sodium intake. It can be calculated using weight, height, age, and measured spot urine creatinine (Cr) and natrium provided from the KNHANES dataset. The estimated 24HUNa (mg/day) is considered to reflect equivalently dietary sodium intake (mg/day) and the equation is as follows:

Estimated 24-hour urinary Cr (mg) = (14.89 × [weight (kg)]+16.14 × [height (cm)]-2.04×Age - 2244.45

Estimated 24HUNa (mg/day)=23 × 21.98 × ((spot urine Na (mmol/L)/spot Cr (mg/dL)×10)×estimated 24-hour urinary Cr (mg))0.392

Statistical analyses
The KNHANES used a stratified, multistage, probability-sampling design to represent the entire population; thus, complex samples analysis procedures using sampling weights were performed. A complex sample plan file was designed to apply the k strata, primary sample units, and proper usage of sampling weight values. Data are expressed as the absolute number or estimated percentage (%) or mean±SE. The χ² test and the t-test were performed to analyse the differences between participants with and without MACE and participants with and without RA. Simple linear regression analyses were used to determine the relationships of a single variable with MACE as dependent variable. Restricted cubic spline (RCS) plots were used to explore the shape of the association between 24HUNa and MACE. Participants were divided into five groups according to 24HUNa as follows: low (<3 g), reference (3–3.999 g), moderate (4–4.999 g), high (5–5.999 g) and extremely high (≥6 g). We selected 3–3.999 g/day as the reference range for 24HUNa based on the trends for MACE in the RCS plot. To determine the association between 24HUNa groups and MACE, we performed multiple logistic regression analyses using three different sequential models: adjusted for age and sex (model 1), further adjusted for total energy intake, BMI, income, education, region of residence, smoking, and family history of MACE (model 2), and adjusted for variables in model 2 and comorbid diseases including hypertension, dyslipidaemia, DM, RA and depression (model 3) in order to explore whether there is a difference when conventional risk comorbidities are included in addition to individual demographic and socioeconomic characteristics. Finally, we used multivariate complex sample logistic regression analysis to identify factors related to MACE, designating all significant covariates, including 24HUNa in two ways; (1) extremely high 24HUNa as a dichotomous variable, (2) five 24HUNa groups as a categorical variable. For the subgroup analysis, the same procedures using coronary artery diseases (myocardial infarction or angina) and cerebrovascular disease (stroke) as dependent variables were conducted. We considered a p<0.05 as statistically significant. Statistical analysis was conducted using SPSS for Windows, V.25 (IBM) and R V.4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS
Comparisons between participants with and without MACE
The prevalence of MACE was 3.7% among the Korean adult population (table 1). Participants with MACE were older, predominantly men, residents of more rural areas, and more likely to be smokers and non-drinkers than...
Table 1  Comparisons of characteristics according to the presence of MACE among the general Korean population included in the analyses

<table>
<thead>
<tr>
<th>Variables With MACE (3.7%)</th>
<th>Without MACE (96.3%)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unweighted, n</td>
<td>676</td>
<td>12 788</td>
</tr>
<tr>
<td>Weighted, n</td>
<td>3 349 365</td>
<td>87 076 524</td>
</tr>
</tbody>
</table>

**Age (years)**
- 20–49: 316 672 (7.0) vs 68 910 214 (32.4) <0.001
- 50–59: 874 425 (19.3) vs 24 310 692 (16.4) <0.001
- 60–69: 1 330 644 (29.3) vs 15 082 772 (10.2) <0.001
- ≥70: 2 020 659 (44.5) vs 12 329 764 (8.3) <0.001

**Sex**
- Men: 1 943 927 (46.8) vs 43 082 845 (49.5) <0.001
- Women: 1 205 437 (42.0) vs 43 993 678 (50.5) <0.001

**Region of residence**
- Metropolitan: 1 506 804 (45.9) vs 40 135 796 (46.1) <0.001
- Urban: 1 150 887 (34.4) vs 34 134 283 (39.2) <0.001
- Rural: 691 672 (20.7) vs 12 806 444 (14.7) <0.001

**Body mass index (kg/m²)**
- 24.61±0.14 vs 23.95±0.04 <0.001

**Income**
- Low: 1 188 254 (35.6) vs 12 706 743 (14.6) <0.001
- Mid: 853 342 (25.6) vs 20 380 006 (25.3) <0.001
- High: 671 627 (20.7) vs 12 806 444 (14.7) <0.001

**Education**
- ≤Elementary: 1 424 388 (42.7) vs 11 891 195 (13.7) <0.001
- Middlehigh: 1 409 969 (42.3) vs 37 048 942 (42.6) <0.001
- ≥College: 501 740 (15.0) vs 37 962 690 (43.7) <0.001

