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Association between 24-h urinary sodium to potassium ratio and mild cognitive impairment in community-based general population

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Abstract

Objective: To explore the relationship between parameters of Na and K excretion using 24-h urine sample and mild cognitive impairment (MCI) in general population.

Design: This is a cross-sectional study.

Setting: Community-based general population in Emin China.

Participants: Totally, 1147 subjects aged ≥18 years were selected to complete the study, with a multistage proportional random sampling method. Cognitive status was assessed with Mini Mental State Examination (MMSE) questionnaire and timed 24-h urine specimens were collected. Finally, 561 participants aged ≥35 years with complete urine sample and MMSE data were included for the current analysis and divided into groups by tertiles of 24-h urinary sodium to potassium ratio (24-h UNa/K) as lowest (T1), middle (T2) and highest (T3) groups.

Results: The MMSE score was significantly lower in T3, compared with the T1 group (26·0 *v.* 25·0, $P = 0·002$), and the prevalent MCI was significantly higher in T3 than in T1 group (11·7 % *v.* 25·8 %, $P < 0·001$). In multiple linear regression, 24-UNa/K (β: −0·184, 95 % CI −0·319, −0·050, $P = 0·007$) was negatively associated with MMSE score. In multivariable logistic regression, compared with T1 group, 24-h UNa/K in the T2 and T3 groups showed 2·01 (95 % CI 1·03, 3·93, $P = 0·041$) and 3·38 (95 % CI 1·77, 6·44, $P < 0·001$) fold odds for presence of MCI, even after adjustment for confounders. More augmented results were demonstrated in sensitivity analysis by excluding individuals taking anti-hypertensive agents.

Conclusions: Higher 24-h UNa/K is in an independent association with prevalent MCI.

Keywords
Urinary sodium
Urinary potassium
Urinary sodium to potassium ratio
Mild cognitive impairment

With accelerated ageing of the world population[1], the number of patients with cognitive impairment including dementia, Alzheimer's disease (AD) and mild cognitive impairment (MCI) is inevitably increasing[2,3], becoming a social, medical, economical and family burden[4]. Yet, there are at present no effective methods to treat dementia and AD or to delay their clinical progression[5]. Therefore, identifying modifiable risk factors of the precursory stage of dementia for early intervention is the priority. MCI is considered to be a preclinical transitional state of dementia[6], for which targeted interventions may be feasible. Previously reported potentially modifiable risk factors for MCI include low physical activity, obesity, diabetes, hypertension and stroke[7].

Recent studies have focused on the possible negative effects on MCI of a well-known risk factor for cardiocerebrovascular disease, high Na and low K intake. Theoretically, it is reasonable to accept the negative effects of high Na and low K intake on MCI, given the fact that high Na and low K intake always leads to hypertension and stroke[8,9], and the latter two are well-established risk factors for MCI[7,10]. Animal studies revealed that excess dietary salt leads to cognitive impairment through gut brain axis by changing adaptive immune response and

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enhancing oxidative stress and inflammation in the central nervous system[11,12], while results are confusing in human studies. A prospective study performed among elderly postmenopausal women reported no association between Na intake and MCI[13]. Afsar and his colleagues showed decreased Na intake was independently related to better cognitive function in essential hypertensive patients[14], while Rush *et al.* found that lower Na intake is associated with poorer cognition[15]. Failure to use recommended 24-h urine collection[16,17] to assess Na and K intake[13,15] and enrollment of specific (older[13,15], single gender[13] or patients[14]) study population may explain the inconsistency.

Therefore, the study aimed to evaluate the hypothesis that high Na and low K intake, assessed by 24-h urine sample, is associated with higher prevalence of MCI in general population.

Materials and methods

Study population

This is a cross-sectional study. We used multistage proportional random sampling method to obtain study population aged ≥18 years from Emin, a county in Northern Xinjiang China, between March and June 2019. At the first stage, whole county was divided into twenty sites, based on the number of primary care hospitals located in the county, townships and villages. At the second stage, ten sites were selected using simple random sampling method. At the third stage of sampling, a given number of participants from each site were selected using lists compiled from local government registers of households. Inclusion criteria encompassed: 1. local inhabitants aged ≥18 years; 2. residing at current address for ≥6 months and 3. agreement to participate and sign an informed consent form. Exclusion criteria included older age with difficulty in moving, menstruation or pregnant women and disabled subjects.

A total of 1147 subjects were selected to complete the study, of whom 167 subjects were unable to participate in urine sample collection due to the advanced age (*n* 17), pregnancy (*n* 11), menstruation (*n* 23), disabled (*n* 9) and unwillingness (*n* 107). Therefore, 980 subjects provided 24-h urine samples, with a response rate of 85·4 % of whom there were 738 individuals aged ≥35 years. Excluding individuals with unqualified 24-h urine samples (*n* 175) and those with incompleteness on Mini-Mental State Examination (MMSE) (*n* 2), finally, 561 participants aged ≥35 years with qualified urine sample and complete data of MMSE were evaluated in current analysis (Fig. 1).

