Ⅲ．研究成果の刊行に関する一覧表

１）学会誌･雑誌等における論文一覧

著者名	論文題目	雑誌名	巻.頁-頁，発行年
Rieko Okada, Kazuyo Tsushita, Kenji Wakai, Kiminori Kato, Takashi Wada and Yukito Shinohara	Healthy lifestyle reduces incidence of trace/positive proteinuria and rapid kidney function decline after 2 years: from the Japan Ningen Dock study	Nephrol Dial Transplant	(2020) 1–10 doi: 10.1093/ndt/gfaa224
Matsushita M, Muramoto A, Nomura E, Eguchi Y, Kato A, Sano Y, Kabayama M, Arakawa M, Oguma Y, Yabe D, Matsunaga M, Yatsuya H, Arima H, Tsushita K.	Smart Life Stay (SLS) program: effects of a lifestyle intervention program in combination with health tourism and health guidance for type 2 diabetes.	Nutrition & Diabetes	https://doi.org/10.1038/s41387-020-00136-x
Kontsevaya A, Drapkina O; Gorniy B, Kalinina A, ;Komkov D, Balanova Y, Bunova A, Kushunina D, Antsiferova A, Myrzamatova A, Lavrenova E, Nomura E; Iwatake M; Waki T; Tanaka-Mizuno S, Miura K; Miyamoto Y, Tsushita K.	Protocol and Rationale for the Russian-Japanese “Tackle Obesity and Metabolic Syndrome Outcome by Diet, Activities and Checking Body Weight Intervention” (RJ-TOMODACHI) Randomized Controlled Trial.	Circulation Reports	doi: 10.1253/circrep.CR-20-0042
R.A. EGANYAN1, A.M. KALININA1, B.E. GORNY1, O.V. IZMAILOVA1, D.S. KOMKOV1, D.V. KUSHUNINA1,A.O. MYRZAMATOVA1, A.A. ANTSIFEROVA1, K. TSUSHITA, A.V. KONTSEVAYA1, O.M. DRAPKINA	The dynamics of nutrition structure of overweight and obese people during preventive counseling and remote monitoring as part of the international Russian-Japanese study ≪Tackle Obesity and Metabolic syndrome Outcome by Diet, Activities and Checking BW Intervention (RJ-TOMODACHI)	The Russian Journal of Preventive Medicine	2020, Vol. 23, no 3. 119-130
Hiroko Hattori, Aya Hirata, Sachimi Kubo, Yoko Nishida, Miki Nozawa , Kuniko Kawamura , Takumi Hirata , Yoshimi Kubota , Mizuki Sata, Kazuyo Kuwabara, Aya, igashiyama, Aya Kadota, Daisuke Sugiyama, Naomi Miyamatsu, Yoshihiro Miyamoto, Tomonori Okamura	Estimated 24 h Urinary Sodium-to-Potassium Ratio Is Related to Renal Function Decline: A 6-Year Cohort Study of Japanese Urban Residents	Int. J. Environ. Res. Public Health	2020, 17, 5811; doi:10.3390/ijerph17165811
佐野喜子	食物繊維の重要性.糖尿病の最新食事療法のなぜに答える基礎編	医歯薬出版	2020.10
佐野喜子	第 3 章 継続外来_基本編（2）_「患者サポートと生活指導_まるわかり糖尿病塾.	医学書院.	2020.11
Sodai K, Liu Y, Iizuka K, Kuwata H, Seino Y, Yabe D	A review of recent findings on meal sequence: an attractive dietary approach to prevention and management of type 2 diabetes.	Nutrients	(2020) 12(9):2502.
矢部大介、加藤丈博、堀川幸男.	糖尿病性腎症重症化予防プログラムと糖尿病連携手帳の活用.	DM Ensemble	9(2)：20-25，2020

矢部大介.	地域一丸で取り組む糖尿病重症化予防.	岐阜県医師会医学雑誌	33：41-46，2020
酒井麻有、窪田創大、加藤丈博、堀川幸男、矢部大介	糖尿病に関する教育と支援.	日本臨牀	78（7）：1066-1071，2020
樋口温子，樺山舞，神出計他.	特定保健指導積極的支援における中性脂肪該当者の特徴と中性脂肪に対する指導効果の検討.	日本循環器病予防学会誌.	2020;55(2):124-133.
真殿亜季，由田克士，栗林徹，奥田奈賀子，中村幸志，渡邉至，樺山舞，神出計，三浦克之，板井一好，岡山明.	遅い夕食習慣は中年男性のメタボリックシンドローム発症リスクを増加させる.	循環器病予防学会誌.	2020；55(1)：40-49.2020
Kawaguchi H, Moriyama M, Hashimoto H.	Does disease management for diabetic nephropathy reduce medical expenditure? Evidence from a three-period difference-in-differences analysis.	BMC Health Services Research,	20: 403, 2020. https://doi.org/10.1186/s12913-020-05297-0
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２）学会等における口頭･ポスター発表

発表者氏名	演題タイトル名	発表の種別	発表した場所（学会等名）	発表した時期
津下一代	地域連携で進める糖尿病性腎症重症化予防プログラム.	講演	第54回糖尿病学の進歩	2020.09 Web
津下一代.	ICT を用いた生活習慣病の克服～ビッグデータと個人の行動変容～	特別講演	日本糖尿病学会九州地方会	.2020.10.17 Web ライブ
津下一代	内科疾患の運動療法：代謝性疾患．糖尿病	教育講演 7	日本臨床スポーツ医学会	2020．11Web
Kazuyo Tsushita.	Remote monitoring and preventive counseling on risk factors in the era of the COVID-19 pandemic: Japanese experience.	シンポジウム	The International Internet Congress for Internists (Russia)	09 Feb. 2021
津下一代	特定保健指導実施状況・効果分析からみた課題と今後の方向性	シンポジウム	第 41 回日本肥満学会. シンポジウム４	2021.3.20 Web
佐野喜子	BMI30以上の糖尿病勤労男性における行動計画と減量成果の関連について	口演	第63回日本糖尿病学会年次学術集会	
佐野喜子	肥満症指導に必要な知識とは.減量実現に向けた効果的な保健指導を考える	シンポジウム	第 41 回日本肥満学会. シンポジウム 7	2021.3.20 Web

井口真由香，樺山舞，権藤恭之，他.	地域在住高齢者における認知機能別に見た血糖コントロール状況に関する検討-SONIC研究-	一般演題	第62回日本老年医学会学術集会.	2020年8月3-6日.WEB
前山友理恵，樺山舞，石﨑達郎，樂木宏実，神出計他	地域在住高齢者における糖尿病の血糖コントロール状況と精神的健康状態に関する検討-SONIC研究-.	一般演題	第62回日本老年医学会学術集会.	2020年8月3-6日.WEB
平田匠.	糖尿病性腎症重症化予防の基礎と最近の話題.	講演	宮城県国民健康保険団体連合会　令和2年度糖尿病性腎症重症化予防研修会	2020．10
Yoshinari Yasuda	Overview of national policy to prevent aggravation of diabetic nephropathy in Japan: Importance of safety prescription of metformin for patients with renal impairment	シンポジウム	The 10th CKD Frontier Meeting	2021．02.28
清水美保、北島信治、遠山直志、坂井宣彦、和田隆志．他	糖尿病性腎症における貧血ならびに間質線維化・尿細管萎縮と腎・生命予後との関連	一般演題	第63回日本腎臓学会学術総会	2020.8.19-8.21 横浜
大島恵・遠山直志・坂井宣彦・和田隆志:	eGFRと尿アルブミンを用いた末期腎不全の代替エンドポイント,	一般演題	第50回日本腎臓学会西部学術大会	2020.10.16-10.17 WEB
和田隆志	:糖尿病例における腎病変―病態と治療	講演	日本糖尿病学会 中国四国地方会第58回総会	2020.10.23-11.8 WEB
清水美保、北島信治、遠山直志、原章規、岩田恭宜、坂井宣彦、和田隆志	糖尿病性腎症による腎複合イベント発症例の生命予後に、貧血と腎間質線維化･尿細管萎縮が及ぼす影響	一般演題	第65回日本透析医学会学術集会・総会	2020.11.2-11.24 WEB

３）その他の講演等

発表者氏名	演題タイトル名	発表の種別	発表した場所（学会等名）	発表した時期
津下一代	保険者として取り組む糖尿病性腎症重症化予防事業～手ごたえを感じる保健事業へ		東京都国保連合会．令和2年度生活習慣病予防対策に関する講演会	2021.01.21. 東京　ハイブリッド型
佐野喜子	生活習慣病重症化予防における保健指導､糖尿病性腎症重症化予防、低栄養、重症化予防	講演	令和2年度神奈川県国民健康保険団体連合会保健事業支援・評価委員会部会｢国保･後期高齢者ヘルスサポート事業申請保険者等への支援｣	2020.8.24 横浜市
矢部大介.	糖尿病をとりまく現状と地域一丸の糖尿病対策の必要性～糖尿病医科歯科連携を中心に～.	特別講演	第63秋季回日本歯周病学会学術大会	2020.10Web
Yoshinari Yasuda	Overview of national policy to prevent aggravation of diabetic nephropathy in Japan: Importance of safety prescription of metformin for patients with renal impairment	シンポジウム	The 10th CKD Frontier Meeting	2021.02.28 Web

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Healthy lifestyle reduces incidence of trace/positive proteinuria and rapid kidney function decline after 2 years: from the Japan Ningen Dock study