**Smoking**
- Never-smoker: 1 579 384 (47.2) vs 50 517 035 (58.1) <0.001
- Ex-smoker: 1 206 389 (36.0) vs 18 584 453 (21.4) <0.001
- Current smoker: 563 590 (16.8) vs 17 812 544 (20.5) <0.001

**Alcohol consumption**
- Never: 1 226 155 (36.6) vs 19 170 781 (22.0) <0.001
- ≤1 month: 846 037 (25.3) vs 24 888 864 (28.6) <0.001
- 2–4/month: 470 455 (14.0) vs 21 869 824 (25.2) <0.001
- 1–week: 806 718 (24.1) vs 21 015 283 (24.2) <0.001

**Comorbidities**
- Hypertension: 2 115 091 (63.1) vs 15 576 175 (17.9) <0.001
- Dyslipidaemia: 1 898 258 (41.8) vs 17 540 299 (11.8) <0.001
- Diabetes mellitus: 945 135 (28.2) vs 5 693 892 (6.5) <0.001
- Depression: 337 066 (10.1) vs 3 338 335 (3.8) <0.001
- Rheumatoid arthritis: 34 692 (1.0) vs 96 004 (1.5) <0.001

**Family history of MACE**
- 75 337 (2.2) vs 97 548 (1.1) 0.013

**Total energy intake (kcal/day)**
- 1726.7±35.8 vs 2045.0±12.4 <0.001

Continued

Table 1  Continued

<table>
<thead>
<tr>
<th>Variables</th>
<th>With MACE (3.7%)</th>
<th>Without MACE (96.3%)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated 24-hour urinary sodium excretion (g/d)</td>
<td>3.299±0.040</td>
<td>3.070±0.001 &lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean±SD or number (%).

*P values were obtained by χ² test or t-test.

MACE, major adverse cardiovascular events.

Table 1  Continued

In the unadjusted regression analyses, older age, male sex, rural residence, higher BMI, low socioeconomic status, and non-drinking showed significant associations with the presence of MACE. Comorbidities such as RA and hypertension, dyslipidaemia, DM and depression, and family history of MACE were also significantly associated with the presence of MACE. Total energy intake (OR 0.99, 95% CI 0.994 to 0.997, p<0.001) was positively associated with MACE, whereas the estimated 24HUNa showed positive associations with MACE (OR 1.37, 95% CI 1.274 to 1.597, p<0.001, table 2). The group with extremely high 24HUNa (≥6 g/day) was significantly associated with an increased risk of MACE.

Next, to explore the elaborate relationship between 24HUNa levels and the presence of MACE, we performed multiple regression analyses using sequential adjustment models (table 3). The highest 24HUNa subgroup (≥6 g/...
day) was more likely to have MACE than the reference group (3–4 g/day) in models 1, 2 and 3 (OR 6.75, 95% CI 1.421 to 32.039 in model 3).

To determine independent risk factors for MACE, multivariate logistic regression analyses were performed including all significant variables. As presented in table 4, old age, male sex, low educational level, ex-smoker, comorbidities such as RA (OR 2.05, 95% CI 1.283 to 3.264, p=0.003), hypertension (OR 2.15, 95% CI 1.683 to 2.739, p<0.001), dyslipidaemia (OR 1.55, 95% CI 1.252 to 1.919, p<0.001), DM (OR 1.63, 95% CI 1.287 to 2.072, p<0.001) and depression, low total energy intake and the group with extremely high 24HUNa (OR 6.35, 95% CI 1.337 to 30.147, p=0.02) were significantly associated with the presence of MACE. When 24HUNa was adopted as five-category groups, the results were similar to those from the aforementioned analyses, and the highest 24HUNa group was significantly associated with the presence of MACE compared with the reference group (3–3.999 g/day) (online supplemental table 2). In the subgroup analyses on coronary artery disease and cerebrovascular disease as separate dependent variables, both RA and the group with extremely high 24HUNa were significantly associated with coronary artery disease, whereas their association with cerebrovascular disease was insignificant (online supplemental tables 3 and 4).

**DISCUSSION**

Using nationally representative data, we investigated the relationship of RA and estimated 24HUNa with MACE.
simultaneously in the Korean adult population. The highest risk for MACE was seen in those with extremely high estimated 24HUNa (≥6 g/day), even after adjusting for traditional comorbidities including hypertension, dyslipidaemia, and DM. Multivariate logistic regression analysis demonstrated that RA and extremely high estimated 24HUNa were significantly associated with the presence of MACE.