In the current analysis, we selected subjects aged ≥35 years as previous researches[18] for following reasons. First, population at this age and older usually have stable lifestyles. Second, most chronic diseases are age dependent, so that the relationship can be established between parameters of interest. Third, some risk factors are getting highly prevalent in younger population and need early attention and intervention such as hypertension[19] and high Na low K intake, which are lifelong lifestyle-related condition. Their effects on health may begin earlier.

24-h urine sample collection and measurement

A timed 24-h urine specimen was collected from each participant. In-person timed collections were started in temporary urine collection point established in each site and completed at the collection point the next day. Each participant was given verbal and written instructions on when to start and complete and how to collect. Urine samples were collected from 09:00 am to 09:00 am the next day (09:00 am was considered for providing convenience of fasting blood sample collection in the second morning) after excluding the first sample of the first day and were poured into two urine collection kits with volume of 2 l labelled with participants respective special code. On the second day, total volume of each collection (samples were put together from two kits when two were used) was measured and recorded. Urine samples were collected in five respective tubes of 5 ml and stored temporarily in −20 °C temperature and the rest were discarded. One of the samples was delivered on the same day to People's Hospital of Tacheng, to where driving takes 40 min, to measure urinary Cr, protein and electrolytes including Na, K and Cl. The other four were sent to Central Laboratory, Xinjiang Hypertension Institute, to be stored at −80 °C for future measurements on ice after frozen at −20 °C for a few days, and the time on the road is about 6–7 h.

The completeness of urine samples was evaluated through following criteria: (1) total urine volume ≥ 500 ml; (2) 20 h or more duration; (3) reported no more than a few drops of urine lost during collection and (4) 24-h urinary creatinine (24-h UCr) per kilogram of body weight ≥20 mg/kg in men and ≥15 mg/kg in women aged <50 years and ≥10 mg/kg in men and ≥7·5 mg/kg in women aged ≥50 years[20,21]. We compared the characteristics of subjects with complete (qualified) and incomplete (unqualified) urine subjects in order to explore any potential differences, which may bring bias to our results.

Dietary salt, sodium, potassium intake assessment

Under normal conditions, 98 % Na is excreted through kidneys[22] and a variation of 50-90 % for K excretion[16]. Therefore, the estimated salt intake is ≈ urine Na concentration (mmol/l) × 24-h urine volume (l) ÷ 1000 × 58·5 (g/mol)[22]; daily Na and K intake (g) are estimated by multiplying with 0·023 for 24-h UNa (mmol) and 0·039 for 24-h UK (mmol)[23]. In line with the standard procedure, urinary Na, K and Cl were measured using ion selecting electrode method by Olympus AU 680 auto-analyzer (CV was 1·5 % for Na and 2·5 % for K). Cr was measured using the picric acid method by Olympus AU640 Analyzer (CV was 3 %).

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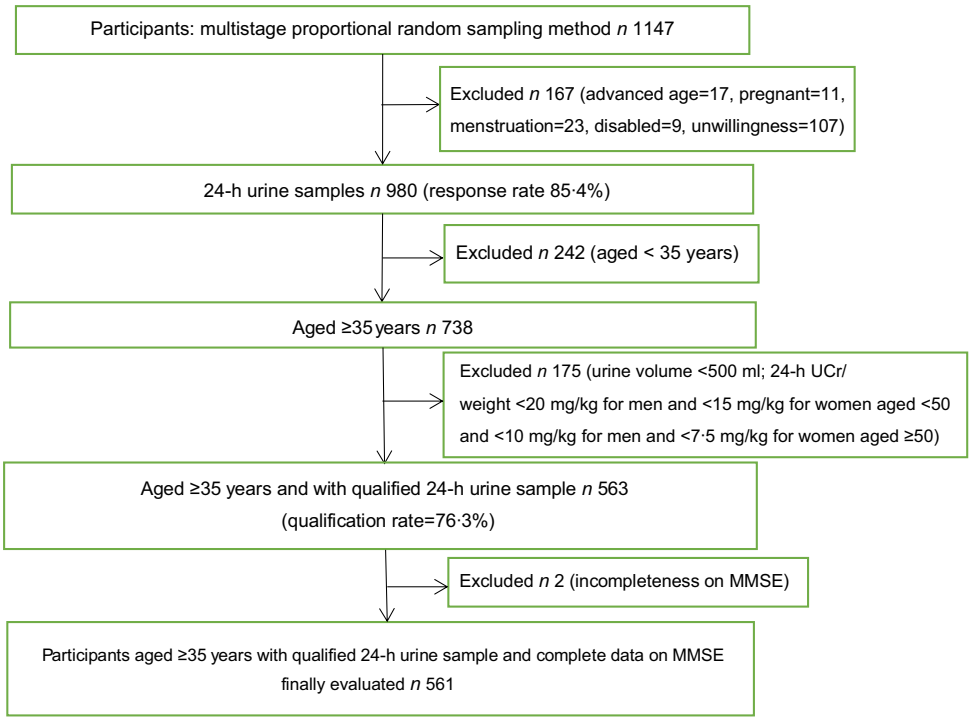