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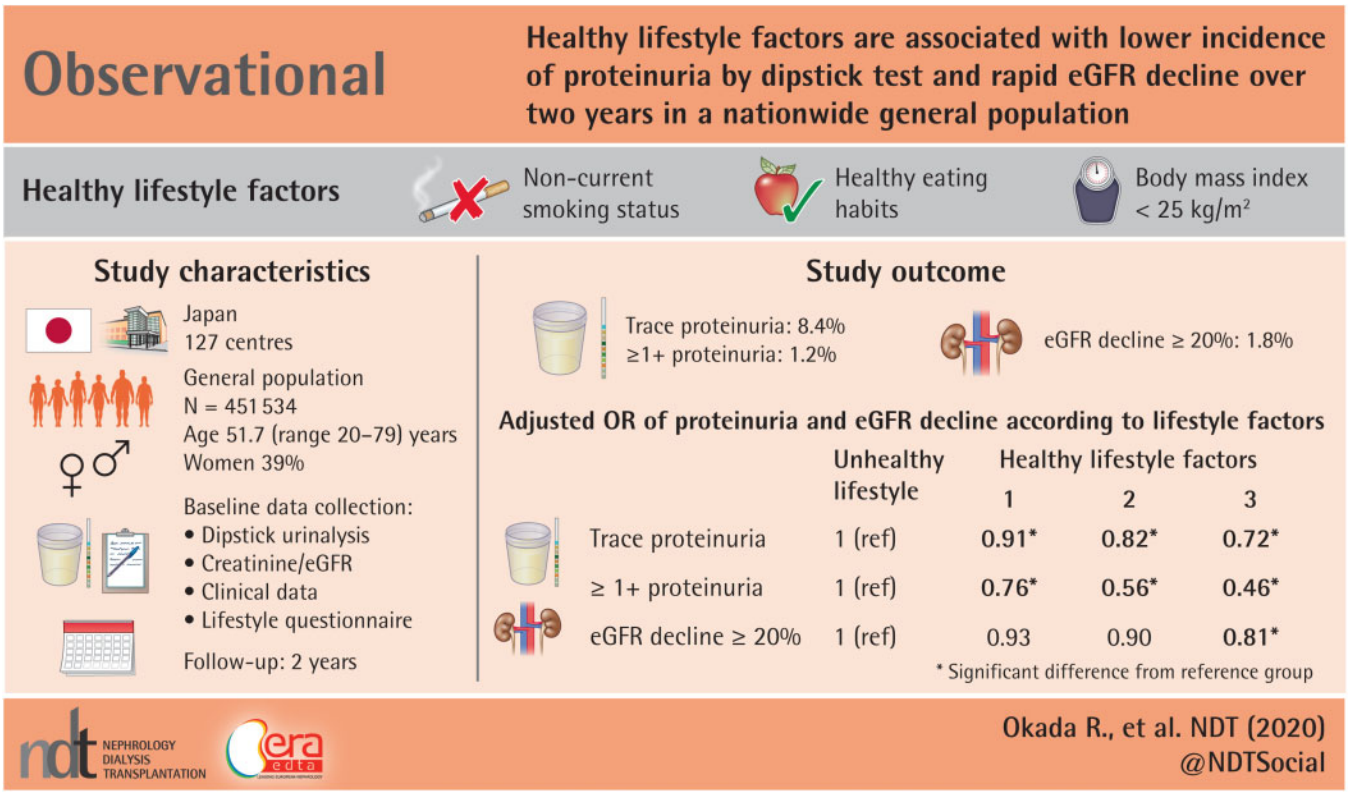
GRAPHICAL ABSTRACT



ABSTRACT

Background. Lifestyle modification is recommended for subjects with trace proteinuria during health checkups. However, whether overall healthy lifestyle reduces the incidence of trace/positive proteinuria or rapid decline in estimated glomerular filtration rate (eGFR) is not clarified.

Methods. A total of 451 534 people (277 494 men and 174 040 women) ages 20–79 years with negative proteinuria were

KEY LEARNING POINTS

What is already known about this subject?

- Lifestyle modification is recommended for subjects with trace proteinuria during health checkups.
- Trace proteinuria and rapid eGFR decline are the strong prognostic values of cardiovascular disease (CVD), end-stage renal disease (ESRD) and mortality.
- Whether overall healthy lifestyle reduces the incidence of trace proteinuria or rapid eGFR decline is not clarified.

What this study adds?

- Subjects with a healthy lifestyle showed a 28% reduced risk of developing trace proteinuria and a 19% reduced risk of rapid eGFR decline (eGFR decline ≥20%) over 2 years.
- The incidence of trace proteinuria and rapid eGFR decline decreased with an increasing number of healthy lifestyle factors.
- This association was similarly observed even among subjects without hypertension (HT) or diabetes mellitus (DM).

What impact this may have on practice or policy?

- Healthy lifestyle reduces the incidence of trace proteinuria and rapid eGFR decline over 2 years.
- Lifestyle modification should be recommended for subjects with trace proteinuria during health checkups, even for subjects without HT or DM.
- Healthy lifestyles that reduce the risk of trace proteinuria and rapid eGFR decline may prevent early stages of kidney disease, which may then delay or prevents subsequent CVD and ESRD.

included. The number of three healthy lifestyle factors (LFs) was assessed: noncurrent smoking, healthy eating habits (late dinner, snacking and skipping breakfast <3 times/week) and body mass index <25. The incidence of trace (±) and positive (≥1+) proteinuria by the dipstick method and eGFR decline ≥20% over 2 years were compared with the number of healthy LFs.

Results. The incidence of trace/positive proteinuria and rapid eGFR decline decreased with an increasing number of healthy LFs as follows: odds ratios (ORs) for trace proteinuria, 0.91 [95% confidence interval (CI) 0.86–0.96], 0.82 (0.78–0.87) and 0.72 (0.68–0.77); ORs for positive proteinuria, 0.76 (95% CI 0.67–0.86), 0.56 (0.50–0.63) and 0.46 (0.40–0.53); and ORs for an eGFR decline ≥20%, 0.93 (95% CI 0.82–1.05), 0.90 (0.79–1.02) and 0.81 (0.70–0.93) for those with one, two and three healthy LFs compared with those with none of the three healthy LFs, respectively. Overall, subjects with a healthy lifestyle showed 28, 54 and 19% reduced risk of developing trace proteinuria, positive proteinuria and eGFR decline ≥20%, respectively, compared with those with an unhealthy lifestyle after 2 years. This association was similarly observed even among subjects without hypertension (HT) or diabetes mellitus (DM).

Conclusions. Subjects with an overall healthy lifestyle showed a lower incidence of trace/positive proteinuria by dipstick test and rapid eGFR decline over 2 years in a nationwide general population. Thus lifestyle modification should be recommended for subjects with trace proteinuria during health checkups, even for subjects without HT or DM.

Keywords: chronic renal insufficiency, eating behavior, lifestyle, proteinuria, smoking

INTRODUCTION

There is accumulating evidence for the significance of the prognostic value of trace proteinuria. In large population studies, the presence of trace proteinuria on dipstick tests is a powerful predictor of future cardiovascular diseases (CVDs) [1–3], end-stage renal disease (ESRD) [4], hypertension (HT) and diabetes mellitus (DM) [5]. As about two-thirds of the population with trace proteinuria have microalbuminuria, trace proteinuria can be used as an indicator of microalbuminuria [6–8], or at least high-normal albuminuria (corresponds to an albumin:creatinine ratio of 10–29 mg/g) [1, 2, 4].

Moreover, declines in estimated glomerular filtration rate (eGFR) of ≥20% are associated with the risk of ESRD and mortality [9–11]. A 20% decline in eGFR over 2 years could be considered as a candidate surrogate endpoint of ESRD [10] and is defined as rapid eGFR decline [12, 13]. Identifying modifiable factors that reduce the risk of trace/positive proteinuria or rapid eGFR decline may facilitate the development of primary prevention programs for early stages of kidney diseases.

It is well known that a healthy lifestyle decreases the risk of CVD and mortality. A recent study investigated whether an overall healthy lifestyle, assessed by the number of healthy lifestyle factors (LFs), could prolong life expectancy [14]. However, the benefits of overall lifestyle behaviors on kidney disease risk are poorly quantified. Only a few studies have examined the influence of the number of healthy LFs on the development of proteinuria [15–18], eGFR decline ≥50% [19] or chronic kidney disease (CKD) [20, 21]. Wakasugi *et al.* [15] demonstrated that the number of healthy LFs, which include noncurrent smoking, less bedtime snacking and skipping breakfast, regular exercise, alcohol consumption <20 g/day and body mass index (BMI) <25, decreases the risk of positive proteinuria (≥1+) after 1 year [15].

Consequently the Japanese Society of Nephrology published a proposal in 2017 that lifestyle modification should be recommended for subjects with trace proteinuria during health checkups [22]. However, whether trace proteinuria, which represents an early stage of kidney damage, can be reduced by increasing the number of healthy LFs is not yet clarified. Moreover, although lifestyle modification is highly recommended for

subjects with HT and DM [23, 24], the effect of lifestyle modification on the prevention of proteinuria or rapid eGFR decline among those without HT or DM is unclear.

The purpose of this study was to determine whether increasing the number of healthy LFs decreases the risk of trace/positive proteinuria and rapid eGFR decline and whether it is applicable even to subjects without HT or DM, in a nationwide general population.

MATERIALS AND METHODS

Study population

The study subjects were participants who underwent health checkups every year from 2010 to 2012 in the 127 facilities throughout Japan that belong to the Japan Society of Ningen Dock. Participants underwent either the comprehensive health checkup 'Ningen Dock' or the basic health checkup provided by employers every year. The details of the two types of health checkups are described elsewhere [25]. In brief, a basic health checkup is provided annually by employers and is required by law, while a comprehensive health checkup is voluntary and paid for by the participant but covered by his/her company (in most cases, at least partially).

Records for 740 000 individuals who underwent health checkups every year in 2010, 2011 and 2012 were obtained. Subjects with complete data for all the LFs (smoking, eating habits, regular exercise and BMI), proteinuria and eGFR at baseline (2010) and after 2 years (2012) were enrolled in this study. First, individuals without information on proteinuria ($n = 91\,410$) or data from facilities where the information on trace proteinuria was not assessed ($n = 40\,316$) were excluded. Then, subjects with incomplete data for any of the LFs ($n = 76\,409$), subjects with incomplete data for eGFR ($n = 8257$) and subjects ≥80 years of age ($n = 2058$) were excluded. Finally, subjects with trace/positive proteinuria at baseline were excluded ($n = 70\,016$), resulting in 451 534 subjects (277 494 men and 174 040 women, ages 20–79 years) in these analyses.

This study was carried out by using the Mega Database belonging to the Japan Society of Ningen Dock with support of the Research Committee for the Mega Database of Japan Society of Ningen Dock [25–27]. Written informed consent was not required, as all records were anonymized by decoding identifying information. The quality control in laboratory testing in all the institutions has been checked by the Japan Society of Ningen Dock. This study was approved by the Ethical Committee of the Japan Society of Ningen Dock (approval number JSND-EC: 2015-0005) and the Ethics Committee of the Nagoya University Graduate School of Medicine (approval number 2015-0313-2).

Measurements

All subjects completed a self-administered questionnaire to document their LFs, such as smoking, eating habits, drinking and regular exercise. Their current medication for HT, DM and dyslipidemia and the history of cardiovascular and cerebrovascular diseases were reported. Each record included systolic and diastolic blood pressure (BP) and anthropometric parameters such as weight and height. BMI was calculated. Circulating factors including hemoglobin A1c (HbA1c), triglycerides (TGs), low-density lipoprotein cholesterol and serum creatinine were measured with autoanalyzers. Serum creatinine was assessed by enzymatic methods. The GFR was estimated using the Japanese eGFR equation [28]. Individuals who sought health checkups were requested to fast overnight for ≥8 h.