In our study, MACE was prominent among aged men. Although smoking is a well-known risk factor for MACE, in this study, only the proportion of ex-smokers in the MACE group was higher than that in the non-MACE group. This can be explained by the fact that a substantial number of MACE patients may have discontinued smoking on medical advice after diagnosis of MACE. In participants with MACE, estimated 24HUNa using the Tanaka formula was significantly higher despite lower energy intake than in those without MACE. As expected, participants with MACE showed significantly higher prevalence of RA, depression, hypertension, DM and dyslipidaemia. Patients with RA also had more comorbidities such as hypertension, dyslipidaemia, DM, MACE and depression, as previous studies have confirmed.

After adjusting for all associated covariates, RA was still an associated risk factor for MACE with an OR of approximately 2. These results were consistent with those of previously reported studies that demonstrated an approximately 2-fold increase in risk for cardiovascular events among Western populations.

A recent study by Jeong et al using the 2010–2012 KNHANES data reported an increased risk for myocardial infarction or angina (OR 1.86, 95% CI 1.17 to 2.96) in patients with RA; however, their analyses were not adjusted for traditional cardiovascular risk factors such as hypertension and DM. Subsequently, Lee et al showed an increased prevalence of coronary artery diseases (OR 2.97, 95% CI 1.15 to 7.68) using propensity-score matching from the KNHANES 2008–2012 data; however, they only considered coronary artery disease.

In this study, the continuous value of the estimated 24HUNa showed significant positive associations with the presence of MACE (OR 1.43, 95% CI 1.274 to 1.597) in the simple regression analyses. However, RCS plots noted a J-shaped association between estimated 24HUNa and the presence of MACE in our population, rather than a linear positive association. Hence, we classified estimated 24HUNa into five groups with ranges of 1 g, as did previous Western studies.

In those studies, the criterion for extremely high urinary sodium excretion was set to ≥7 g/day. Because few participants belonged to the ≥7 g/day group in our population, we designated ≥6 g/day as the extremely high group. In addition, we selected 3–4 g/day as the reference range for sodium intake based on the trends for MACE in the RCS plots. This range corresponds to the recently reported mean sodium intake among the Korean adult population.

A recent pooled analysis, which identified a U-shaped association between CVD and sodium excretion, found that an estimated sodium excretion between 4 and 5 g/day led to the lowest risk of CVD. This difference is attributed to the fact that salt intake by Koreans is still higher than that prescribed by the WHO guidelines (≤2 g/day) but less than observed in Western countries. High dietary sodium intake is associated with high morbidity and mortality, which is predominantly mediated by its harmful effect on blood pressure in the general population. Many epidemiological and prospective cohort studies have investigated the association between urinary sodium excretion and CVD events and mortality; however, the relationship has not been resolved. Some studies suggested a positive association between high sodium intake and higher risk of CVD events whereas other research reported a U-shaped or J-shaped association, with an increased risk at

### Table 3 Logistic regression analyses to determine the association between estimated urinary sodium excretion groups and major adverse cardiovascular events

<table>
<thead>
<tr>
<th>Estimated 24-hour urinary sodium excretion using Tanaka equation</th>
<th>&lt;3 g</th>
<th>3–3.999 g</th>
<th>4–4.999 g</th>
<th>5–5.999 g</th>
<th>≥6 g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unweighted no</td>
<td>6166</td>
<td>5537</td>
<td>1528</td>
<td>182</td>
<td>15</td>
</tr>
<tr>
<td>Unweighted no of MACE</td>
<td>254</td>
<td>278</td>
<td>117</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>Weighted no</td>
<td>42 953 228</td>
<td>36 493 867</td>
<td>9 580 096</td>
<td>1 087 154</td>
<td>80 517</td>
</tr>
<tr>
<td>Weighted no of MACE</td>
<td>1 273 626</td>
<td>1 373 922</td>
<td>559 434</td>
<td>70 641</td>
<td>33 006</td>
</tr>
<tr>
<td>Univariate</td>
<td>0.78 (0.638–0.957) ref</td>
<td>1.56* (1.206–2.083)</td>
<td>1.78 (0.920–3.431)</td>
<td>17.76* (5.635–55.963)</td>
<td></td>
</tr>
<tr>
<td>Multivariate</td>
<td>Model 1†</td>
<td>1.11 (0.901–1.365) ref</td>
<td>1.33* (1.006–1.755)</td>
<td>1.27 (0.952–1.701)</td>
<td>6.75* (1.421–32.039)</td>
</tr>
<tr>
<td>Model 2‡</td>
<td>1.13 (0.916–1.394) ref</td>
<td>1.33 (1.000–1.765)</td>
<td>1.04 (0.486–2.234)</td>
<td>8.68* (1.846–40.827)</td>
<td></td>
</tr>
<tr>
<td>Model 3§</td>
<td>1.06 (0.857–1.314) ref</td>
<td>1.27 (0.952–1.701)</td>
<td>1.02 (0.478–2.164)</td>
<td>6.75* (1.421–32.039)</td>
<td></td>
</tr>
</tbody>
</table>

