Table 3
Age- and multivariate-adjusted ORs and 95% CIs for the presence of CKD, low eGFR, and proteinuria according to the quartiles of TG/HDL-C.

(A) Men					
	TG/HDL-C				*P* for trend
	Q_1	Q_2	Q_3	Q_4	
	<1.26	1.26–1.98	1.99–3.18	>3.18	
	(*n* = 22,126)	(*n* = 22,126)	(*n* = 22,142)	(*n* = 22,122)	
CKD					
Cases, *n* (%)	4115 (18.6)	4847 (21.9)	5618 (25.4)	6079 (27.5)	
Age-adjusted OR (95% CI)	Reference	1.23 (1.18–1.29)	1.55 (1.48–1.62)	1.90 (1.82–1.99)	<0.001
Multivariate-adjusted OR (95% CI)[a]	Reference	1.13 (1.08–1.18)	1.34 (1.28–1.40)	1.57 (1.49–1.65)	<0.001
Low eGFR					
Cases, *n* (%)	3045 (13.8)	3732 (16.9)	4349 (19.6)	4538 (20.5)	
Age-adjusted OR (95% CI)	Reference	1.28 (1.22–1.35)	1.62 (1.53–1.70)	1.92 (1.82–2.02)	<0.001
Multivariate-adjusted OR (95% CI)[b]	Reference	1.21 (1.15–1.28)	1.47 (1.39–1.55)	1.72 (1.63–1.82)	<0.001
Proteinuria					
Cases, *n* (%)	1404 (6.3)	1605 (7.3)	1915 (8.6)	2333 (10.5)	
Age-adjusted OR (95% CI)	Reference	1.15 (1.07–1.24)	1.41 (1.31–1.52)	1.81 (1.69–1.94)	<0.001
Multivariate-adjusted OR (95% CI)[c]	Reference	0.96 (0.89–1.03)	1.03 (0.95–1.11)	1.13 (1.04–1.21)	<0.001
(B) Women					
	TG/HDL-C				*P* for trend
	Q_1	Q_2	Q_3	Q_4	
	<0.96	0.96–1.44	1.45–2.22	>2.22	
	(*n* = 31,894)	(*n* = 31,817)	(*n* = 31,918)	(*n* = 31,862)	
CKD					
Cases, *n* (%)	3551 (11.1)	4226 (13.3)	4812 (15.1)	5901 (18.5)	
Age-adjusted OR (95% CI)	Reference	1.14 (1.09–1.20)	1.28 (1.22–1.34)	1.63 (1.56–1.71)	<0.001
Multivariate-adjusted OR (95% CI)[a]	Reference	1.08 (1.03–1.14)	1.16 (1.10–1.22)	1.41 (1.34–1.48)	<0.001
Low eGFR					
Cases, *n* (%)	2720 (8.5)	3370 (10.6)	3848 (12.1)	4614 (14.5)	
Age-adjusted OR (95% CI)	Reference	1.17 (1.11–1.23)	1.30 (1.23–1.37)	1.60 (1.52–1.68)	<0.001
Multivariate-adjusted OR (95% CI)[b]	Reference	1.13 (1.07–1.20)	1.23 (1.17–1.30)	1.47 (1.39–1.55)	<0.001
Proteinuria					
Cases, *n* (%)	974 (3.1)	1075 (3.4)	1250 (3.9)	1838 (5.8)	
Age-adjusted OR (95% CI)	Reference	1.09 (0.99–1.19)	1.25 (1.15–1.37)	1.88 (1.74–2.04)	<0.001
Multivariate-adjusted OR (95% CI)[c]	Reference	0.94 (0.86–1.03)	0.96 (0.88–1.05)	1.23 (1.13–1.34)	<0.001

Abbreviations: CKD; chronic kidney disease, TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate, OR; odds ratio, CI; confidence interval.

[a] Multivariate analyses were adjusted for age, waist circumstance, hypertension, obesity, diabetes, current smoking, daily alcohol consumption, regular exercise habits, history of stroke and heart disease, and medication for dyslipidemia (Model 1 covariates).

[b] Multivariate analyses were adjusted for the presence of proteinuria in addition to Model 1 covariates.

[c] Multivariate analyses were adjusted for eGFR in addition to Model 1 covariates.

low eGFR, and proteinuria significantly increased as the quartiles of TG/HDL-C increased (*P* for trend <0.001). In both men and women, ORs for Q_2, Q_3, and Q_4 were significantly higher than the ORs for Q_1. We also calculated the ORs for CKD, low eGFR, and proteinuria after adjustment for age, waist circumference, hypertension, obesity, diabetes, a current smoking habit, daily alcohol consumption, regular exercise habits, history of stroke and heart disease, and medication for dyslipidemia. Proteinuria was adjusted in the analysis of eGFR, and vice versa. The OR for the presence of CKD increased progressively with higher TG/HDL-C levels in men [Q_2: OR 1.13 (95% CI 1.08–1.18); Q_3: 1.34 (1.28–1.40); Q_4: 1.57 (1.49–1.65); *P* for trend <0.001] and in women [1.08 (1.03–1.14), 1.16 (1.10–1.22), 1.41 (1.34–1.48), respectively; *P* for trend <0.001]. Furthermore, there were significant associations with risk of low eGFR and proteinuria in both genders. We also performed stratified analyses to assess the association between TG/HDL-C and CKD according to the presence of hypertension, diabetes, or obesity, and found that the risk of CKD increased linearly with greater TG/HDL-C levels in participants with and without hypertension, diabetes, and obesity. Moreover, higher TG/HDL-C level was a relevant factor for CKD, especially in participants with hypertension and diabetes (*P* for interaction <0.001, respectively) (Fig. 2).