Definition of healthy LFs

Five LFs were assessed according to previous studies [15, 17, 20]: noncurrent smoking (never smoker and ex-smoker); healthy eating habits for all the following: late dinner (eating dinner <2 h before bedtime) less than three times a week, snacking (snacking between meals or after dinner) less than three times a week and skipping breakfast less than three times a week; adequate weight (BMI <25); regular exercise (doing exercise to sweat lightly ≥30 min/time and two or more times per week) and alcohol intake <20 g/day. Among these, three LFs (noncurrent smoking, healthy eating habits and adequate weight), which were significantly associated with the risk of positive proteinuria and eGFR decline, were included as healthy LFs. The number of healthy LFs at baseline was calculated (range 0–3). Healthy lifestyle was defined as having all three healthy LFs, whereas unhealthy lifestyle was defined as having none of the three healthy LFs.

Assessment of outcomes

The dipstick method was used to determine proteinuria as trace (±) or positive (≥1+). The decrease in eGFR was calculated as (eGFR at baseline – eGFR at Year 2)/eGFR at baseline. An eGFR decline ≥20% was defined as rapid, in accordance with former studies showing an eGFR decline ≥20% as a risk factor for ESRD and mortality [9–13]. After the participants were stratified into four groups by the number of healthy LFs at baseline (score 0–3), the incidence of trace/positive proteinuria and eGFR decline ≥20% was assessed in 2012 after a 2-year follow-up and was compared between the groups. Sensitivity analysis was conducted for participants whose urine test was positive in both 2011 and 2012.

Statistical analyses

The baseline characteristics of participants were compared according to the number of healthy LFs. Odds ratios (ORs) and 95% confidence intervals (CI) were estimated for the development of trace/positive proteinuria and eGFR decline ≥20% by each LF and by the number of healthy LFs using unconditional logistic regression analysis. ORs were adjusted for age, sex, eGFR, systolic BP, use of antihypertensive drugs, HbA1c, use of glucose-lowering drugs, TGs, use of lipid-lowering drugs, history of cardiovascular/cerebrovascular diseases and BMI (adjusted ORs). BMI was not adjusted in the analysis of BMI <25 and the number of healthy LFs. Age, eGFR, systolic BP, HbA1c, TGs and BMI were treated as continuous variables. Socioeconomic factors such as education level, income or social class were not adjusted for as no data were available on socioeconomic factors.

Table 1. Baseline characteristics of subjects according to the number of healthy LFs among subjects without trace/positive proteinuria (n = 451 534)

Characteristics	Number of healthy LFs			
	0	1	2	3
	'Unhealthy lifestyle'			'Healthy lifestyle'
Subjects, *n*	16 138	89 570	181 093	164 733
Age (years)	48.0 ± 7.8	49.4 ± 8.6	51.0 ± 9.4	53.9 ± 10.2
Men	47.9 ± 7.8	49.3 ± 8.6	51.3 ± 9.6	55.2 ± 10.3
Women (years)	48.4 ± 7.6	49.8 ± 8.4	50.3 ± 9.2	52.8 ± 9.9
Women, *n* (%)	1351 (8.3)	17 944 (20.0)	67 876 (37.5)	86 869 (52.7)
Systolic BP (mmHg)	123 ± 15	121 ± 16	119 ± 17	118 ± 17
Diastolic BP (mmHg)	79 ± 12	77 ± 12	75 ± 12	73 ± 12
Antihypertensive medication, *n* (%)	2837 (17.7)	15 709 (17.6)	27 774 (15.4)	23 017 (14.1)
HbA1c (%)	5.78 ± 0.76	5.65 ± 0.65	5.57 ± 0.53	5.56 ± 0.45
Glucose-lowering medication, *n* (%)	1026 (6.4)	4251 (4.8)	6374 (3.6)	4551 (2.8)
TGs (mg/dL), median (IQR)	140 (101–201)	111 (78–160)	88 (63–128)	78 (58–110)
LDL cholesterol (mg/dL)	132 ± 31	126 ± 32	123 ± 30	121 ± 29
HDL cholesterol (mg/dL)	50 ± 11	57 ± 14	63 ± 17	68 ± 17
Lipid-lowering medication, *n* (%)	1897 (11.8)	10 311 (11.6)	19 371 (10.8)	19 325 (11.8)
History of cardio-/cerebrovascular diseases, *n* (%)	505 (3.1)	3062 (3.4)	6397 (3.5)	6301 (3.8)
eGFR (mL/min/1.73 m^2)	79.7 ± 13.9	78.5 ± 13.8	77.0 ± 13.7	75.7 ± 13.7
Regular exercise, *n* (%)	2849 (17.7)	17 933 (20.0)	45 166 (24.9)	51 249 (31.1)
Alcohol intake <20 g/day, *n* (%)	6919 (42.9)	42 921 (47.9)	104 887 (57.9)	114 876 (69.7)
BMI	27.7 ± 2.6	25.1 ± 3.8	23.0 ± 3.3	21.4 ± 2.1
Healthy LFs, *n* (%)				
Noncurrent smoking	0 (0)	41 189 (46)	154 835 (86)	164 733 (100)
Healthy eating habits	0 (0)	9723 (11)	69 539 (38)	164 733 (100)
BMI <25	0 (0)	38 658 (43)	137 812 (76)	164 733 (100)

Data are presented as mean ± SD unless stated otherwise.
Healthy eating habits: less than three times a week for late dinner, snacking and skipping breakfast; regular exercise: doing exercise to sweat lightly ≥30 min/time and two or more time per week. Subjects with trace or positive proteinuria at baseline were excluded.
IQR: interquartile range; LDL: low-density lipoprotein; HDL: high-density lipoprotein.

Stratified analyses by sex, age group (20–39, 40–59 and 60–79 years), eGFR category (eGFR ≥60 and <60 mL/min/1.73 m^2) and the status of HT and DM were conducted. Subjects were categorized as having no HT (BP <140/90 mmHg) or HT (BP ≥140/90 mmHg or the use of antihypertensive drugs) [29]. Subjects were also categorized as having no DM (HbA1c <6.5%) or DM (HbA1c ≥6.5% or the use of glucose-lowering drugs) [30]. All analyses were carried out using Stata software version 9 (StataCorp, College Station, TX, USA).

RESULTS

The baseline characteristics of the subjects were compared according to the number of healthy LFs in Table 1. The mean age was 51.7 years and ∼40% of the subjects were women. Participants with a healthy lifestyle were more likely to be older women and more likely to have lower BP and glucose, a better lipid profile, less alcohol intake and lower eGFR compared with those with an unhealthy lifestyle. Age was not different between men and women in the same group.

During the 2-year follow-up, 38 079 cases (8.4%) of trace proteinuria, 5257 cases (1.2%) of positive proteinuria and 8078 cases (1.8%) of eGFR decline ≥20% occurred. First, the incidence of trace/positive proteinuria and rapid eGFR decline was compared by the presence of each LF (Table 2). Subjects with healthy LFs (noncurrent smoking, healthy eating habits and adequate weight) showed a lower incidence of trace/positive proteinuria and rapid eGFR decline. For trace/positive proteinuria, noncurrent smoking showed the strongest effect, whereas for rapid eGFR decline, adequate weight showed the strongest effect (ORs for trace proteinuria: 0.82, 0.88 and 0.94; ORs for positive proteinuria: 0.67, 0.77 and 0.78; ORs for rapid eGFR decline: 0.95, 0.93 and 0.90 for noncurrent smoking, healthy eating habits and adequate weight, respectively; Table 2). Regular exercise and alcohol intake were not associated with positive proteinuria and rapid eGFR decline.

The incidence of trace/positive proteinuria and rapid eGFR decline was lower in subjects with a greater number of healthy LFs (ORs for trace proteinuria: 0.91, 0.82 and 0.72; ORs for positive proteinuria: 0.76, 0.56 and 0.46; ORs for eGFR decline ≥20%: 0.93, 0.90 and 0.81 for subjects with one, two and three healthy LFs, respectively) compared with those with none of the three healthy LFs ('unhealthy lifestyle') after full adjustment including metabolic factors such as BP, HbA1c and TGs (Table 3). Sensitivity analysis using participants with twice-positive urine tests showed similar results [ORs for trace proteinuria (twice): 0.90 (95% CI 0.82–0.98), 0.78 (0.71–0.85) and 0.67 (0.61–0.74); ORs for positive proteinuria (twice): 0.91 (95% CI 0.68–1.22), 0.64 (0.48–0.87) and 0.42 (0.29–0.60) for subjects with one, two and three healthy LFs, respectively], compared with those with none of the three healthy LFs.

When stratified analyses were conducted, the risk reduction was similarly observed in both men and women, in any age group and in any eGFR category (ORs for trace proteinuria among subjects with a healthy lifestyle: 0.69 in men, 0.72 in

Table 2. Incidence of trace/positive proteinuria and eGFR decline ≥20% over 2 years according to the components of healthy LFs (*N* = 451 534)