Fig. 1 (colour online) Flowchart reporting analysis

Cognitive assessment

Trained investigators evaluated participants' cognitive status with the MMSE[24], including orientation, registration, attention, calculation, language and recall, with a total score ranging from 0 to 30. MCI is defined as total MMSE score <17 for those with no formal education, <20 for subjects with 1–6 years of education and <24 for subjects with ≥7 years of education[25,26]. Since its introduction in 1975, the MMSE has been modified and translated into several languages[24]. In 1988, the MMSE was translated into Chinese and back-translated by a bi-national team of psychiatrists and social scientists. The process emphasised both translation accuracy and cultural propriety of the wording of the questions[27]. It was validated that these cut-off points of MMSE score had higher diagnostic efficiency for MCI in Chinese population[25].

Covariate assessment

Each participant completed a standardised questionnaire through a face-to-face interview. Data were collected on participants' demographic characteristics, socio-economic status, lifestyles, medical histories and therapeutic agents. Trained investigators measured blood pressure (BP), height, body weight and waist circumference according to the standardised protocol.

BP was presented as the mean of three measurements using the Omron HEM-1000 electronic sphygmomanometer[28]. All participants were advised to avoid cigarette, alcohol, caffeinated beverages, tea and exercise for at least 30 min prior to measurement. Three BP measurements were taken after a rest of at least 5 min from the unclothed right arm in a sitting position at intervals of at least 1 min. Height and weight were measured to the nearest 0·1 cm and 0·1 kg, respectively, with participants in light-weight clothing and without shoes. Waist circumference was measured at the midpoint between the lower rib and upper margin of iliac crest to the nearest 0·1cm at the end of normal expiration[29]. BMI was calculated by dividing weight by height squared (kg/m^2). After an overnight fasting, blood samples were obtained for the measurements of serum Cr, lipids and glucose. The specimens were sent to the People's hospital of Tacheng, after stored at onsite refrigerators temporarily.

Hypertension is defined as systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg and/or receiving antihypertensive medication within previous 2 weeks[30]. Diabetes mellitus is defined as fasting blood glucose ≥7·0 mmol/l, and/or self-reported previously diagnosed by physicians and/or intake of hypoglycemic agents within past 2 weeks[31]. Dyslipidaemia is defined as total cholesterol ≥6·2 mmol/l and/or triglyceride ≥2·3 mmol/l and/or high density lipoprotein cholesterol <1·0 mmol/l and/or low-density lipoprotein cholesterol ≥4·2 mmol/l and/or having received treatment during past 2 weeks[32]. Stroke is defined as 'rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24-h, with no apparent cause other than that of vascular origin'[33]. In this survey, stroke is determined by clinical presentation and confirmation by computed

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tomography or MRI based on medical records at least from secondary level hospitals. Overweight and obesity are defined as BMI ≥ 25 kg/m^2 and BMI ≥ 30 kg/m^2, respectively. Abdominal obesity is defined as having a waist circumference ≥ 102 cm for men and ≥88 cm for women[34].

Statistical analysis

Continuous variables including age, BMI, BP, estimated glomerular filtration rat, 24-h UNa/K, 24-h UNa and 24-h UK were presented as means ± standard deviations and were analysed using *t*-test or ANOVA test if normally distributed, otherwise, presented as median and 25th–75th percentiles and analysed by Mann-Whitney *U* test or Kruskal–Wallis *H* test. Categorical variables were expressed as proportion (%) and frequency (*n*), in which ordinal variables were analysed with H test and others were analysed using the χ^2 test. We performed propensity score matching analysis to compare the MMSE score and MCI prevalence between two groups by the median of 24-h UNa/K. Multiple linear regression model was used to estimate the unadjusted and adjusted beta (β) and 95 % CIs of parameters of 24-h UNa/K, 24-h UNa and 24-h UK and MMSE score as continuous variables. Logistic regression model was used to calculate the unadjusted and adjusted OR and the 95 % CI of above parameters by tertiles and the presence of MCI. Independent variables significantly relevant to MMSE (i.e. $P < 0{\cdot}1$) in bivariate analysis were adjusted in multivariate analysis. Tolerance and the variance inflation factor were examined to identify multicollinearity, which could be concerned if the variance inflation factor was >10 and the tolerance was <0·10. Similar approach was applied to logistic regression and multicollinearity was not an issue. Model a was performed including age, gender, education attainment status, occupation, cigarette and alcohol consumption, BMI category, estimated glomerular filtration rate, 24-h urinary protein, systolic blood pressure, stroke, dyslipidaemia, diabetes mellitus. Model a plus 24-h UNa and 24-h UK were model b (removing 24-h UNa in model b when it was the predictor variable, and vice versa). Additionally, restricted cubic spline (rcs) was plotted between 24-h UNa (continuous) and MCI, after adjusted above confounders. Sensitivity analysis was conducted by excluding the participants under anti-hypertensive treatment and in those aged ≥45 years. Results were considered statistically significant if two-tailed *P* value was less than 0·05. RCS was performed with R package (version 4.0.3) and others were performed with SPSS statistical software, version 24.0.