4. Discussion

CKD is a major public health problem, and the identification of risk factors for the development of CKD may well be useful for early intervention and prevention strategies. The results of our large cohort study, which represented the general population of Japan, show that higher TG/HDL-C level in Japanese adults is significantly associated with the risk of CKD. We found that an elevated TG/HDL-C level was an independent and relevant factor for CKD in both men and women, even after adjustment for the relevant potential confounding factors. In stratified analyses, elevated TG/HDL-C levels were significantly associated with the likelihood of having CKD, independently of hypertension, diabetes, and obesity. Higher TG/HDL-C levels were relevant for CKD, especially in participants with hypertension and diabetes.

It seems strange that the trends for history of stroke and heart disease are not statistically significant in men. We suspected that it might be attributed to the inverse trend between age and TG/HDL-C, thus examined the association of TG/HDL-C with history of stroke and heart disease with adjustment for age. As a result, significant positive trends for history of stroke (*P* for trend <0.001) and heart disease (*P* for trend <0.001) were observed in TG/HDL-C after

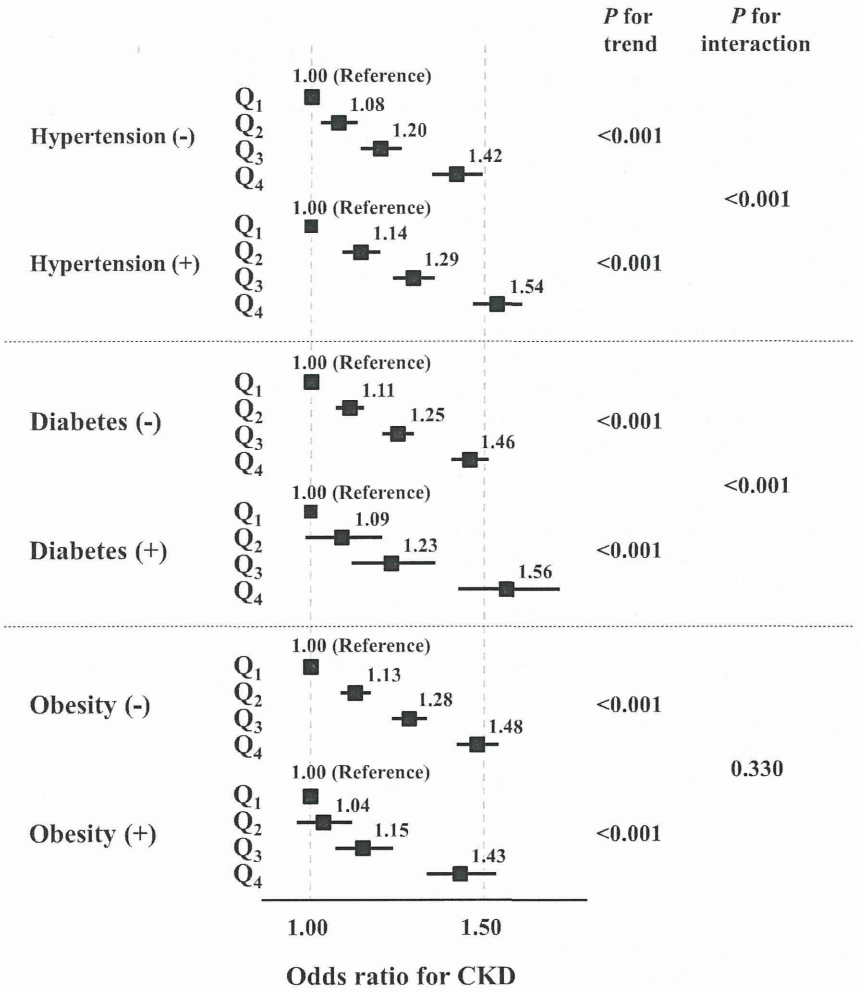

Fig. 2. Multivariate-adjusted odds ratios with 95% confidence intervals for prevalent CKD in the quartile groups after stratification for the presence or absence of hypertension, diabetes, and obesity. Logistic regression analysis was adjusted for age, gender, waist circumference, hypertension, obesity, diabetes, a current smoking habit, daily alcohol consumption, regular exercise habits, history of stroke and heart disease, as well as medication for dyslipidemia in participants with and without hypertension, diabetes, and obesity. The variable relevant to the subgroup was excluded from each model. Odds ratios and 95% confidence intervals for CKD are shown. Abbreviations: CKD, chronic kidney disease; TG/HDL; triglycerides/high-density lipoprotein cholesterol.

adjustment for age. Thus, we confirmed that no significant trends between history of cardiovascular disease and TG/HDL-C in men are influenced by the inverse trend for age in TG/HDL-C.

It is well-known that moderate CKD increases TG and decreases HDL-C levels [2–7]. A relationship between dyslipidemia and the incidence of CKD remains controversial [17–19]; however, there is a growing body of evidence to show that abnormalities in lipid metabolism contribute to the progression of renal disease [20–24]. Others have reported that the vicious cycle between renal dysfunction and dyslipidemia is activated in CKD, and this seems to contribute to cardiovascular and all-cause mortality [25,26].