Components		Subjects, *n*	Trace proteinuria (±)				Positive proteinuria (≥1+)				eGFR decline ≥20%			
			Incidence	Incidence rate[a]	Adjusted OR[b]	95% CI	Incidence	Incidence rate[a]	Adjusted OR[b]	95% CI	Incidence	Incidence rate[a]	Adjusted OR[b]	95% CI
All subjects														
Noncurrent smoking	No	90 777	9812	5.40	1	ref	1 552	0.85	1	ref	1 854	1.02	1	ref
	Yes	360 757	28 267	3.92	**0.82**	0.80–0.84	3705	0.51	**0.67**	0.63–0.72	6224	0.86	0.95	0.89–1.01
Healthy eating habits	No	207 539	19 981	4.81	1	ref	2934	0.71	1	ref	3875	0.93	1	ref
	Yes	243 995	18 098	3.71	**0.88**	0.86–0.90	2323	0.48	**0.77**	0.73–0.82	4203	0.86	**0.93**	0.88–0.97
BMI <25	No	110 331	10 483	4.75	1	ref	1818	0.82	1	ref	2221	1.01	1	ref
	Yes	341 203	27 596	4.04	**0.94**	0.91–0.96	3439	0.50	**0.78**	0.73–0.83	5857	0.86	**0.90**	0.85–0.95
Regular exercise	No	334 337	28 827	4.31	1	ref	4015	0.60	1	ref	6167	0.92	1	ref
	Yes	117 197	9252	3.95	0.98	0.95–1.01	1242	0.53	0.95	0.88–1.01	1911	0.82	1.02	0.96–1.08
Alcohol intake	No	181 931	16 408	4.51	1	ref	2328	0.64	1	ref	3247	0.89	1	ref
<20 g/day	Yes	269 603	21 671	4.02	1.02	1.00–1.05	2929	0.54	1.01	0.95–1.08	4831	0.90	1.05	0.99–1.10
Men														
Noncurrent smoking	No	77 632	8723	5.62	1	ref	1379	0.89	1	ref	1379	0.89	1	ref
	Yes	204 364	18 479	4.52	**0.82**	0.80–0.85	2529	0.62	**0.69**	0.64–0.74	2529	0.62	**0.90**	0.84–0.97
Healthy eating habits	No	141 223	14 878	5.27	1	ref	2237	0.79	1	ref	2415	0.86	1	ref
	Yes	136 271	11 783	4.32	**0.89**	0.87–0.92	1610	0.59	**0.78**	0.73–0.84	2016	0.74	**0.89**	0.84–0.95
BMI <25	No	83 061	8504	5.12	1	ref	1506	0.91	1	ref	1486	0.89	1	ref
	Yes	194 433	18 157	4.67	**0.95**	0.92–0.97	2341	0.60	**0.80**	0.74–0.86	2945	0.76	0.95	0.88–1.02
Regular exercise	No	199 315	19 754	4.96	1	ref	2865	0.72	1	ref	3245	0.81	1	ref
	Yes	78 179	6907	4.42	**0.95**	0.92–0.98	982	0.63	0.93	0.86–1.00	1186	0.76	1.01	0.94–1.08
Alcohol intake	No	148 703	14 081	4.73	1	ref	2034	0.68	1	ref	2549	0.86	1	ref
<20 g/day	Yes	128 791	12 580	4.88	1.04	1.00–1.06	1813	0.70	1.04	0.97–1.11	1882	0.73	1.04	0.98–1.11
Women														
Noncurrent smoking	No	14 717	1273	4.32	1	ref	200	0.68	1	ref	200	0.68	1	ref
	Yes	163 078	10 480	3.21	**0.79**	0.74–0.84	1259	0.39	**0.57**	0.48–0.67	1259	0.39	0.97	0.86–1.10
Healthy eating habits	No	66 316	5103	3.85	1	ref	697	0.53	1	ref	1460	1.10	1	ref
	Yes	107 724	6315	2.93	**0.84**	0.80–0.87	713	0.33	**0.73**	0.65–0.82	2187	1.02	0.94	0.87–1.02
BMI <25	No	27 270	1979	3.63	1	ref	312	0.57	1	ref	735	1.35	1	ref
	Yes	146 770	9439	3.22	**0.89**	0.84–0.94	1098	0.37	**0.68**	0.59–0.79	2912	0.99	**0.81**	0.74–0.90
Regular exercise	No	135 022	9073	3.36	1	ref	1150	0.43	1	ref	2922	1.08	1	ref
	Yes	39 018	2345	3.01	**1.08**	1.02–1.13	260	0.33	1.01	0.88–1.17	725	0.93	1.05	0.95–1.15
Alcohol intake	No	33 228	2327	3.50	1	ref	294	0.44	1	ref	698	1.05	1	ref
<20 g/day	Yes	140 812	9091	3.23	1.01	0.96–1.07	1116	0.40	1.00	0.87–1.15	2949	1.05	1.08	0.98–1.18

[a]Cases per 100 person-years.

[b]Adjusted for age, sex, eGFR, systolic BP, antihypertensive drug use, HbA1c, glucose-lowering drug use, TGs, lipid-lowering drug use, history of cardio-/cerebrovascular diseases and BMI. BMI was not adjusted in the analysis of BMI <25.

Healthy eating habits: less than three times a week for late dinner, snacking and skipping breakfast; regular exercise: doing exercise to sweat lightly ≥30 min/time and two or more times per week. Bold type represents statistically significant ORs.

Table 3. Incidence of trace/positive proteinuria and eGFR decline ≥20% over 2 years according to the number of healthy LFs by sex, age and eGFR groups (*N* = 451 534)

Healthy LFs, *n*	Subjects, *n*	Trace proteinuria (±)				Positive Proteinuria (≥1+)				eGFR decline ≥20%			
		Incidence	Incidence rate[a]	Adjusted OR[b]	95% CI	Incidence	Incidence rate[a]	Adjusted OR[b]	95% CI	Incidence	Incidence rate[a]	Adjusted OR[b]	95% CI
All subjects													
0 ('Unhealthy lifestyle')	16 138	1941	6.01	1	ref	390	1.21	1	(ref)	362	1.12	1	ref
1	89 570	9372	5.23	**0.91**	0.86–0.96	1529	0.85	**0.76**	0.67–0.86	1782	0.99	0.93	0.82–1.05
2	181 093	15 709	4.34	**0.82**	0.78–0.87	2076	0.57	**0.56**	0.50–0.63	3300	0.91	0.90	0.79–1.02
3 ('Healthy lifestyle')	164 733	11 057	3.36	**0.72**	0.68–0.77	1262	0.38	**0.46**	0.40–0.53	2434	0.74	**0.81**	0.70–0.93
Men													
0 (Unhealthy lifestyle')	14 787	1821	6.16	1	ref	362	1.22	1	ref	317	1.07	1	ref
1	71 626	7867	5.49	**0.90**	0.85–0.95	1275	0.89	**0.77**	0.68–0.87	1332	0.93	0.95	0.83–1.08
2	113 217	10 773	4.76	**0.81**	0.77–0.86	1461	0.65	**0.56**	0.50–0.64	1802	0.80	0.97	0.81–1.06
3 ('Healthy lifestyle')	77 864	6200	3.98	**0.69**	0.65–0.74	749	0.48	**0.46**	0.39–0.53	980	0.63	**0.77**	0.66–0.90
Women													
0 ('Unhealthy lifestyle')	1351	120	4.44	1	ref	28	1.04	1	ref	45	1.67	1	ref
1	17 944	1505	4.19	1.00	0.81–1.23	254	0.71	0.69	0.46–1.04	450	1.25	0.81	0.58–1.14
2	67 876	4936	3.64	0.91	0.74–1.12	615	0.45	**0.46**	0.30–0.68	1498	1.10	0.76	0.54–1.05
3 ('Healthy lifestyle')	86 869	4857	2.80	**0.72**	0.59–0.89	513	0.30	**0.32**	0.21–0.48	1654	0.95	0.74	0.52–1.04
Age 20–39 years													
0 ('Unhealthy lifestyle')	2117	306	7.23	1	ref	45	1.06	1	ref	49	1.16	1	ref
1	10 453	1424	6.81	0.91	0.78–1.05	228	1.09	1.08	0.76–1.53	175	0.84	0.71	0.50–1.02
2	18 920	2314	6.12	**0.82**	0.71–0.95	291	0.77	0.78	0.54–1.13	345	0.91	**0.66**	0.46–0.94
3 ('Healthy lifestyle')	12 271	1247	5.08	**0.73**	0.62–0.87	155	0.63	0.70	0.45–1.07	260	1.06	**0.60**	0.39–0.92
Age 40–59 years													
0 ('Unhealthy lifestyle')	12 785	1482	5.80	1	ref	312	1.22	1	ref	265	1.04	1	ref
1	68 117	7005	5.14	**0.93**	0.87–0.99	1126	0.83	**0.73**	0.63–0.83	1353	0.99	1.03	0.89–1.19
2	128 329	11 062	4.31	**0.84**	0.79–0.89	1440	0.56	**0.54**	0.47–0.62	2251	0.88	1.01	0.87–1.17
3 ('Healthy lifestyle')	101 805	7029	3.45	**0.74**	0.69–0.79	767	0.38	**0.45**	0.38–0.53	1593	0.78	0.92	0.77–1.08
Age 60–79 years													
0 ('Unhealthy lifestyle')	1236	153	6.19	1	ref	33	1.33	1	ref	48	1.94	1	ref
1	11 000	943	4.29	**0.70**	0.57–0.85	175	0.80	**0.64**	0.43–0.96	254	1.15	**0.58**	0.42–0.82
2	33 844	2333	3.45	**0.60**	0.50–0.73	345	0.51	**0.40**	0.27–0.59	704	1.04	**0.55**	0.40–0.76
3 ('Healthy lifestyle')	50 657	2781	2.74	**0.48**	0.40–0.59	340	0.34	**0.30**	0.20–0.46	781	0.77	**0.42**	0.30–0.59
eGFR ≥60 mL/min/1.73 m^2													
0 ('Unhealthy lifestyle')	15 267	1843	6.04	1	ref	367	1.20	1	ref	348	1.14	1	ref
1	83 205	8789	5.28	**0.91**	0.86–0.96	1391	0.84	**0.75**	0.67–0.86	1708	1.03	0.94	0.82–1.07
2	165 655	14 564	4.40	**0.83**	0.78–0.88	1847	0.56	**0.55**	0.49–0.63	3169	0.96	0.91	0.80–1.04
3 ('Healthy lifestyle')	147 407	9939	3.37	**0.72**	0.67–0.76	1091	0.37	**0.46**	0.40–0.54	2514	0.85	**0.82**	0.71–0.95
eGFR <60 mL/min/1.73 m^2													
0 ('Unhealthy lifestyle')	871	98	5.63	1	ref	23	1.32	1	ref	14	0.80	1	ref
1	6365	583	4.58	0.92	0.72–1.18	138	1.08	0.78	0.49–1.23	74	0.58	0.61	0.33–1.13
2	15 438	1145	3.71	**0.75**	0.58–0.95	229	0.74	**0.61**	0.38–0.97	131	0.42	**0.43**	0.24–0.81
3 ('Healthy lifestyle')	17 326	1118	3.23	**0.73**	0.57–0.95	171	0.49	**0.40**	0.24–0.67	120	0.35	**0.32**	0.17–0.63

[a]Cases per 100 person-years.

[b]Adjusted for age, sex, baseline eGFR, systolic BP, antihypertensive drug use, HbA1c, glucose-lowering drug use, TGs, lipid-lowering drug use and history of cardio-/cerebrovascular diseases.

The three components of healthy LFs are noncurrent smoking, healthy eating habits (less than three times a week for late dinner, snacking and skipping breakfast) and BMI <25. Bold type represents statistically significant ORs.

women; 0.73 in subjects ages 20–39 years, 0.74 in subjects ages 40–59 years and 0.48 in subjects ages 60–79 years; 0.72 in subjects with eGFR ≥60 mL/min/1.73 m^2 and 0.73 in subjects with eGFR <60 mL/min/1.73 m^2] compared with those with an 'unhealthy lifestyle' (Table 3). When further stratified by age groups separated by sex, the risk reduction was observed in any age groups in both men and women, although some of the risk reductions were weak and were not statistically significant (Supplementary data, Table S1).

Finally, stratified analysis was conducted by the status of HT and DM (Figure 1). The risk reduction by healthy LFs was observed in any status of HT and DM. Although subjects with HT and DM showed a stronger risk reduction, even subjects without HT or DM showed a significant risk reduction by healthy LFs, except eGFR decline in subjects without HT (ORs for trace proteinuria for those with a 'healthy lifestyle': 0.62 and 0.74 among those with HT and those without HT, respectively; and 0.58 and 0.73 among those with DM and those without DM, respectively) compared with those with an 'unhealthy lifestyle'.