Values are in OR (95% CIs).
*P<0.05, p values from univariate and multivariable logistic regression with MACE as dependent variable.
†Model 1 adjusted for age, sex.
‡Model 2 further adjusted for total energy intake, body mass index, income, education, region of residence, smoking, alcohol consumption, family history of MACE.
§Model 3 adjusted for factors in model 2 and rheumatoid arthritis, depression, hypertension, dyslipidaemia, diabetes mellitus.

MACE, major adverse cardiovascular events.
P values from multivariable logistic regression with MACE as dependent variable. 24HUNa, 24-hour urinary sodium excretion; MACE, major adverse cardiovascular events.

<table>
<thead>
<tr>
<th>Variables</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–49 Ref</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50–59</td>
<td>4.41</td>
<td>2.677 to 7.258</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>60–69</td>
<td>7.43</td>
<td>4.322 to 12.784</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥70</td>
<td>12.53</td>
<td>7.041 to 22.313</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men Ref</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>0.50</td>
<td>0.369 to 0.690</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Region of residence</td>
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<tr>
<td>Metropolitan Ref</td>
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<td></td>
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<tr>
<td>Urban</td>
<td>0.94</td>
<td>0.752 to 1.184</td>
<td>0.629</td>
</tr>
<tr>
<td>Rural</td>
<td>0.94</td>
<td>0.729 to 1.211</td>
<td>0.973</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>1.01</td>
<td>0.978 to 1.034</td>
<td>0.701</td>
</tr>
<tr>
<td>Income</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Ref</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mid-low</td>
<td>1.03</td>
<td>0.786 to 1.345</td>
<td>0.199</td>
</tr>
<tr>
<td>Mid-high</td>
<td>1.18</td>
<td>0.875 to 1.598</td>
<td>0.123</td>
</tr>
<tr>
<td>High</td>
<td>0.80</td>
<td>0.573 to 1.123</td>
<td>0.012</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥College Ref</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Middle-High Ref</td>
<td>1.54</td>
<td>1.094 to 2.176</td>
<td>0.013</td>
</tr>
<tr>
<td>≤Elementary Ref</td>
<td>1.41</td>
<td>1.035 to 1.923</td>
<td>0.030</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never-smoker Ref</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Ex-smoker</td>
<td>1.54</td>
<td>1.121 to 2.117</td>
<td>0.130</td>
</tr>
<tr>
<td>Current smoker Ref</td>
<td>1.32</td>
<td>0.922 to 1.875</td>
<td>0.323</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never Ref</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1 month</td>
<td>1.16</td>
<td>0.890 to 1.517</td>
<td>0.939</td>
</tr>
<tr>
<td>2–4/month</td>
<td>0.80</td>
<td>0.459 to 1.073</td>
<td>0.315</td>
</tr>
<tr>
<td>1≥week</td>
<td>0.99</td>
<td>0.737 to 1.325</td>
<td>0.192</td>
</tr>
<tr>
<td>Comorbidities</td>
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<tr>
<td>Rheumatoid arthritis</td>
<td>No Ref</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2.05</td>
<td>1.283 to 3.264</td>
<td>0.003</td>
</tr>
<tr>
<td>Hypertension</td>
<td>No Ref</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2.15</td>
<td>1.693 to 2.739</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>No Ref</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.55</td>
<td>1.252 to 1.919</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>No Ref</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.63</td>
<td>1.287 to 2.072</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Depression</td>
<td>No Ref</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2.26</td>
<td>1.594 to 3.190</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Family history of MACE</td>
<td>No Ref</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.99</td>
<td>0.998 to 3.974</td>
<td>0.051</td>
</tr>
<tr>
<td>Total energy intake (kcal/day)</td>
<td>0.75</td>
<td>0.631 to 0.880</td>
<td>0.001</td>
</tr>
<tr>
<td>Group with extremely high 24HUNa (24HUNa ≥6 g/day)</td>
<td>No Ref</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6.35</td>
<td>1.337 to 30.147</td>
<td>0.020</td>
</tr>
</tbody>
</table>

Both low and high sodium intake. However, a subsequent pooled analysis suggested that the association was different depending on hypertension status. In our multiple model regression analyses of estimated 24HUNa groups, the highest 24HUNa group (≥6 g/day) was significantly associated with the presence of MACE after adjustment for well-known socioeconomic and lifestyle risk factors (models 1 and 2). Furthermore, its statistical significance remained even after additional adjustment were made for comorbidities including hypertension, dyslipidaemia, DM, depression, and RA (model 3). These factors were also consistently associated with MACE in the multivariate logistic regression analyses. Therefore, the optimal control of these comorbidities as well as avoidance of extremely high sodium intake will be beneficial to prevent MACE in the adult Korean population.