In Asian population, Kang et al. showed that there were significant associations between TG/HDL-C and reduced eGFR or albuminuria among Korean adults [27,28]. Likewise, the present study clearly showed that TG/HDL-C was associated with the risk of both decreased eGFR and proteinuria on the basis of individual data from 216,007 Japanese participants. Therefore, these findings highlight the potential clinical value of the measurement of both TG and HDL-C for risk assessment of CKD in the Japanese population.

The mechanism by which the relationship between TG/HDL-C and the risk of CKD might be mediated is an area of great interest. Previous investigations reported a relationship between a high TG/HDL-C and elevated levels of small, dense LDL-C particles [12–14]. These LDL-C particles are highly atherogenic [29], and their level is considered a useful marker of insulin resistance [8–11], which, in turn, mediates risk factors for cardiovascular disease and CKD such as diabetes, hypertension, obesity, lipid abnormalities, and atherosclerosis [30]. These findings suggest us that the association between TG/HDL-C and CKD might be influenced by the relevant confounding factors such as diabetes, hypertension, and obesity. Because of the large number of the participants, we could perform stratified analyses to assess whether diabetes, hypertension, or obesity influenced the association between TG/HDL-C and CKD, and we found that the association between TG/HDL-C and CKD was robust regardless of the presence of these diseases, suggesting that TG/HDL-C is independently associated with the risk of CKD, regardless of the presence of known atherogenic variables. This finding is in accordance with previous studies suggesting insulin resistance as an independent risk factor for the progression of renal dysfunction in nondiabetic subjects [31].

On the other hand, the association between TG/HDL-C and CKD was stronger in participants with diabetes and hypertension than in participants without these diseases. It is thus possible that lipid disorders and diabetes or hypertension are linked in a vicious cycle

and that CKD is a consequence of diabetes or hypertension in individuals with dyslipidemia. Taken together, these results highlight the importance of TG/HDL-C as a relevant factor for CKD, especially in diabetic/hypertensive individuals, and we suggest aggressive management of dyslipidemia to prevent the incidence and progression of CKD. However, the pathophysiology of influence of TG/HDL-C requires further exploration.

Our study had some limitations. First, the cross sectional study design limits the interpretation of causality between TG/HDL-C and CKD. Second, single measurements of TG, HDL-C, serum creatinine, and dipstick measurements of urinary protein could have resulted in the misclassification of some comorbidities. Third, GFR was not directly measured, but was estimated with a serum creatinine-based equation, which could have over- or underestimated the actual GFR in the Japanese general population. Fourth, our study participants were generally healthy and were interested in their own health; therefore, the prevalence of dyslipidemia or CKD may have been underestimated. Fifth, although we argued the possible pathogenetic role of small, dense LDL, but we have not shown any data directly as to the small, dense LDL. One may argue that the availability of apolipoprotein B levels, which is not an unreasonable parameter to demand nowadays, might have helped our argument. However, we cannot provide the data because we had not examined the levels of apolipoprotein B and also had not stored any blood samples.

In conclusion, the present findings, representative of a general population of Japanese adults, indicated that high TG/HDL-C level significantly associated with prevalent CKD. Further prospective studies are needed to clarify the causative relationship between serum TG/HDL-C and CKD.

Contributors

Kazuhiko Tsuruya and Hisako Yoshida contributed to the study design, acquisition of data, statistical analysis, interpretation of data, and drafting of the manuscript. Masaharu Nagata contributed to the study design, acquisition of data, statistical analysis, and interpretation of data. Takanari Kitazono contributed to the critical revision of the manuscript and study supervision. Hideki Hirakata contributed to acquisition of data and critical revision of the manuscript. Kunitoshi Iseki, Toshiki Moriyama, Kunihiro Yamagata, Hideaki Yoshida, Shouichi Fujimoto, and Koichi Asahi contributed to acquisition of data and critical revision of the manuscript. Issei Kurahashi and Yasuo Ohashi contributed to acquisition of data, statistical analysis, and interpretation of data. Tsuyoshi Watanabe contributed to the funding, acquisition of data, critical revision of the manuscript and study supervision. All authors provided critical reviews of the draft and approved the final version.

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ORIGINAL ARTICLE

A combination of healthy lifestyle factors is associated with a decreased incidence of chronic kidney disease: a population-based cohort study

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A combination of healthy lifestyle factors is associated with lower risks of coronary heart disease, diabetes and stroke, but little is known about its association with chronic kidney disease (CKD). This study analyzed the effect of a combination of healthy lifestyle factors on the incidence of proteinuria among participants without CKD. Of the 7565 persons aged 40–79 years who participated in the Specific Health Checkups and Guidance System in Sado Island, Japan in 2008, 4902 participants (2015 males) without CKD were included. The healthy lifestyle score was calculated by summing the total number of lifestyle factors for which the participants were at low risk. Low risk was defined as (1) nonsmoker, (2) body mass index (BMI) $<25\,kg\,m^{-2}$, (3) moderate or less alcohol consumption, (4) regular exercise and (5) better eating patterns. Logistic analysis was used to examine the relationship between the baseline score in 2008 and the development of proteinuria in 2009. Proteinuria developed in 2.2% of participants (males, 3.2; females, 1.5%). Compared with participants with a healthy lifestyle score of 0 to 2, participants with a score of 5 had a lower risk (odds ratio: 0.39, 95% confidence interval: 0.16–0.94), independently of having diabetes, hypertension and hypercholesterolemia. Overall, 47% of the cases in this cohort could be attributed to lack of adherence to this low-risk pattern. These findings underscore the importance of a healthier lifestyle in preventing CKD.
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Keywords: eating patterns; epidemiology; preventive factors; proteinuria