DISCUSSION

To the best of our knowledge, this is the first study to show that subjects with a greater number of healthy LFs showed a lower incidence of trace/positive proteinuria by dipstick test and rapid eGFR decline (eGFR decline ≥20%) in a nationwide general population. Subjects with a healthy lifestyle, defined by those with noncurrent smoking, healthy eating habits and adequate weight, showed 28, 54 and 19% lower incidence of trace proteinuria, positive proteinuria and eGFR decline ≥20%, respectively, after 2 years of follow-up compared with those with an unhealthy lifestyle, independent from baseline eGFR. This association was similarly observed even among subjects without HT or DM.

An overall healthy lifestyle, quantified as the number of healthy LFs, is reported to decrease the incidence of proteinuria [15], microalbuminuria [18] and CKD progression [19]. A few studies reported that the number of healthy LFs (i.e. noncurrent smoking, healthy eating habits, adequate weight, regular exercise and less alcohol) was associated with the incidence of proteinuria ≥1+ by dipstick measurement after a 1-year period [15] and with the incidence of microalbuminuria after a 15-year period [18]. Another study reported that the number of healthy LFs (i.e. noncurrent smoking, healthy diet, adequate weight and regular exercise) decreased the incidence of CKD progression, defined as eGFR decline ≥50% or ESRD, after a4-year period [19]. Our study showed for the first time that an overall healthy lifestyle decreased the risk of developing not only positive proteinuria or eGFR decline ≥50%, but also trace proteinuria and eGFR decline ≥20%, which represents an earlier stage of kidney damage.

Current smoking showed the stronger effect on trace/positive proteinuria, whereas overweight showed the stronger effect on eGFR decline in our study. One large community-based study in Japan reported that smoking showed a greater increased risk of proteinuria (46–74%) than excess BMI (2% per

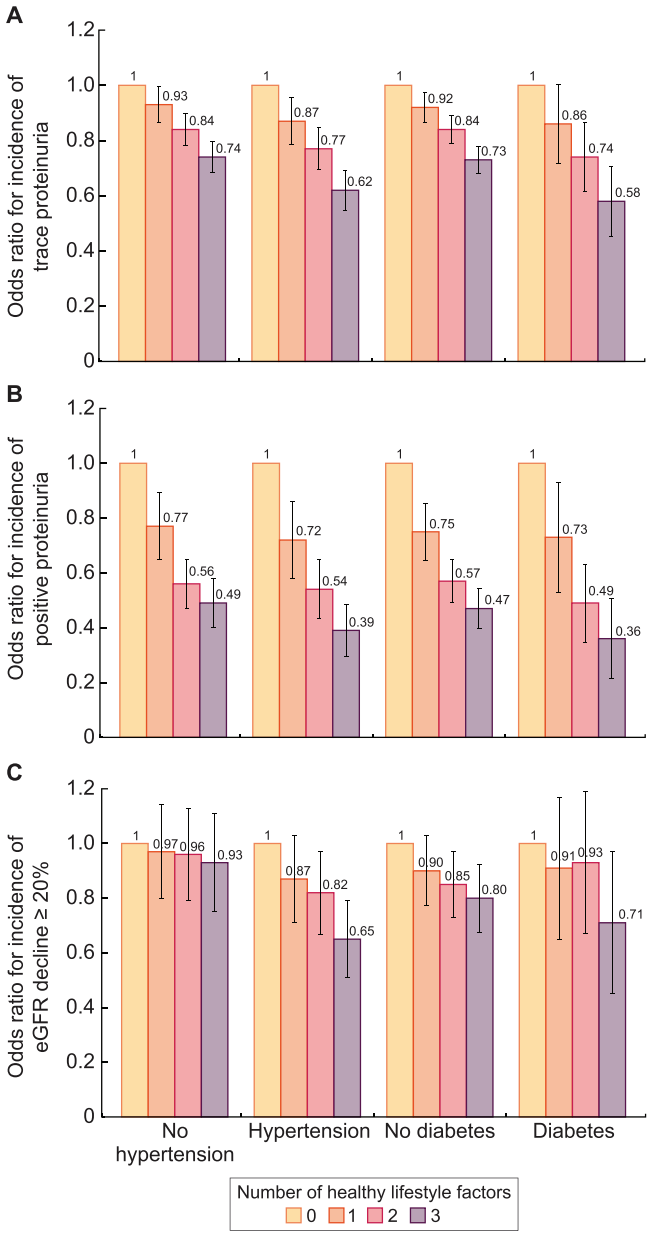


FIGURE 1: Adjusted ORs for incidence of (**A**) trace proteinuria, (**B**) positive proteinuria and (**C**) eGFR decline ≥20% according to the number of healthy LFs by status of HT and diabetes. The three components of healthy LFs are noncurrent smoking, healthy eating habits (less than three times a week for late dinner, snacking and skipping breakfast) and BMI <25. Subjects were categorized as having no HT (BP <140/90 mmHg) or HT (BP ≥140/90 mmHg or the use of antihypertensive drugs). Subjects were also categorized as having no DM (HbA1c <6.5%) or DM (HbA1c ≥6.5% or the use of glucose-lowering drugs). ORs were adjusted for age, sex, eGFR, systolic BP, antihypertensive drug use, HbA1c, glucose-lowering drug use, TGs, lipid-lowering drug use and history of cardio-/cerebrovascular diseases. Error bar represents 95% CIs.

1-unit increase) after 6 years [31], which is consistent with our study. Other studies have shown similar results, but overweight had a greater effect than smoking [32, 33]. In contrast, obesity increased the risk of CKD more than smoking [34], partly because fat mass gain increased the risk of CKD [35], which

is consistent with our study. Overall, quitting smoking and maintaining adequate weight are the most important healthy LFs to prevent the progression of kidney diseases.

There are some mechanisms underlying the risk of proteinuria and rapid eGFR decline by smoking and overweight. Smoking may lead to proteinuria through endothelial dysfunction, oxidative stress and hemodynamic changes [36]. Overweight may increase the risk of proteinuria by increasing BP and insulin resistance or altering glomerular hemodynamics and adipocyte-derived bioactive molecules such as leptin or adiponectin [37]. Overweight is also a risk factor for HT, DM and hyperlipidemia, all of which increase the risk of ESRD [34].

Few studies have investigated the link between eating habits and the risk of proteinuria and rapid eGFR decline. Late dinner and skipping breakfast were associated with proteinuria and overweight [38]. Eating habits (avoiding late dinner, snacking and skipping breakfast) are also associated with a decreased risk of CKD [21]. The possible mechanism for this association is that nocturnal life and irregular mealtimes have been shown to be associated with impaired regulation of hormones such as leptin, insulin and glucocorticoids [39]. Late dinner can therefore affect cardiometabolic and endocrine functions during sleep and the following morning. Unhealthy eating behaviors may thus increase the risks of proteinuria and overweight [39].

Although the individual effects of these LFs on proteinuria and rapid eGFR decline were small, studying the combined impact of LFs instead of their individual impact on proteinuria/rapid eGFR decline is highly relevant. This is because multiple lifestyle behaviors coexist and may interact each other; e.g. a habit of skipping breakfast highly coexists with current smoking and overweight [38]. As a result, our study showed a stronger effect by assessing the overall lifestyle behaviors than the effect by the individual factors, although we could not show clear dose dependency on rapid eGFR decline as on proteinuria. Proteinuria precedes eGFR decline [40], thus overall lifestyle behaviors may have a greater effect on the development of proteinuria than on eGFR decline. Moreover, the Ministry of Health, Labour and Welfare in Japan promoted the National Health Promotion in the 21st Century (Health Japan 21), which focuses on healthy LFs including noncurrent smoking, healthy eating habits, regular exercise and adequate weight [41]. Japanese people are commonly educated for all of the LFs as a whole, especially when they undertake health checkups [25]. As a result, overall healthy lifestyle has a greater combined impact than individual effects.

The important finding in our study is that an overall healthy lifestyle was associated with a reduced risk of trace/positive proteinuria even among subjects without HT or DM. Therefore the recommendation from the Japanese Society of Nephrology that subjects with trace proteinuria should undergo lifestyle modification is highly relevant. This recommendation can be applicable not only to those with metabolic disorders such as HT or DM, but also to presumably healthy individuals with normal BP and normal glucose levels.

Several limitations of this study should be mentioned. First, participants with a healthy lifestyle had a much healthier health profile at baseline than their counterparts with an unhealthy lifestyle. Subjects with a healthy lifestyle showed substantially lower BP levels and a better lipid profile despite the older mean age, reflecting excellent overall health status in those subjects. Although BP, glucose and lipid levels were adjusted and stratified analyses by HT and DM were conducted, some of the underlying factors could not be considered. Second, wealth, education, occupational and environmental risk factors, which are major potential confounders, were not taken into account in this study. The observational nature of this study and the lack of some major potential confounders, such as social and environmental factors, preclude any strong causal interpretation of these findings. Third, proteinuria was not adjusted for the urine concentration of creatinine as recommended in the guideline [42]. As the dipstick test has an advantage in the cost-effectiveness and convenience of the examination [3], detecting trace proteinuria can be useful in assessing early stages of kidney damage despite being a less precise measure of albuminuria [1, 4]. Fourth, the reproducibility of trace proteinuria is low and may vary from time to time. As for our data, 60% of the subjects with trace proteinuria at baseline showed negative proteinuria after 1 year. However, overall, it is known that two-thirds of subjects with trace proteinuria already have microalbuminuria [6–8], and they have a high risk for future CVD and ESRD [1–4]. Thus, detecting the modifiable risk of trace proteinuria is highly relevant. Fifth, the follow-up (1 year) was relatively short for assessing the progression of kidney damage. Finally, as we did not assess changes in the number of healthy LFs, it should be investigated in another prospective study with longer follow-up whether changing the number of healthy LFs by lifestyle modification reduces the risk of development of trace proteinuria.

In conclusion, we demonstrated for the first time that subjects with an overall healthy lifestyle showed a lower incidence of trace/positive proteinuria by dipstick test and rapid eGFR decline over 2 years in a nationwide general population. Thus lifestyle modification should be recommended for subjects with trace proteinuria in health checkups. As the presence of trace proteinuria or rapid eGFR decline are powerful predictors of future CVD and ESRD [1–4, 9], a healthy lifestyle that reduces the risk of trace/positive proteinuria and rapid eGFR decline may prevent early stages of kidney diseases, which may then delay or prevent subsequent CVD and ESRD.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

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AUTHORS' CONTRIBUTIONS

R.O. analyzed the data and drafted the article. K.T. contributed to the conception and design of the study. K.W., K.K., T.W. and Y.S. revised the article critically for important intellectual content. All the authors approved the final version of the article to be published.