Results

Participants characteristics at baseline

Finally, 561 participants aged 52·7 ± 9·3 years with 42·6 % men were enrolled, with a median estimated salt intake of 8·6 g and estimated potassium intake of 1·2 g/d. Compared with subjects with unqualified urine samples, participants enrolled in the analysis were older, more likely to be female, less likely to smoke and having a lower BMI (online Supplementary material, Supplementary Table 1).

Individuals in T3 of 24-h UNa/K were younger, more likely to be male, preferred to smoke and had lower fasting blood glucose and triglyceride levels (*P* for all <0·05), compared with T1 (Table 1).

The Mini Mental State Examination scores and prevalence of mild cognitive impairment

The median of MMSE score among the participants was 26 and the overall prevalence of MCI was 19·1 %. The MMSE total score decreased significantly in T3 of 24-h UNa/K, compared with T1 (26·0 *v.* 25·0, $P = 0{\cdot}002$). Accordingly, the prevalent MCI was significantly higher in T3 than in T1 group (11·7 % *v.* 25·8 %, $P < 0{\cdot}001$). Similar results were demonstrated among people aged ≥ 45 years (Table 2).

By the method of propensity score matching, the results showed that MMSE score was lower in higher 24-h UNa/K group and accordingly the prevalence of MCI was higher, after we matched all of the relevant factors of baseline characteristics (online Supplementary material, Supplementary Tables 2 and 3).

Relationship between parameters of sodium, potassium excretion and Mini Mental State Examination score

In multiple linear regression, 24-h UNa/K (β: −0·184, 95 % CI −0·319, −0·050, $P = 0{\cdot}007$) and 24-UNa (β: −0·007, 95 % CI −0·013, −0·001, $P = 0{\cdot}025$) were negatively associated with MMSE score, while 24-h UK showed a positive effect (β: 0·028, 95 % CI 0·001, 0·055, $P = 0{\cdot}045$) after adjusted for age, gender, education status, occupation, smoking status, alcohol assumption, BMI, estimated glomerular filtration rate, twenty-four urinary protein, systolic blood pressure, stroke, dyslipidaemia and diabetes mellitus (24-h UK and 24-h UNa adjusted for each other). The association was significantly strengthened after excluding individuals under anti-hypertensive treatment ($\beta = -0{\cdot}257$, 95 % CI −0·429, −0·084; $\beta = -0{\cdot}008$, 95 % CI −0·015, −0·001; $\beta = 0{\cdot}038$, 95 % CI 0·005, 0·072; respectively, P for all <0·05). The relationship between 24-h UNa/K and MMSE score remained significant in the middle-aged and the elderly (Table 3).

In multi-variable logistic regression, compared with T1 group, 24-h UNa/K in the T2 and T3 groups showed 2·01 (95 % CI 1·03, 3·93, $P = 0{\cdot}041$) and 3·38 (95 % CI 1·77, 6·44, $P < 0{\cdot}001$) ($P_{\text{for trend}}$ <0·001) fold odds for the presence of MCI, even after adjustment for relevant confounders. In the fully adjusted model, the odds for MCI in T1 and T2 groups of 24-h UK were 3·23 (95 % CI 1·58, 6·57, $P = 0{\cdot}001$) and 3·04 (95 % CI 1·52, 6·09, $P = 0{\cdot}002$) ($P_{\text{for trend}} = 0{\cdot}001$), respectively. Additionally, odds for MCI in iT2 groups of 24-h UNa were 2·80 (95 % CI 1·49, 5·24, $P = 0{\cdot}001$), when compared with the corresponding

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Table 1 Characteristics of study participants by tertiles of 24-h urine sodium to potassium ratio