INTRODUCTION

A combination of healthy lifestyle factors, including abstaining from smoking, maintaining a BMI of $25\,kg\,m^{-2}$ or lower, consuming alcohol moderately, exercising regularly and having a healthy diet, produce a significant risk reduction for coronary heart disease,[1,2] type 2 diabetes mellitus[3] and stroke.[4] A clear linear relationship was observed between the risk reduction and the number of healthy lifestyle factors in each study, suggesting that an analysis using a combination of lifestyle factors may capture the influence of multiple health behaviors better than an analysis based on single health behaviors because health behaviors are complex and consist of multiple dimensions.

Chronic kidney disease (CKD) is also closely associated with lifestyle. Several lifestyle factors have been shown to be independently associated with primary prevention of CKD. Obesity, weight gain after maturity and metabolic syndrome increase the risk of CKD, independently of having diabetes mellitus and hypertension.[5–7] Cigarette smoking is also associated with an increased risk of CKD.[5,8–10] Alcohol may have both positive and negative effects. While moderate alcohol consumption is associated with a decreased risk,[5] heavy alcohol consumption is associated with an increased risk of CKD.[11] However, the combined effects of lifestyle factors on the risk of CKD have not been studied. CKD would also be closely associated with combined lifestyle modification rather than with changes in each factor alone.

Therefore, we hypothesized that a combination of healthy lifestyle factors would be associated with a significant reduction in the risk of CKD. The proportion of CKD that could theoretically be avoided through the simultaneous adoption of multiple types of low-risk behaviors was also estimated.

METHODS

Study design

A population-based cohort study of adults aged from 40 to 79 years in Sado City, Japan, who participated in the Specific Health Checkups and Guidance System (SHC) in 2008 and 2009, was performed. Sado City is an island located in the Sea of Japan off the coast of Niigata Prefecture, which is one of the most rapidly aging areas in Japan. The population on the island was 64 310 as of

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1 October 2008; >35% of the population was 65 years or older, of whom half was older than 75 years. This proportion of elderly is almost equal to the projected population of Japan in 2039.[12] The details of the SHC have been described elsewhere.[6,13] In brief, participants answered a self-administered questionnaire that covered their smoking, alcohol consumption, exercise and dietary habits. Then, trained staff measured the height, weight and blood pressure of each participant, after which serum and spot urine samples were collected.

Study participants

Participants aged from 40 to 79 years without CKD at baseline in 2008 were included. CKD was defined as a GFR $<60\,ml\,min^{-1}\,1.73\,m^{-2}$ calculated using the estimated GFR (eGFR) formula for Japanese,[14] 1+ or greater proteinuria on urinalysis, or both.[15] The data extraction process is shown in the Supplementary information. Of the 7565 participants aged 40 to 79 years screened in 2008, 6429 participants had normal renal function ($eGFR \geqslant 60\,ml\,min^{-1}\,1.73\,m^{-2}$) and negative proteinuria on dipstick examination. Of these participants with normal renal function, 4940 participants were re-examined in the 2009 SHC program. A total of 37 participants with missing information on lifestyle factors was excluded, leaving 4902 for this analysis. All of the participants remained anonymous, and the study was conducted according to Japanese privacy protection laws and the ethical guidelines for epidemiological studies published by the Ministry of Education, Science and Culture and the Ministry of Health, Labor and Welfare in 2005.

Outcomes ascertainment

The primary end point was incident proteinuria, defined by a dipstick urinalysis score of 1+ or greater proteinuria (equivalent to $\geqslant 30\,mg\,dl^{-1}$) because of poor discrimination between negative and trace positive dipstick readings,[16] at the SHC in 2009. Because the follow-up duration was relatively short and proteinuria is a significant risk factor for end-stage renal disease,[17,18] development of proteinuria, but not decreased GFR, was adopted as the end point in the present study.

Lifestyle factors and covariates

For each lifestyle factor (smoking, BMI, alcohol, exercise and eating patterns), a binary low-risk variable was created, where the participants were given a score of 1 if they met the criteria for low risk and a 0 if otherwise, in accordance with the previous studies.[1–4] The *a priori* definition of low risk was based on the current literature and recommended guidelines, as well as on the levels realistically obtainable within the general population. A healthy lifestyle score was calculated by summing the total number of lifestyle factors for which the participants were at low risk. The participants could obtain a healthy lifestyle score from 0 (least healthy) to 5 (most healthy).