CONFLICT OF INTEREST STATEMENT

None declared. The results presented in this article have not been published previously in whole or part, except in abstract format.

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Article

Estimated 24 h Urinary Sodium-to-Potassium Ratio Is Related to Renal Function Decline: A 6-Year Cohort Study of Japanese Urban Residents

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Abstract: The effect of the sodium-to-potassium ratio (Na/K) on renal function within the clinically normal range of renal function are limited. We investigated the effects of an estimated 24 h urinary Na/K (e24hUNa/K) on a 6-year renal function decline among 927 urban Japanese community dwellers with no history of cardiovascular diseases and medication for hypertension, diabetes, or dyslipidemia. We partitioned the subjects into quartiles according to the e24hUNa/K. The estimated glomerular filtration rate (eGFR) was calculated using the chronic kidney disease epidemiology collaboration (CKD/EPI) formula and renal function decline was defined as an absolute value at or above the third quartile of the eGFR decline rate. A multivariable logistic regression model was used for estimation. Compared with the first quartile of the e24hUNa/K, multivariable-adjusted odds ratios (ORs) for eGFR decline in the second, third, and fourth quartiles were 0.96 (95% confidence interval: 0.61–1.51), 1.06 (0.67–1.66), and 1.65 (1.06–2.57), respectively. These results were similar when the simple spot urine Na/K ratio was used in place of the e24hUNa/K. Apparently healthy urban residents with an almost within normal range mean baseline eGFR and high e24hUNa/K ratios had an increased risk for a future decline in renal function. Reducing the Na/K ratio may be important in the prevention of chronic kidney disease in its early stage.

Keywords: urinary sodium-potassium ratio; urinary sodium; estimated GFR; renal function

1. Introduction

The number of patients with chronic kidney disease (CKD) continues to rise due to population ageing. CKD is a critical global health concern because it is a major risk factor for end-stage renal disease and cardiovascular diseases [1–3]. The examination of the risk factors for age-related kidney function decline could help in understanding the mechanisms of kidney ageing. CKD progression can be reduced by improving dietary habits and receiving appropriate treatment from an early stage [4,5]. In a large group of normotensive and never-treated patients with essential hypertension an important role for sodium intake on the interaction between systolic arterial pressure and albuminuria was demonstrated. High salt intake increased the excretion of protein in the urine, resulting in a decrease in renal function [6]. Increased intake of potassium increases the excretion of sodium in the urine and decreases blood pressure and reducing kidney damage [7]. Recently, it was reported that a high dietary sodium-to-potassium ratio (Na/K) was associated with increased risk of CKD incidence [8] and a high 24 h urinary Na/K ratio was also associated with CKD progression [9]. Twenty-four hour urinary sodium excretion [10], salt intake [11], and low urinary potassium excretion [12] were associated with CKD progression. However, relevant findings on the effect of the Na/K ratio on the development of CKD are still limited [8,9,13,14]; furthermore, although estimated glomerular filtration rate (eGFR) and proteinuria are insensitive indicators for predicting renal function decline, and future development of CKD, little is known about the association between Na/K ratio and renal function in a population with a clinically normal range of renal function.

Therefore, this study aimed to investigate the effects of an estimated 24 h urinary sodium-to-potassium ratio (e24hUNa/K) on renal function decline among apparently healthy urban residents in Japan.

2. Materials and Method

2.1. Study Participants

This was a 6-year follow-up study of the Kobe Orthopedic and Biomedical Epidemiological (KOBE) study, a population-based cohort study of citizens living in Kobe City. Detailed information about the KOBE study has been previously published [15–19]. In a nutshell, 1117 residents of Kobe City were recruited between July 2010 and December 2011 through Kobe City's website and public relations. The inclusion criteria were as follows: (1) Age 40 to 74 years, (2) no history of malignant neoplasm or cerebral or cardiovascular disease, (3) not on medication for hypertension, diabetes, or dyslipidemia, (4) subjectively healthy, (5) having the ability to arrive at the study site for requisite investigations, and (6) consent to participation in follow-up studies. Research participants were invited for an onsite survey every two years. The survey was done with a 2-year interval for each participants because we recruited apparently healthy community residents, of which examination cycle is as follows: Baseline survey (2010–2011), Follow-up 1 (2012–2013), Follow-up 2 (2014–2015), Follow-up 3 (2016–2017), Follow-up 4 (2018–2019).

This study is a follow-up study from the baseline survey to the 6-year follow-up survey. A number of participants were excluded for the following reasons: Missing data in the baseline survey (n = 2), incomplete follow-up (n = 186), and missing data in the 6-year survey (n = 2). Finally, 927 participants (282 men and 645 women) were included in this study. The participant flow diagram is shown in Figure 1.

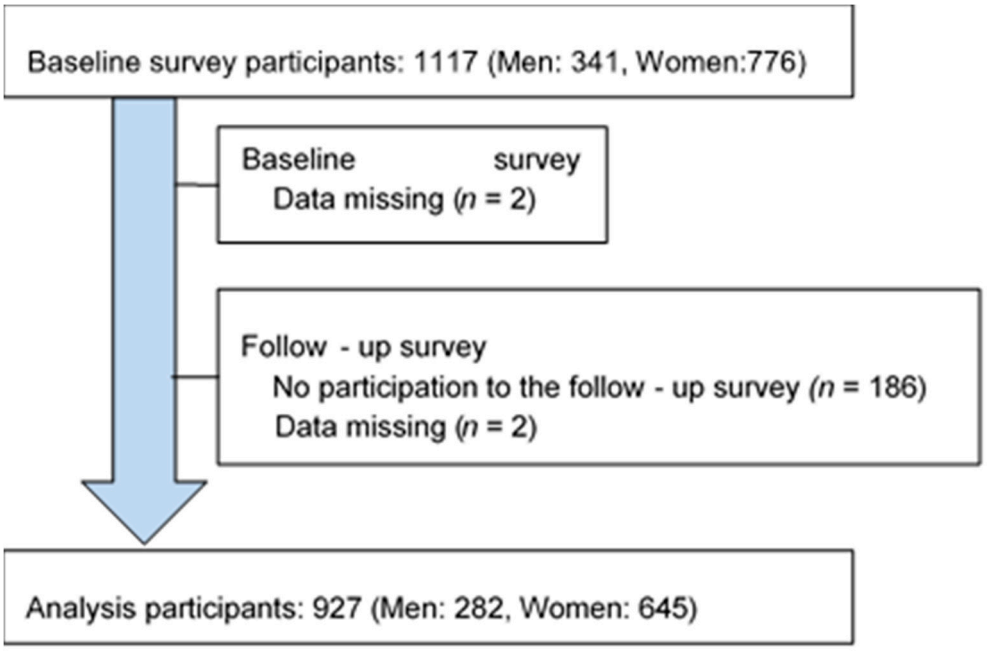

Figure 1. Study participants.

2.2. Measurements

Participants completed a standardized questionnaire of their medical history and lifestyle habits (e.g., smoking, alcohol consumption, and physical activity), and trained researchers confirmed the response contents through face-to-face communications. The height and weight of the participants in socks and light clothing were measured using a combined meter (U-WELL2; Elk Corp, Oosaka, Japan). Body mass index (BMI) was calculated as weight (kg) divided by squared height (m^2). Blood pressure measurements were taken twice with an automatic sphygmomanometer (BP-103i II; Nihon Colin, Tokyo, Japan) after participants were allowed to rest in a seated position for at least 5 min (measured by hourglass), and the mean value was recorded.

Blood samples were collected after ≥10 h of fasting, and all blood samples from the participants were assessed by the largest designated laboratory (SRL Inc., the largest clinical laboratory in Japan; https://www.srl-group.co.jp/english/). Blood glucose levels (mg/dL) were measured using the glucose oxidase method and hemoglobin A1c was assessed using the latex agglutination test. Total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) levels were measured using enzymatic methods, and low-density lipoprotein cholesterol (LDL-C) levels were calculated using the Friedewald equation [20]. Serum high-sensitivity C-reactive protein (hs-CRP) was measured using a BN II nephelometer (Dade Behring, Deerfield, IL, USA) as previously reported [18].

Urine samples were collected at the research site in the morning without breakfast. The collected fresh urine was taken in a clean urine test cup and immediately dispensed into a sterile tube and was under refrigeration before measurement. The urine albumin level was measured by turbidimetric immunoassay. The urine creatinine level was measured using the enzymatic method. Urine sodium and potassium levels were measured using the electrode method.

The e24hUNa/K was defined as the ratio of estimated 24 h urinary sodium to estimated 24 h urinary potassium as calculated using a spot urine by Tanaka et al.'s equations [21]. The equations were as follows:

$$\text{PRCr (mg/day)} = -2.04 \times \text{age} + 14.89 \times \text{weight (kg)} + 16.14 \times \text{height (cm)} - 2244.45; \quad (1)$$

$$\text{Estimated 24 h urinary sodium (e24hUNa) (mEq/day)} = 21.98 \times \text{XNa}^{0.392}; \quad (2)$$

$$\text{Estimated 24 h urinary potassium (e24hUK) (mEq/day)} = 7.59 \times XK^{0.431}; \quad (3)$$

$$\text{Estimated 24 h Na and K excretion (e24hUNa/K)} = \text{e24hUNaV/e24hUKV}. \quad (4)$$

where PRCr = predicted value of 24hUCr, SUNa = Na, SUK = K concentration in the spot voiding urine, SUCr = creatinine concentration in the spot voiding urine, XNa (or XK) = SUNa (or SUK)/(SUCr × 10) × PRCr.

We partitioned the subjects into quartiles according to the 24 h urinary Na/K ratio. (Q1: e24hUNa/K < 2.8, Q2: 2.8 ≤ e24hUNa/K < 3.2, Q3: 3.2 ≤ e24hUNa/K < 3.6, Q4: e24hUNa/K ≥ 3.6.)

Additional analysis using simple urinary Na/K ratio (UNa/K) was also performed.

2.3. Renal Function Decline

Serum creatinine was also measured in SRL Inc. using the enzymatic method. Our serum creatine values were not IDMS-traceable, but based upon acid metric titration method primarily calibrated by reference standard NIST SRM914. This reference standard is also used for primary calibration for the reference material JCCRM 521 which is determined by IDMS. Moreover, serum creatine is evaluated by external accuracy audit in Japan; the intra and inter method coefficient of variation for serum were 3.45% and 5.60%, respectively.