Characteristics	Total population		T1: ≤3·918		T2: 3·919–5·905		T3: ≥5·906		
Categorical variables	*n*	%	*n*	%	*n*	%	*n*	%	X^2, *F*, *H*/*P*
n	561		188	33·5	187	33·3	186	33·2	
Age groups									7·306/0·026
35–44	102	18·2	24	12·8	39	20·9	39	21·0	
45–59	341	60·8	116	61·7	116	62·0	109	58·6	
≥60	118	21·0	48	25·5	32	17·1	38	20·4	
Gender (men)	239	42·6	62	33·0	79	42·2	98	52·7	14·868/0·001 b
Education									19·516/<0·001
Primary and lower	213	38·0	60	31·9	63	33·7	90	48·4	
Junior	147	26·2	46	24·5	49	26·2	52	28·0	
Senior and higher	201	35·8	82	43·6	75	40·1	44	23·7	
Occupation									22·899/<0·001
Mental labour	157	28·0	67	35·6	60	32·1	30	16·1	
Physical labour	353	62·9	109	58·0	113	60·4	131	70·4	
Unemployed/unclassified	51	9·1	12	6·4	14	7·5	25	13·4	
Cigarette consumption	101	18·2	24	12·9	31	16·7	46	25·1	9·714/0·008 b
Alcohol intake	137	24·6	40	21·6	52	28·0	45	24·3	2·020/0·364
BMI category									7·459/0·024
<25 kg/m^2	186	33·2	79	42·0	50	26·7	57	30·6	
25–30 kg/m^2	250	44·6	72	38·3	94	50·3	84	45·2	
≥30 kg/m^2	125	22·3	37	19·7	43	23·0	45	24·2	
Abdominal obesity	218	38·9	71	37·8	75	40·3	72	38·7	0·263/0·877
Hypertension	278	49·6	90	47·9	90	48·1	98	52·7	1·096/0·578
Dyslipemia	204	36·8	68	36·8	79	42·5	57	31·1	5·087/0·079
Diabetes	64	11·5	19	10·2	26	14·0	19	10·3	1·731/0·421
Stroke	48	8·9	16	8·8	17	9·5	15	8·4	0·141/0·932
Anti-hypertensive drugs	144	25·7	50	55·6	48	53·3	46	46·9	1·521/0·467
Continuous variables	Mean/P_{50}	SD/P_{25}–P_{75}	Mean/P_{50}	SD/P_{25}–P_{75}	Mean/P_{50}	SD/P_{25}–P_{75}	Mean/P_{50}	SD/P_{25}–P_{75}	
Age (years)	52·7	9·3	54·1	9·8	52·1	8·8	51·8	9·0	3·534/0·030 ab
BMI (kg/m^2)	26·7	24·1–29·6	25·8	23·5–28·8	27·0	24·8–29·7	27·2	24·1–30·0	6·733/0·035 a
Abdominal circumference (cm)	91·0	82·2–97·1	89·0	80·4–96·0	91·1	84·0–99·1	91·0	84·1–98·0	5·613/0·060
Systolic blood pressure (mmHg)	129·7	118·3–143·7	128·5	117·2–141·8	128·7	118·3–142·3	132·2	118·7–146·2	3·121/0·210
Diastolic blood pressure (mmHg)	82·3	74·7–90·0	81·3	75·4–88·9	80·7	74·0–90·3	84·0	75·2–91·1	0·935/0·627
Fasting blood glucose (mmol/l)	5·3	4·7–6·0	5·4	5·0–6·0	5·2	4·7–6·1	5·1	4·6–5·8	8·505/0·014 b
Serum total cholesterol (mmol/l)	4·7	4·0–5·4	4·6	4·0–5·5	4·7	4·1–5·5	4·8	4·0–5·4	0·004/0·998
Serum triglyceride (mmol/l)	1·1	0·8–1·7	1·3	0·9–1·8	1·3	0·8–1·8	1·1	0·7–1·5	10·946/0·004 bc
Serum creatinine (umol/l)	71·1	57·0–90·0	69·2	58·0–91·5	71·0	55·6–91·5	73·8	57·4–89·0	0·017/0·992
24-h urinary sodium (mmol)	156·2	71·0	106·5	45·9	163·5	59·7	199·2	71·6	127·429/<0·001 abc
24-h urinary potassium (mmol)	30·6	22·9–39·5	34·7	26·5–46·8	32·5	26·5–41·0	24·1	18·8–30·1	93·950/<0·001 bc
24-h urinary sodium to potassium ratio	4·8	3·3–6·6	2·9	2·3–3·3	4·8	4·3–5·3	7·5	6·6–9·0	497·776/<0·001 abc
24-h urinary creatinine (mmol)	8·4	6·4–10·6	8·4	6·1–10·1	8·5	7·0–11·5	8·1	6·1–10·5	4·528/0·104
24-h urinary protein (mg)	42·0	25·0–67·1	34·5	20·0–51·8	45·0	28·0–75·0	47·0	32·0–73·9	23·176/<0·001 ab
eGFR (ml/min*1·73m^2)	92·7	70·9–105·1	92·7	66·5–104·6	90·5	69·3–105·8	94·3	74·5–105·3	1·968/0·374
Estimated salt intake (g)	9·1	4·2	6·2	2·7	9·6	3·5	11·7	4·2	127·429/<0·001abc

BMI, body mass index; eGFR, estimated glomerular filtration rate. a: T1 *v.* T2; b: T1 *v.* T3; c:T2 *v.* T3. We conducted among groups and between group comparisons using ANOVA followed by post-hoc analysis (Least Significant Difference test), Chi-square tests and nonparametric test. α value was corrected by Bonferroni method ($\alpha = 0{\cdot}017$).