For smoking, low risk was defined as not currently smoking. Optimal body weight was defined as a BMI $<25\,kg\,m^{-2}$, the standard World Health Organization cutoff for healthy weight. For alcohol, average daily alcohol consumption of less than 20 g was considered low risk, because previous literature showed that average daily alcohol intake of <20 g reduced the risk of developing proteinuria in men,[5] while intake of >30 g increased the risk of developing albuminuria.[19] For exercise, two questions were used. One was 'Are you in the habit of doing exercise to sweat lightly for over 30 min a time, 2 times weekly, for over a year?' the other was 'In your daily life do you walk or do any equivalent amount of physical activity more than one hour a day?' Low risk was defined as those who answered 'Yes' to both these questions on the basis of a current Japanese guideline.[20] For eating patterns, two questions were used. One was 'Do you skip breakfast more than 3 times per week?' and the other was 'Do you eat snacks after supper more than 3 times a week?' Low risk was defined as those who answered 'No' to both of these questions.

Diabetes mellitus was defined as the use of insulin or oral antidiabetic medications, hemoglobin A1c (HbA1c) ≥6.1%, or both. Hypertension was defined as the use of antihypertensive medications, a systolic blood pressure ≥140 mm Hg and/or a diastolic blood pressure ≥90 mm Hg, or both. Hypercholesterolemia was defined as the use of cholesterol-lowering medications, a low-density lipoprotein cholesterol level $\geqslant 140\,mg\,dl^{-1}$, or both.

Statistical analysis

Differences in the distribution of baseline characteristics across the healthy lifestyle score categories were compared using the χ^2 test for categorical variables and analysis of variance for continuous variables. Spearman and Pearson correlation coefficients were calculated to evaluate the relationships among the independent variables. The association between each variable of the healthy lifestyle scores and the incidence of proteinuria was first evaluated individually using logistic regression models, and then the association between the healthy lifestyle scores and the incidence of proteinuria was evaluated. A healthy lifestyle score from 0 (least healthy) to 2 was combined to make one category because of the small number of cases. Multivariate-adjusted odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were calculated using the category conventionally believed to be the least healthy as the reference group. Two multivariate models were developed. The data were initially adjusted for age and sex. Because hypertension, diabetes and hypercholesterolemia are likely to be intermediate factors in the pathway between lifestyle factors and proteinuria, they were added sequentially to the multivariate models.

To assess the robustness of the main results, several subsidiary analyses were conducted. First, to enhance the association between healthy lifestyle and the outcome, analyses stratified by obesity ($BMI \geqslant 25\,kg\,m^{-2}$) were conducted, because obese participants would modify their lifestyle to lose weight. For participants with obesity, the healthy lifestyle score ranged from 0 to 4 points. Scores from 0 to 2 were combined into one category because of the small number of cases. For participants without obesity, the healthy lifestyle score ranged from 1 to 5 points. Scores from 1 to 3 were combined into one category because of the small number of cases. Second, sensitivity analyses stratified by sex were conducted to establish whether sex had any effect on the relationship, because female sex is associated with a reduced risk of proteinuria. Finally, to avoid the possibility of antiproteinuric effects of medications, subgroup analyses stratified by use or nonuse of medications were conducted.

The population-attributable risk fraction and the corresponding 95% CIs[21] were calculated as an estimate of the percentage of developing proteinuria that would not have occurred in this population if all participants had been in the healthiest lifestyle group, on the assumption that there was a causal relation between the risk factors and CKD.

A *P*-value of <0.05 was considered significant, and all tests were two-tailed. All statistical analyses were performed with the SPSS for Windows statistical package (Version 18.0; SPSS, Chicago, IL, USA).

RESULTS

Demographic characteristics of patients

Table 1 shows the associations between various clinical characteristics and healthy lifestyle scores. Participants with a higher healthy lifestyle score had an older age, a lean BMI, a lower blood pressure, lower triglyceride levels, higher high-density lipoprotein cholesterol levels, a lower serum creatinine and a lower eGFR. Males were more likely to have a low healthy lifestyle score. While low-density lipoprotein cholesterol did not differ between the categories, the proportion of cholesterol-lowering medication users was higher in the categories with a high healthy lifestyle score. There were no differences between participants who repeated the program in 2009 and those who did not with regard to baseline characteristics such as sex and BMI, but the latter group was slightly younger and had a high rate of smoking, a higher percentage of medication for diabetes and a higher blood pressure (Supplementary information).

Associations between the healthy lifestyle score and proteinuria

After 1 year of follow-up, 110 (66 males) of the 4902 participants (2015 males) developed proteinuria. When considered individually, there were no apparent associations between each variable of the healthy lifestyle score and the incidence of proteinuria, except BMI (Table 2). There were no significant interactions among these variables.

Table 1 Clinical characteristics of the 4902 participants by healthy lifestyle score