The estimated glomerular filtration rate (eGFR) was calculated using the serum creatinine from serum samples, collected at the time of the survey, by the following CKD/EPI formula [22]:

$$\text{eGFR} = 141 \times \min(\text{Scr}/\kappa, 1)^{\alpha} \times \max(\text{Scr}/\kappa, 1)^{-1.209} \times 0.993^{\text{age}} \times 1.018\ [\text{if female}] \times 0.813\ [\text{if Japanese}] \quad (5)$$

In this equation, Scr is serum creatine in mg/dL; κ is 0.7 and 0.9 for men and women, respectively; α is −0.329 and −0.411 for men and women, respectively; min indicates the minimum of Scr/κ or 1, and max indicates maximum of Scr/κ or 1.

The rate of eGFR decline from baseline to 6 years was divided into quartiles for all participants. We defined eGFR decline as the decline value at or above the third quartile of the decline rate (−8.02% during 6 years = −1.34%/year).

2.4. Statistical Analysis

Analysis of variance and the chi-squared test were used to estimate the means and the prevalence of baseline characteristics. The multivariable-adjusted odds ratios (ORs) and 95% confidence intervals (CI) of each quartile group of e24hUNa/K for eGFR decline compared with the first quartile group were estimated using a multivariable logistic regression model. Adjusted variables were age, BMI, alcohol consumption (current drinking, past drinking, and no drinking), smoking (current smoking, past smoking, and no smoking), HbA1c, HDL-C, LDL-C, eGFR (baseline), and hypertension (baseline: SBP ≥ 130 or/and DBP ≥ 80) [23]. There was no interaction between men and women regarding the relationship between e24hUNa/K and renal function decline; thus, sex-combined analysis with adjustment for sex was performed in the multivariable analysis. All the analyses were repeated using UNa/K in place of e24hUNa/K.

Statistical analysis was performed using IBM SPSS Statistics version 25 (IBM Corp., Armonk, NY, USA), with a two-tailed 5% level of significance.

2.5. Statement of Ethics

This research has been approved by the Pharmaceutical Clinical Research Review Committee (Ethics Committee) of the Institute of Biomedical Research and Innovation at the Kobe Biomedical Innovation Cluster (approval no. 10–20) and the Ethics Committee of Keio University School of Medicine (approval no. 20170142). Participants were given written and oral explanations, and written informed consent was obtained.

3. Results

In the baseline survey, means (standard deviations (SDs)) for e24hUNa/K, e24hUNa, and e24hUK were 3.2(0.7), 145(32) mEq/day, and 46(8) mEq/day, respectively. The mean (SD, min–max) eGFR was 79.2 (8.0, 48.8–104.8) mL/min/1.73 m^2.

3.1. Baseline Characteristics of Study Participants According to the Quartile Groups of e24hUNa/K Levels

Table 1 shows participant characteristics according to the e24hUNa/K quartile group. Waist circumference, BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), and prevalence of hypertension were lower in the lowest Na/K group (Q1) than in the other groups (Q2–4). HDL-C was higher in the lowest group (Q1) than the other groups (Q2–4).

3.2. Multivariable Adjusted Means of eGFR and Its 6-Year Change According to the Quartile Groups of e24hUNa/K Levels

Table 2 shows the multivariable-adjusted means of the e24hUNa/K quartile group for the eGFR-decrease during the 6-year period. Means of absolute amount of change in eGFR were higher in higher e24hUNa/K quartiles (Q1: −0.72 (95% CI: −0.81–−0.64), Q2: −0.75 (−0.84–−0.67), Q3: −0.81 (−0.90–−0.73), Q4: −0.96 (−1.05–−0.87) mL/min/1.73 m^2/year) (p = 0.001). The same was in the means of absolute change rate in eGFR (Q1: −0.91 (95% CI: −1.03–−0.78), Q2: −0.95 (−1.07–−0.83), Q3: −1.04 (−1.16–−0.92), Q4: −1.22 (−1.34–−1.10) %/year) (p = 0.002). These results were similar according to the UNa/K quartile group (Table S1).

3.3. Multivariable-Adjusted Odds Ratio for eGFR Decrease According to the Quartile Groups of e24hUNa/K Levels

Figure 2 shows the multivariable-adjusted OR for the eGFR decrease according to the e24hUNa/K quartile group. Compared with Q1, ORs (95% CI) for eGFR decline were as follows: Q2: 0.96 (0.61–1.51); Q3: 1.06 (0.67–1.66); and Q4: 1.65 (1.06–2.57), respectively. These results were similar according to the UNa/K quartile group (Figure S1). Furthermore, the above-mentioned findings were not substantially affected when a 10% decrease of eGFR in each participant (mean absolute decline −15.1%) was set as an outcome (Figure S2).

Urinary albumin was measured at baseline, and we defined being 300 mg/g·Cre or more as overt proteinuria (n = 2), both of which were in menstruating women. In the follow-up survey 6 years later, a urine qualitative test was conducted by a dipstick test not by urinary albumin; and ≥1+ on dipstick was defined as proteinuria (n = 16). However, the results of Figure 2 (Figure S1) did not change even if these subjects were excluded (n = 18). Further adjustment for baseline hs-CRP (log-transformed) did not also alter the results (date not shown).

Table 1. Baseline characteristics of study participants according to the quartile groups of e24hUNa/K levels.

Characteristics	Total		Q1		Q2		Q3		Q4		*p* for Trend
Number	927		232		232		232		231		
Age, years	58.9	(8.6)	58.2	(9.1)	59.3	(8.6)	58.8	(8.5)	59.3	(8.0)	0.43
Women	645	(69.6)	174	(75.0)	161	(69.4)	163	(70.3)	147	(63.6)	0.07
Waist circumference, cm	79.7	(8.4)	78.3	(8.3)	79.9	(8.4)	80.3	(8.4)	80.4	(8.4)	0.03
BMI, kg/m^2	21.5	(2.8)	21.1	(2.7)	21.5	(2.8)	21.8	(2.7)	21.8	(3.0)	0.01
Current smoking	40	(4.3)	12	(5.2)	6	(2.6)	8	(3.4)	14	(6.1)	0.24
Current drinking	473	(51.0)	111	(47.8)	115	(49.6)	119	(51.3)	128	(55.4)	0.40
SBP, mmHg	116.3	(17.4)	111.6	(15.2)	117.7	(17.3)	116.3	(17.3)	119.7	(18.9)	<0.001
DBP, mmHg	72.0	(11.1)	69.2	(9.9)	73.5	(10.9)	71.5	(11.5)	73.8	(11.3)	<0.001
Hypertension	274	(29.6)	42	(18.1)	79	(34.1)	69	(29.7)	84	(36.4)	<0.001
HbA1c, %	5.2	(0.4)	5.2	(0.4)	5.2	(0.6)	5.2	(0.4)	5.2	(0.4)	0.98
Glucose, mg/dL	89.8	(11.7)	89.3	(8.6)	90.2	(17.6)	89.7	(8.7)	90.0	(9.2)	0.85
HDL-C, mg/dL	68.6	(16.3)	70.8	(17.1)	68.8	(16.3)	69.0	(15.1)	65.8	(16.3)	0.01
LDL-C, mg/dL	131.0	(28.2)	129.6	(28.6)	132.3	(28.3)	131.5	(28.0)	130.5	(27.9)	0.76
TG, mg/dL	74.0 (55.0, 104.0)		69.0 (52.0, 96.8)		76.0 (56.0, 98.0)		72.0 (55.3, 105.5)		80.0 (57.0, 116.0)		0.02
hs-CRP, mL/L	225.0 (184.0, 480.0)		179.5 (93.9, 475.8)		248.5 (104.3, 509.0)		226.5 (120.0, 421.0)		232.0 (101.0, 469.0)		0.27
e24hUNa, mEq/day	144.6	(32.2)	117.4	(25.4)	138.7	(23.4)	153.9	(26.2)	168.7	(28.9)	<0.001
e24hUK, mEq/day	45.9	(8.1)	48.9	(8.8)	46.8	(7.7)	45.9	(7.6)	41.9	(6.8)	<0.001
e24hUNa/K	3.2	(0.7)	2.4	(0.3)	3.0	(0.1)	3.4	(0.1)	4.0	(0.4)	<0.001
e24hUsalt, g/day	8.5	(1.9)	6.9	(1.5)	8.2	(1.4)	9.1	(1.5)	9.9	(1.7)	<0.001
e24hUK, mg/day	1794	(318)	1910	(343)	1830	(300)	1794	(298)	1640	(268)	<0.001
ACR, mg/g·Cre	8.6 (5.7, 13.8)		8.4 (5.7, 12.4)		7.9 (5.8, 13.8)		8.7 (5.5, 13.4)		9.5 (5.8, 17.1)		0.32
eGFR, mL/min/1.73 m^2	79.2	(8.0)	78.6	(8.1)	78.5	(8.8)	79.7	(7.6)	80.2	(7.1)	0.07

Q1: e24hUNa/K < 2.8, Q2: 2.8 ≤ e24hUNa/K < 3.2 Q3: 3.2 ≤ e24hUNa/K < 3.6 Q4: e24hUNa/K ≥ 3.6; Continuous data were analyzed using Student's *t*-test, and were shown in the mean (standard deviation). Values of TG, hs-CRP, and ACR are the median (inter-quartile range); Categorical data were analyzed using the χ^2 test, and were shown as number (%); BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, hypertension: SBP ≥ 130 or/and DBP ≥ 80; HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, TG: Triglyceride, hs-CPR: High-sensitivity C-reactive protein; e24hUNa: Estimated 24 h urine sodium excretion, e24hUK: Estimated 24 h urinary potassium excretion; e24hUNa/K: Estimated 24 h urine sodium-potassium ratio, e24hUsalt: Estimated 24 h urinary salt excretion. Salt equivalent (g) = Na (mEq) × molecular weight 23.0 × 2.54 (Na 23.0/NaCl 58.4) ÷ 1000, ACR: Albumin creatinine ratio; eGFR: Estimated glomerular filtration rate.

Table 2. Multivariable-adjusted means of estimated glomerular filtration rate (eGFR) and its 6-year change according to the quartile groups of e24hUNa/K levels.

	Q1 (*n* = 232)		Q2 (*n* = 232)		Q3 (*n* = 232)		Q4 (*n* = 231)		*p*-Value
	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	Mean	(95% CI)	
eGFR (6 years later), mL/min/1.73 m^2	74.9	(74.4–75.4)	74.7	(74.2–75.2)	74.4	(73.8–74.9)	73.5	(73.0–74.0)	0.001
eGFR amount of change, mL/min/1.73 m^2/year	−0.72	(−0.81–−0.64)	−0.75	(−0.84–−0.67)	−0.81	(−0.90–−0.73)	−0.96	(−1.05–−0.87)	0.001
change rate in eGFR%/year	−0.91	(−1.03–−0.78)	−0.95	(−1.07–−0.83)	−1.04	(−1.16–−0.92)	−1.22	(−1.34–−1.10)	0.002

Q1: e24hUNa/K < 2.8, Q2: 2.8 ≤ e24hUNa/K < 3.2, Q3: 3.2 ≤ e24hUNa/K < 3.6, Q4: e24hUNa/K ≥ 3.6; Data are presented as mean and 95% confidence interval. Analysis of variance were used to adjust for sex, age, BMI, cigarettes smoking (current/past/none), alcohol drinking; (current/past/none), HDL-C, LDL-C, HbA1c, eGFR (baseline), hypertension; *p*-Values for difference between groups; eGFR: estimated glomerular filtration rate, BMI: Body mass index, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol; hypertension: SBP ≥ 130 or/and DBP ≥ 80.