Table 2 Mini Mental State Examination (MMSE) score and prevalence of mild cognitive impairment (MCI) by tertiles of 24-h urinary sodium to potassium ratio

	T1		T2		T3					
	n/P_{50}	%/P_{25}–P_{75}	*n*/P_{50}	%/P_{25}–P_{75}	*n*/P_{50}	%/P_{25}–P_{75}	P (total)	P1	P2	P3
Total subjects										
n (%)	188	33·5	187	33·3	186	33·2				
Total MMSE score	26·0	23·0–29·0	26·0	22·0–29·0	25·0	21·0–28·0	0·008	0·375	0·002	0·038
Orientation	10·0	9·0–10·0	10·0	9·0–10·0	10·0	8·0–10·0	0·090			
Registration	3·0	3·0–3·0	3·0	3·0–3·0	3·0	3·0–3·0	0·149			
Attention and calculation	4·0	2·0–5·0	4·0	2·0–5·0	3·0	1·0–5·0	0·014	0·591	0·007	0·023
Recall	2·0	1·0–3·0	2·0	1·0–3·0	2·0	1·0–3·0	0·117			
Language and Praxis	9·0	7·0–9·0	9·0	7·0–9·0	8·0	7·0–9·0	0·031	0·630	0·012	0·056
Prevalence of MCI (*n*, %)	22	11·7	37	19·8	48	25·8	0·002	0·032	<0·001	0·166
Population aged ≥45										
n (%)	164	35·7	148	32·2	147	32·0				
Total MMSE score	26·0	23·0–29·0	26·0	21·0–28·0	25·0	20·0–28·0	0·010	0·140	0·002	0·126
Orientation	10·0	8·0–10·0	9·0	8·0–10·0	9·0	8·0–10·0	0·043	0·070	0·017	0·573
Registration	3·0	3·0–3·0	3·0	3·0–3·0	3·0	2·0–3·0	0·094			
Attention and calculation	4·0	2·0–5·0	4·0	2·0–5·0	3·0	1·0–5·0	0·038	0·372	0·011	0·109
Recall	2·0	1·0–3·0	2·0	1·0–3·0	2·0	1·0–3·0	0·090			
Language and Praxis	9·0	7·0–9·0	9·0	7·0–9·0	8·0	7·0–9·0	0·061			
Prevalence of MCI (*n*, %)	21	12·8	36	24·3	41	27·9	0·003	0·009	0·001	0·486

MCI, mild cognitive impairment. We conducted among group and between group comparisons using nonparametric test and provided specific *P*-values as P (total) for among group comparison and as P1 (T1 *v.* T2), P2 (T1 *v.* T3) and P3 (T2 *v.* T3) for between group comparisons. α value was corrected by Bonferroni method ($\alpha = 0{\cdot}017$).

Table 3 Multiple linear regression for the correlation of parameters of sodium and potassium excretion and Mini Mental State Examination (MMSE)

	Unadjusted			Adjusted*		
	β	95 % CI	*P*	β	95 % CI	*P*
Total subjects						
24-h UNa/K	−0·240	−0·375, −0·104	0·001	−0·184	−0·319, −0·050	0·007
24-h UNa	0·002	−0·003, 0·008	0·405	−0·007	−0·013, −0·001	0·025
24-h UK	0·049	0·023, 0·074	<0·001	0·028	0·001, 0·055	0·045
After excluding individuals under anti-hypertensive treatment						
24-h UNa/K	−0·286	−0·441, −0·132	<0·001	−0·257	−0·429, −0·084	0·004
24-h UNa	0·000	−0·005, 0·006	0·907	−0·008	−0·015, −0·001	0·031
24-h UK	0·051	0·023, 0·080	<0·001	0·038	0·005, 0·072	0·026
Individuals aged ≥45 years						
24-h UNa/K	−0·243	−0·393, −0·092	0·002	−0·174	−0·322, −0·026	0·022
24-h UNa	0·002	−0·004, 0·009	0·498	−0·007	−0·014, 0·001	0·068
24-h UK	0·047	0·020, 0·075	0·001	0·027	−0·003, 0·057	0·077

95% CI, 95% confidence interval; 24-h UNa/K, 24-hour urinary sodium to potassium ratio; 24-h UNa, 24-hour urinary sodium; 24-h UK, 24-hour urinary potassium.
*Adjusted for age, gender, education status, occupation, smoking status, alcohol assumption, body mass index, systolic blood pressure, stroke, dyslipidemia, diabetes mellitus, estimated glomerular filtration rate, 24-h urinary protein, additionally adjusted 24-h UK for 24-h UNa, vice versa.

reference group. Rcs further demonstrated threshold effects between 24-h UNa and MCI (Fig. 2). Above results were partially strengthened after excluding subjects under anti-hypertensive treatment. Considering previous studies about the association between Na, K and cognition were mainly focused on the middle aged and the elderly[15,35], and MCI was more common in this group[36], we further performed subgroup analysis in those aged ≥45 years and the results remained significant (Table 4).

Discussion

In the sub-sample of individuals eligible for current analysis, we observed an independent association between higher 24-h UNa/K, an indicator of unbalanced intake of Na and K, and MCI presence in community-based general population using 24 h urine sample, possibly underlining the importance of interactions between the two nutrients in the presence of MCI, which are independent of two well-established risk factors, hypertension and stroke of MCI.