Characteristics [a]	*Total* (N = 4902)	*Healthy lifestyle score* 0 (N = 6 [0.1%])	1 (N = 118 [2.4%])	2 (N = 498 [10.2%])	3 (N = 1405 [28.7%])	4 (N = 2239 [45.7%])	5 (N = 636 [13.0%])	P *for trend*
Age, years	66.7 (8.4)	64.8 (6.1)	58.1 (8.9)	62.6 (9.5)	65.7 (8.7)	67.8 (8.0)	68.4 (7.0)	<0.0001
Males, *n* (%)	2015 (41.1)	6 (100.0)	98 (83.1)	345 (69.3)	636 (45.3)	727 (32.5)	203 (31.9)	<0.0001
Current smoker, *n* (%)	619 (12.6)	6 (100.0)	97 (82.2)	233 (46.8)	224 (15.9)	59 (2.6)	0 (0.0)	<0.0001
Body mass index, kg m^{-2}	23.0 (3.1)	27.5 (1.4)	24.9 (3.1)	24.8 (3.5)	24.2 (3.3)	22.2 (2.5)	21.8 (2.0)	<0.0001
Alcohol > 20 g per day, *n* (%)	635 (13.0)	6 (100.0)	95 (80.5)	221 (44.4)	234 (16.7)	79 (3.5)	0 (0.0)	<0.0001
Regular exercise								
Exercise to sweat lightly, *n* (%)	1438 (29.3)	0 (0.0)	6 (5.1)	42 (8.4)	185 (13.2)	569 (25.4)	636 (100.0)	<0.0001
Walking > 1 h per day, *n* (%)	3467 (70.7)	2 (33.3)	76 (64.4)	301 (60.4)	935 (66.5)	1517 (67.8)	636 (100.0)	<0.0001
Eating pattern								
Snacks after supper, *n* (%)	708 (14.4)	3 (50.0)	40 (33.9)	208 (41.8)	345 (24.6)	112 (5.0)	0 (0.0)	<0.0001
Skipping breakfast, *n* (%)	329 (6.7)	5 (83.3)	59 (50.0)	99 (19.9)	123 (8.8)	43 (1.9)	0 (0.0)	<0.0001
Systolic pressure, mmHg	127 (17)	137 (19)	134 (17)	131 (17)	128 (17)	126 (16)	126 (15)	<0.0001
Diastolic pressure, mmHg	74 (10)	84 (13)	81 (11)	78 (11)	75 (10)	73 (10)	73 (10)	<0.0001
Antihypertensive medication, *n* (%)	1505 (30.7)	2 (33.3)	38 (32.2)	158 (31.7)	479 (34.1)	643 (28.7)	185 (29.1)	0.01
Hemoglobin A_{1c}, %	5.4 (0.6)	5.1 (0.2)	5.3 (0.7)	5.4 (0.7)	5.4 (0.6)	5.4 (0.5)	5.4 (0.6)	0.48
Antidiabetic medication, *n* (%)	220 (4.5)	0 (0.0)	1 (0.8)	31 (6.2)	78 (5.6)	79 (3.5)	31 (4.9)	0.24
LDL cholesterol, mg per 100 ml	128 (31)	117 (32)	126 (31)	125 (36)	128 (31)	128 (31)	129 (30)	0.03
Cholesterol-lowering medication, *n* (%)	697 (14.2)	0 (0.0)	11 (9.3)	49 (9.8)	198 (14.1)	335 (15.0)	104 (16.4)	<0.0001
Triglycerides, mg per 100 ml	111 (78, 156)	96 (81, 261)	134 (93, 212)	131 (90, 195)	116 (83, 165)	105 (75, 146)	103 (74, 144)	<0.0001
HDL cholesterol, mg per 100 ml	57 (14)	47 (10)	58 (16)	55 (14)	56 (14)	57 (14)	58 (14)	<0.0001
Creatinine, mg per 100 ml	0.67 (0.13)	0.80 (0.11)	0.73 (0.12)	0.71 (0.13)	0.67 (0.13)	0.65 (0.12)	0.65 (0.12)	<0.0001
eGFR, ml min^{-1} 1.73 m^{-2}	79 (13)	78 (8)	84 (15)	81 (13)	79 (13)	78 (14)	79 (13)	<0.0001
Outcome data								
Development of proteinuria, *n* (%)	110 (2.2)	0 (0.0)	4 (3.4)	19 (3.8)	41 (2.9)	39 (1.7)	7 (1.1)	<0.0001

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein.
The definitions of the clinical characteristics are described in the text.
[a]Numbers in the table shown are mean values (s.d.) for continuous variables except triglycerides (median and interquartile range) or numbers (percentages) for categorical variables.

A dose–response relationship was observed between the healthy lifestyle scores and the incidence of proteinuria for all participants ($P<0.0001$ for trend) and for females ($P=0.01$ for trend, Figure 1). A similar trend was observed for males, but it was not significant ($P=0.08$ for trend). Table 3 shows that participants with a score of 5 (healthiest category) had an age- and sex-adjusted OR of 0.35 (95% CI: 0.15–0.85) for the incidence of proteinuria compared with participants with a score of 0 to 2. Additional adjustment for the potential consequences of an unhealthy lifestyle (that is, hypertension, diabetes mellitus and hypercholesterolemia) only partially attenuated the risk (OR: 0.39, 95% CI: 0.16–0.94).

This analysis was repeated with participants who were not obese (BMI < 25 kg m^{-2}) (Table 4). The association between the healthy lifestyle score and the incidence of proteinuria showed a similar but slightly stronger association compared with the whole study population. Participants with a score of 5 had a multivariate-adjusted OR of 0.40 (95% CI: 0.17–0.92) for the incidence of proteinuria compared with participants with a score of 1 to 3. In contrast, the association was not significant among the participants with obesity. Subgroup analysis stratified by sex showed that the point estimates of the OR were similar in both male and female participants compared with the whole study population, although the association was not significant.

Of the participants who currently took antihypertensive medications, the association was similar but stronger than that for the whole study population. The association was not significant among the participants not on antihypertensive medications (data not shown). Of the participants who were not currently taking cholesterol-lowering medications, the association between the healthy lifestyle score and the incidence of proteinuria was similar to that of the whole study population (data not shown).