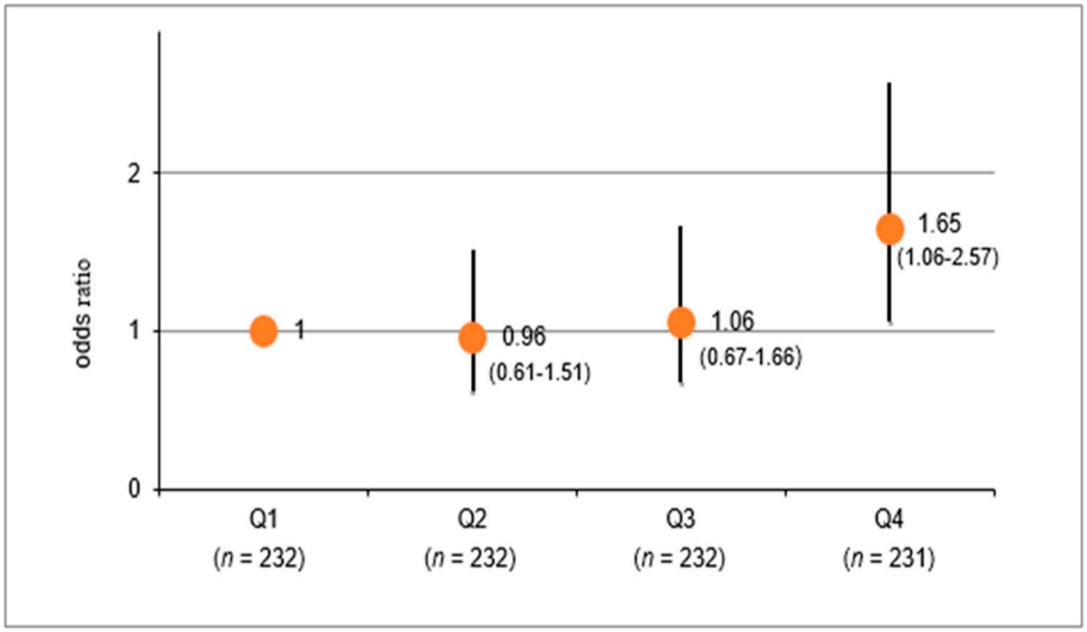

Figure 2. Multivariable-adjusted odds ratio for eGFR decrease according to the quartile groups of e24hUNa/K levels. Q1: e24hUNa/K < 2.8, Q2: 2.8 ≤ e24hUNa/K < 3.2, Q3: 3.2 ≤ e24hUNa/K < 3.6, Q4: e24hUNa/K ≥ 3.6; Data are odds ratio and 95% confidence interval. Logistic regression models were used; Adjusted for sex, age, BMI, cigarette smoking (current/past/none), alcohol drinking (current/past/none), HDL-C, LDL-C, HbA1c, eGFR (baseline), hypertension; eGFR: Estimated glomerular filtration rate; BMI: Body mass index, HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; Hypertension: SBP ≥ 130 or/and DBP ≥ 80.

4. Discussion

In the present study, the mean eGFR decrease was 0.8 mL/min/1.73 m^2/year, which was similar to those of previous studies [24–26]; and during the 6-year follow-up period, increased ORs for eGFR decline were observed with higher 24hUNa/K ratios in the apparently healthy urban residents with mean baseline eGFR of about 80 mL/min/1.73 m^2, who had no past history of neoplasms, cardiovascular diseases, or medication for hypertension, diabetes, or dyslipidemia. There were no participants with stage 3b or more of CKD (eGFR < 45 mL/min/1.73 m^2). Similar results were observed when UNa/K was used instead of e24hUNa/K in our statistical models. The present study demonstrated that higher e24hUNa/K levels were associated with a higher risk of eGFR decline within an almost normal range of eGFR. This finding suggests that increased intake of potassium in addition to reduced intake of sodium might prevent renal function decline in the early stage of CKD.

A prospective cohort study of Iranian adults that estimated sodium and potassium levels using a food frequency questionnaire examined the risk of CKD within a 6.3-year period [8]; participants in the highest tertile of the Na/K ratio had a higher OR of CKD (OR = 1.52) than those in the lowest tertile. Furthermore, the researchers found out that sodium and potassium alone were not associated with a risk of CKD. The Korean N Cohort Study of Outcomes in Patients with CKD (KNOW-CKD) was analyzed in a 5-year prospective study of 1001 patients with non-dialysis-dependent CKD with a mean baseline eGFR of about 50 mL/min/1.73 m^2 [9]. Subjects were divided into quartiles according to 24 h urinary Na/K ratio. Compared to the lowest quartile of 24 h urinary Na/K ratio, the odds ratio for renal outcomes were 2.48 (95% CI 1.30–4.90) in the third quartile and 2.95 (95% CI 1.56–5.81) in the fourth quartile, respectively.

In the previous studies, 24 h urinary sodium excretion [10] or salt intake and eGFR based on a food frequency questionnaire [11] were associated with CKD progression. Regarding the association between dietary potassium intake and CKD, a cohort study involving 5315 Dutch men and women reported that low urinary potassium excretion increased the risk of CKD onset 5 years later [12].

Consequently, the combination of sodium and potassium such as e24hUNa/K or 24 h urinary Na/K ratio is supposed to be a useful marker for future decline in renal function. Our study also suggested that urinary Na/K ratio may be a simple marker for this purpose.

The following mechanism is considered to be a factor to explain the relationship between the sodium–potassium ratio and blood pressure. A large amount of sodium intake causes cardiac dysfunction and renal dysfunction, and it is known that the main mechanism is the enhancement of oxidative stress, which enhances insulin resistance [27]. On the contrary, potassium has an antioxidant effect at the same time as a natriuretic effect, and it is known in animal experiments that potassium administration improves insulin resistance due to sodium [28]. It has also been suggested that there is a common mechanism in the process of formation of salt sensitivity and insulin sensitivity of blood pressure [29].

High sodium intake and low potassium intake are common dietary problems in Japan. In the 2018 National Health and Nutrition Survey, the average daily sodium intake (salt equivalent) measured by the one-day weighing method in Japanese subjects aged 20 years or older was 11.0 g per day for men and 9.3 g per day for women. In 2012, the WHO proposed a recommended potassium intake of 3510 mg per day for hypertension prevention in adults [30]; yet the average potassium intake was only 2386 mg per day for men and 2205 mg per day for women [31]. The results of the International Study of Macro-/Micro-nutrients and Blood Pressure (INTERMAP Study) [32] from a four-country collaborative study including Japan, China, the United Kingdom, and the United States showed that sodium excretions measured by 24 h urine collections were low at 2929–4202 mg/day (salt equivalent 7.4–10.7 g/day) in Westerners and high at 4843 mg/day (salt equivalent 12.3 g/day) in men and at 4278 mg/day (salt equivalent 10.9 g/day) in Japanese women. Conversely, potassium was high in Western populations, ranging from 1982–2912 mg/day, and low in Japanese populations, at 1920 mg/day in men and 1891 mg/day in women. The Na/K ratio calculated by 24 h urine collections also tended to be low at 2.2–3.1 in Western populations, and high for Japanese subjects at 4.5 in men and 4.1 in women. Therefore, lifestyle modification guidance for the prevention of renal function decline and focusing on the Na/K ratio may be particularly helpful in the Japanese population.

This study had several limitations. First, the KOBE study consisted of subjectively healthy participants from an urban area who voluntarily participated in the survey. Therefore, caution is required when applying the results of this study to other populations. Indeed, even compared to Japanese workers in a study that used the same estimation formula to measure e24hUNa and e24hUK (HIPOP-OHP study) [33–35], participants in the present study had higher e24hUK and lower e24hUNa and BMI. Second, a 24 h urine collection is recommended for accurate measurement of salt intake, but estimations were calculated from spot urine for participants in the present study. However, this method is considered to be capable of estimating salt excretion to a certain extent at least at the general population level [36]. Third, in this study, we were not able to examine whether nutrients other than sodium and potassium influenced the results because a detailed nutrition survey was not conducted at baseline. Fourth, the participants of this survey are completely healthy participants, who cannot follow the course of eGFR on a monthly basis like hospital patients, and it is predicted that few patients will have renal impairment in the first few years. Therefore, it was designed like this research. A study design that can more closely track the eGFR of healthy participants is needed, and this is a future subject.

5. Conclusions

In conclusion, individuals with high e24hUNa/K ratios had an increased risk for a future decline in renal function in the apparently healthy urban Japanese residents, who had a mean baseline eGFR almost within the normal range and had no past history of cardiovascular diseases, neoplasms, or medication for hypertension, diabetes, or dyslipidemia. These findings suggest that reducing the Na/K ratio is important in the prevention of the progression of renal function decline in its early stage. A dietary guidance focusing on the Na/K ratio may be a useful first step in the prevention of CKD.

Supplementary Materials: The following are available online at http://www.mdpi.com/1660-4601/17/16/5811/s1, Figure S1: Multivariable-adjusted odds ratio for eGFR decrease according to the quartile groups of UNa/K levels; Figure S2: Multivariable-adjusted odds ratio for eGFR decrease according to the quartile groups of e24hUNa/K levels (eGFR decrease was set as 10% decline of eGFR of each participant: mean absolute decline −15.1% in six-year follow-up); Table S1: Multivariable-adjusted means of eGFR and its 6-year change according to the quartile groups of UNa/K levels.

Author Contributions: H.H., A.H. (Aya Hirata) and T.O. developed the study hypothesis; H.H. conducted the analysis and drafted the manuscript; T.O. and A.H. (Aya Hirata) advised data analyses and writing manuscript; A.H. (Aya Hirata), S.K., Y.N., M.N., K.K. (Kuniko Kawamura), T.H., Y.K., M.S., K.K. (Kazuyo Kuwabara), A.H. (Aya Higashiyama), A.K., D.S., N.M., Y.M. and T.O. contributed to organizing data collection; T.O. organized the KOBE study. All authors have read and agreed to the published version of the manuscript.

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