Current observation may add evidence on the on-going debate of Na, K, salt intake and cognitive function. Previous cross-sectional and cohort studies reported conflicting positive, negative or null effects of Na, K and salt intake on cognition using various populations, parameters and study designs[13–15,37–40]. However, when assessing Na, K or salt intake, the studies used three-day food diary[37], FFQ[13,15,38,39], instead of the 24-h urine sample, which

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Table 4 Associations between tertiles of parameters of sodium and potassium excretion and mild cognitive impairment (MCI) by logistic regression

	Unadjusted			Adjusted*			Adjusted†		
	OR	95 % CI	*P*	OR	95 % CI	*P*	OR	95 % CI	*P*
Total subjects									
24-h UNa/K									
T1	Ref			Ref					
T2	1·86	1·05, 3·30	0·033	2·01	1·03, 3·93	0·041			
T3	2·63	1·51, 4·56	0·001	3·38	1·77, 6·44	<0·001			
$P_{for\ trend}$	0·001			<0·001					
24-h UNa									
T1	Ref			Ref			Ref		
T2	1·69	1·02, 2·81	0·043	2·27	1·22, 4·23	0·009	2·80	1·49, 5·24	0·001
T3	0·92	0·53, 1·61	0·778	1·19	0·61, 2·35	0·610	1·88	0·94, 3·78	0·076
$P_{for\ trend}$	0·792			0·696			0·123		
24-h UK									
T1	3·26	1·79, 5·94	<0·001	2·70	1·37, 5·33	0·004	3·23	1·58, 6·57	0·001
T2	3·08	1·69, 5·62	<0·001	2·83	1·43, 5·62	0·003	3·04	1·52, 6·09	0·002
T3	Ref			Ref			Ref		
$P_{for\ trend}$	<0·001			0·002			0·001		
After excluding individuals under anti-hypertensive treatment									
24-h UNa/K									
T1	Ref			Ref					
T2	2·03	0·91, 4·53	0·086	2·27	0·85, 6·09	0·103			
T3	3·79	1·78, 8·07	0·001	5·46	2·11, 14·11	<0·001			
$P_{for\ trend}$	<0·001			<0·001					
24-h UNa									
T1	Ref			Ref			Ref		
T2	1·65	0·85, 3·21	0·137	2·15	0·95, 4·87	0·067	3·30	1·36, 8·03	0·008
T3	1·02	0·50, 2·07	0·964	1·19	0·47, 2·99	0·718	2·47	0·89, 6·87	0·084
$P_{for\ trend}$	0·983			0·716			0·078		
24-h UK									
T1	4·12	1·87, 9·06	<0·001	4·02	1·60, 10·11	0·003	5·80	2·12, 15·82	0·001
T2	3·21	1·43, 7·21	0·005	2·49	0·96, 6·44	0·060	2·69	1·02, 7·06	0·045
T3	Ref			Ref			Ref		
$P_{for\ trend}$	<0·001			0·003			0·001		
Individuals aged ≥45									
24-h UNa/K									
T1	Ref			Ref					
T2	2·19	1·21, 3·96	0·010	2·32	1·14, 4·72	0·020			
T3	2·63	1·47, 4·72	0·001	3·25	1·60, 6·60	0·001			
$P_{for\ trend}$	0·001			0·001					
24-h UNa									
T1	Ref			Ref			Ref		
T2	1·76	1·04, 2·99	0·036	2·50	1·28, 4·87	0·007	3·06	1·52, 6·13	0·002
T3	0·87	0·48, 1·56	0·634	0·97	0·46, 2·05	0·930	1·46	0·66, 3·20	0·350
$P_{for\ trend}$	0·718			0·972			0·269		
24-h UK									
T1	3·04	1·65, 5·62	<0·001	3·16	1·49, 6·70	0·003	3·63	1·63, 8·09	0·002
T2	2·58	1·38, 4·83	0·003	2·49	1·18, 5·25	0·016	2·54	1·18, 5·45	0·017
T3	Ref			Ref			Ref		
$P_{for\ trend}$	<0·001			0·003			0·002		

OR, odds ratio; 95% CI, 95% confidence interval; 24-h UNa/K, 24-hour urinary sodium to potassium ratio; 24-h UNa, 24-hour urinary sodium; 24-h UK, 24-hour urinary potassium.

*Adjusted for age, sex, education status, occupation, smoking status, alcohol assumption, BMI category, systolic blood pressure, estimated glomerular filtration rate, 24-h urinary protein, stroke, dyslipidaemia, diabetes mellitus.

†Model a plus 24-h UNa and 24-h UK (removing 24-h UNa in model b when it was the predictor variable, and vice versa).

may explain the inconsistency at least in part. In addition, except for one[37], others were conducted in older[13,15,38,39], single gender[13] and patient population[14,37], which may limit application of the results to the general population. Contrary to the human studies, animal models show high salt intake impairs cognition[12], and K supplement prevents cognitive alteration in the early stage AD[41]. A new gut–brain axis linking dietary salt to cognitive dysfunction through a gut-initiated adaptive immune response has been reported[11].