Population-attributable risk fraction among the cohorts

The population-attributable risk fraction was 47%, suggesting that nearly half of the incidence of proteinuria might have been prevented by compliance with the remaining components of the low-healthy lifestyle score in this population. The number of cases was too small, however, to provide separate estimates for the population-attributable risk fraction (95 CI: −8 to 74%).

DISCUSSION

The present study demonstrated that a combination of healthy lifestyle factors was associated with a substantial reduction in the development of proteinuria, even after controlling for well-known biological mediators such as hypertension, diabetes mellitus and hypercholesterolemia. Moreover, this finding was confirmed in subgroup analyses, such as in nonobese individuals or participants on antihypertensive medications. No significant results were obtained in subgroup analyses stratified by sex or obesity. This is probably due to the small number of participants, because the numbers of cases in the reference categories were small, which led to wide CIs. It is also possible that residual confounding by sex might affect the result in the whole study population, because males were more likely to have a low healthy lifestyle score, and female sex was strongly associated with a reduced risk of proteinuria. Although further study is needed to establish the association between the combined healthy lifestyle and CKD, these results also support the possibility that the combined healthy lifestyle could reduce the risk of developing CKD.

The combined effects of lifestyle factors, including abstaining from smoking, maintaining a BMI of 25 kg m^{-2} or lower, moderate or less alcohol consumption, regular exercise and healthy diet, have been reported to produce a significant risk reduction for coronary heart

Table 2 Multivariate analysis of the relationships between the components of the healthy lifestyle score and the incidence of proteinuria ($N=4902$)

Variable	*Model 1 odds ratios* [a] *(95% CI)*	*Model 2 odds ratios*[b] *(95% CI)*
Categories		
Current smoker		
Yes (ref)	1.00	1.00
No	0.67 (0.40–1.12)	0.66 (0.40–1.10)
Body mass index		
$\geqslant 25\,kg\,m^{-2}$ (Ref)	1.00	1.00
$<25\,kg\,m^{-2}$	0.54 (0.37–0.81)**	0.62 (0.41–0.93)*
Alcohol consumption		
⩾20 g per day (Ref)	1.00	1.00
<20 g per day	0.89 (0.53–1.49)	0.97 (0.57–1.65)
Regular exercise		
No (ref)	1.00	1.00
Yes	0.90 (0.58–1.42)	0.89 (0.57–1.40)
Eating pattern		
Less healthy (ref)	1.00	1.00
Healthy	0.88 (0.55–1.40)	0.87 (0.55–1.39)
Sex		
Male (ref)	1.00	1.00
Female	0.52 (0.34–0.81)**	0.58 (0.37–0.90)*
Age, years		
40–49 (Ref)	1.00	1.00
50–59	0.42 (0.17–1.03)	0.37 (0.15–0.92)*
60–69	0.60 (0.29–1.23)	0.50 (0.24–1.04)
70–79	0.74 (0.36–1.51)	0.56 (0.27–1.17)
Hypertension		
Yes (ref)		1.00
No		0.58 (0.38–0.87)**
Diabetes mellitus		
Yes (ref)		1.00
No		0.53 (0.31–0.90)*
Hypercholesterolemia		
Yes (ref)		1.00
No		1.12 (0.75–1.69)

Abbreviation: CI, confidence interval.
*$P<0.05$, **$P<0.01$.
[a]Adjusted for age, sex and the other components of the healthy lifestyle score.
[b]Adjusted for the variables in model 1 plus hypertension, diabetes and hypercholesterolemia.
The definitions of these factors are described in the text.

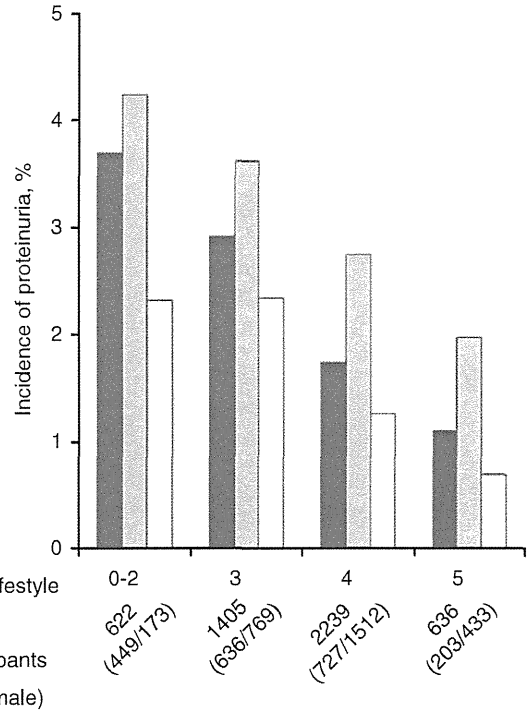

Figure 1 Incidence of proteinuria by healthy lifestyle score. Trends are significant for all participants (■; $P<0.0001$) and females (□; $P=0.01$), but not significant for males (▩; $P=0.08$).

disease,[1,2] type 2 diabetes mellitus[3] and stroke.[4] Because CKD is closely associated with these diseases, these results suggest that the combined healthy lifestyle might act in a common pathway to avoid developing these diseases. In addition, a clear linear reduction of risk has been observed based on adherence to the healthy lifestyle factors in each study. In other words, the more these healthy lifestyle factors are adhered to, the greater the reduction of the risks of these diseases. These suggest that not only single health behaviors but also a combination of these behaviors should be achieved to decrease the incidence of these diseases. Of course, an unhealthy lifestyle, such as poor dietary habits and inadequate physical activity, strongly influences blood pressure, glucose-insulin homeostasis and lipid levels. Furthermore, these lifestyle risk factors also seem to influence novel risk factors such as endothelial dysfunction, oxidative stress, inflammation and other intermediary pathways.[22] Further research is needed to clarify the combined effect of the healthy lifestyle factors on the primary prevention of these chronic diseases.