When extremely high estimated 24HUNa was included as a dichotomous or five-group categorical variable in the multivariate logistic regression analyses, the highest 24HUNa group was an independent risk factor for MACE (OR 6.35, 95% CI 1.337 to 30.147 and OR 6.75, 95% CI 1.421 to 32.039, respectively). In line with these findings, Mente et al also reported that individuals with hypertension consuming ≥6 g/day of sodium had higher risk for CVD and death. Relatively few studies have investigated the association between sodium intake and cardiovascular risk in Asians. It was recently shown that although sodium excretion was correlated with cardiovascular events, statistical significance disappeared after adjusting for hypertension and use of anti-hypertensive medication among the Chinese population. Another recently published study using the KNHANES data noted a higher risk of CVD-associated mortality in women with top-quartile sodium intake (energy-adjusted sodium intake >5625 mg/day). In the subgroup analyses, only the coronary artery disease group showed the same results. Hence, our results for MACE may be mainly attributable to those with coronary artery disease.

Excess salt intake can trigger and/or worsen autoimmune responses. A recent Japanese study has shown significant association between salt load index (urinary sodium-to-potassium ratio) and current disease activity in patients with RA. Unfortunately, we could not determine a similar relationship owing to the absence of relevant items on disease activity for RA in KNHANES dataset. Besides, since the estimated 24HUNa in the RA group was higher than that in the non-RA group, we attempted to perform a similar multivariate regression analysis confined to the RA population, to confirm whether salt intake affects the presence of MACE particularly in patients with RA. However, the small number of patients with RA (unweighted n=298) and the events of interest (MACE, unweighted n=36) limited the logistic regression analysis of only the RA subgroup.

This study had several limitations. First, due to its cross-sectional nature, the causal relationship between the variables of interest could not be evaluated. Second, drugs such as anti-hypertensive agents, metformin and glucocorticoids could affect urinary sodium excretion or MACE. However, we were not able to adjust for them because of the absence of information on medication in the KNHANES dataset.
since definitions of main diseases were based on self-reported physician-diagnosed status, their prevalence might have been overestimated. Besides, the exclusion of approximately half of the participants could have led to a selection bias. Moreover, participants with MACE risks could have preventedly reduced dietary sodium intake. Finally, the gold standard for the assessment of sodium intake is the multiple assessments of 24HUNa.49,50 In this study, the Tanaka equation was used to calculate the estimated 24HUNa from spot urine values. Despite these limitations, our study had significant contributions. To the best of our study, we were the first to comprehensively analyse the conjoint association of RA and sodium intake with MACE using representative data of the Korean population. In addition, we approximated the modern dietary pattern by using the most recent dataset and our analyses included the most associated confounders relevant to MACE. Further prospective research with a large sample size is warranted to elucidate firm evidence about the association between sodium intake and cardiovascular risk among the Korean population.

In conclusion, we showed that RA and extremely high sodium intake were independently associated with an increased risk of MACE in the Korean adult population. In addition to the management of traditional risk factors, it is necessary to promote awareness regarding avoidance of extremely high sodium intake and to consider RA as an important risk factor for MACE. Our results could help in the recommendation of a policy for salt reduction policy for the Korean population and patients with RA to achieve potential cardiovascular benefits.

Contributors J-HB contributed to data collection, performed statistical analyses and drafted the initial manuscript. M-YS and EHK collected the data, performed statistical analyses and contributed to the interpretation of data. YJL contributed to the interpretation of data and critically reviewed the data. Y-JH is the guarantor of the study. All authors have critically revised the manuscript and approved the final version for publication.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study was approved by the Institutional Review Board of Seoul National University Bundang Hospital. Written informed consent was obtained from participants before completing the survey (IRB No. X-1902/524–901).

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Data availability statement Data are available on reasonable request.

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ORCID iDs
Yun Jong Lee http://orcid.org/0000-0001-7615-8611
Yoo-Jung Ha http://orcid.org/0000-0001-6107-9523

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