Compared with the recommended salt intake of 5–6 g/d[22,42], the average of estimated salt intake in the current study is 8·6 g. Based on a meta-analysis[43], the Chinese national average of 24-h UNa and 24-h K is 189·1 and 36·4 mmol respectively, higher than the amount of 147·6 and 30·6mmol in the current study. The possible reasons

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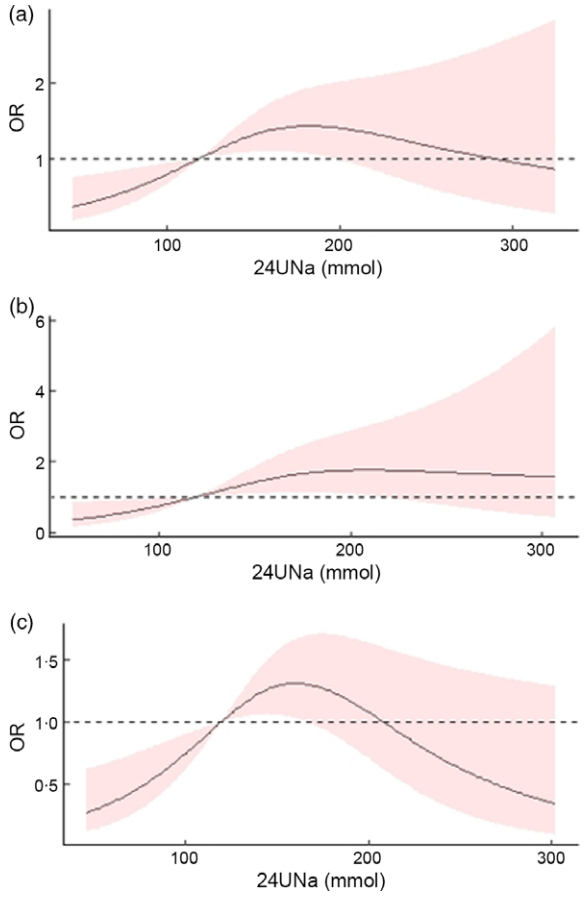

Fig. 2 (colour online) Restricted cubic spline plots of 24-h UNa and mild cognitive impairment (MCI) after adjusted for age, gender, education attainment status, occupation, cigarette and alcohol consumption, BMI, estimated glomerular filtration rate (EGFR), 24-h urinary protein, systolic blood pressure (SBP), stroke, dyslipidaemia, diabetes mellitus and 24-h UK (a: in total population, b: population excluding for individuals undertaking anti-hypertensive drugs, c: population aged ≥45 years)

may include the following. First, we conducted the survey between spring and summer, in which Na and K intake may not reach the peak level of a year. It is reported that in certain local population 24-h UNa can be up to 319·2 mmol in winter[44], Second, this may be a reflection of low K intake in spring. In addition, local population are prone to low K intake, due to lifestyle factors such as low intake of fruits[45]. The mean 24-h UNa/K in the survey is 4·80, almost 5 fold higher than the recommended level[46]. A higher UNa/K serves as an indicator for higher Na and lower K intake[47]. Based on the current independent negative association of 24-h UNa/K with MMSE scores and MCI, reducing Na intake and increasing K intake by fresh fruits and vegetables or by salt substitute may help prevent cognition decline given its increasing burden[10,48,49], as one of the feasible and cost-effective ways.

As an outstanding strength of the current study, we estimated Na and K intake and excretion using 24-h urine sample. Serum Na serves as an indicator of the homoeostasis of one's internal environment, less associated with the dietary salt intake. However, a few limitations should also be considered, while explaining the data. First, as a cross-sectional study, it does not show a causal relationship between 24-h UNa/K and MCI, whereas the results are consistent with those from the cohort study[39], and we minimised the limitation using the propensity score matching method. Second, although we used a multistage proportional random sampling method, subjects finally analysed were partially distinct from those excluded. We should be cautious when applying the results to general population. Third, the sample size might be underpowered in terms of calculating the prevalence of MCI in general population. Forth, we failed to consider Na-altering drugs other than anti-hypertensive agents. Fifth, single assessment of cognitive function by MMSE may also be a limitation[50,51]. However, the MMSE is a worldwide used measurement for cognitive screening[24] with the same cut-offs demonstrating high validity[25] and even in younger population[52]. Furthermore, 24-h urine sample was collected only once which might result in a relative limitation because of daily and or seasonal variability in urinary Na excretion. However, given that the study is conducted in the long-term local residents of a single county, their lifestyle is not likely to fluctuate too much. In addition, it might be better to assess dietary Na intake with another method at the same time.

Conclusion

The survey demonstrated an independent association between higher 24-h UNa/K, a parameter of high Na and low K intake and prevalent MCI in general population. Reducing intake of salts and increasing fresh fruits and vegetables abundant for K may be one of the feasible and low-cost ways to prevent development of MCI.

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and agreed to the published version of the manuscript. *Ethics of human subject participation*: The current study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving research study participants were approved by The Independent Ethics Committee of People's Hospital of Xinjiang Uygur Autonomous Region. Signed informed consent was obtained from all of the eligible participants.

Supplementary material

To view supplementary material for this article, please visit https://doi.org/10.1017/S1368980021001452

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