With regard to individual components of the healthy lifestyle score, there was no significant reduction of CKD risk except for BMI. Previous literature has shown that obesity,[5–7] cigarette smoking[5,8–10] and heavy alcohol consumption[11,19] are independently associated with an increased risk of CKD. As for smoking and alcohol, the small numbers of cases in the present study might limit the power to detect these possible associations. It is also possible that using binary variables could not detect this association between alcohol and CKD, because alcohol may have both positive and negative effects.[5,11,19] As for exercise, one study showed that physical inactivity was associated with the risk of CKD in the general population,[23] but epidemiological studies of this relationship are sparse. As for diet, a classical nutritional factor investigated as a risk factor for CKD has primarily been salt intake,[24] but information about eating patterns, such as snacking and skipping breakfast, in the primary prevention of CKD has been lacking. A growing body of evidence suggests that eating patterns may affect body weight. Although it remains controversial whether snacking contributes to obesity,[25] a positive association between skipping breakfast and obesity is globally observed, independent of cultural diversity among countries.[26–30] In addition, skipping breakfast has been found to be associated with increased blood pressure in adolescents[31] and with health-compromising behaviors in adults and adolescents.[32] These suggest that these lifestyle factors cooperate with one another, and a combined effect of the healthy lifestyle factors on the primary prevention of CKD would be

Table 3 Multivariate analysis of the relationship between the healthy lifestyle score and the incidence of proteinuria ($N=4902$)

Variable	*Age- and sex-adjusted odds ratio (95% CI)*	*Multivariate odds ratio[a] (95% CI)*
Healthy lifestyle score		
0–2 (Ref)	1.00	1.00
3	0.89 (0.52–1.52)	0.94 (0.55–1.61)
4	0.56 (0.32–0.98)*	0.63 (0.36–1.10)
5	0.35 (0.15–0.85)*	0.39 (0.16–0.94)*
Sex		
Male (ref)	1.00	1.00
Female	0.52 (0.35–0.78)**	0.58 (0.38–0.87)**
Age, years		
40–49 (ref)	1.00	1.00
50–59	0.41 (0.17–1.00)	0.36 (0.15–0.89)*
60–69	0.59 (0.29–1.21)	0.49 (0.24–1.00)
70–79	0.72 (0.35–1.46)	0.54 (0.26–1.12)
Hypertension		
Yes (ref)		1.00
No		0.57 (0.38–0.85)**
Diabetes mellitus		
Yes (ref)		1.00
No		0.52 (0.30–0.87)*
Hypercholesterolemia		
Yes (ref)		1.00
No		1.09 (0.73–1.63)

Abbreviation: CI, confidence interval.
*$P<0.05$, **$P<0.01$.
[a]Adjusted for age (years), sex, hypertension, diabetes and hypercholesterolemia. The definitions of these factors are described in the text.

Table 4 Subgroup analyses of the relationship between the healthy lifestyle score and the incidence of proteinuria

Healthy lifestyle score	*Age- and sex-adjusted odds ratio (95% CI)*	*Multivariate odds ratio[a] (95% CI)*
Nonobese individuals ($N=3724$)		
1–3 (Ref)	1.00	1.00
4	0.55 (0.32–0.93)*	0.56 (0.33–0.95)*
5	0.40 (0.17–0.94)*	0.40 (0.17–0.92)*
Obese individuals ($N=1178$)		
0–2 (Ref)	1.00	1.00
3	0.92 (0.43–1.97)	0.97 (0.45–2.06)
4	1.60 (0.64–3.98)	1.71 (0.69–4.27)
Males ($N=2015$)		
0–2 (Ref)	1.00	1.00
3	0.87 (0.46–1.63)	0.88 (0.47–1.66)
4	0.67 (0.34–1.29)	0.71 (0.36–1.38)
5	0.49 (0.16–1.42)	0.47 (0.15–1.43)
Females ($N=2887$)		
0–2 (Ref)	1.00	1.00
3	0.92 (0.30–2.775)	1.07 (0.35–3.25)
4	0.46 (0.15–1.40)	0.55 (0.18–1.69)
5	0.25 (0.05–1.14)	0.31 (0.07–1.41)
Participants on antihypertensive medications ($N=1505$)		
0–2 (Ref)	1.00	1.00
3	0.82 (0.39–1.73)	0.81 (0.38 –1.71)
4	0.38 (0.17–0.90)*	0.32 (0.17 –0.90)*
5	0.19 (0.04–0.87)*	0.13 (0.04 –0.88)*

Abbreviation: CI, confidence interval.
*$P<0.05$.
[a]Adjusted for age (years), sex, hypertension, diabetes and hypercholesterolemia. The definitions of these factors are described in the text.

significant, whereas the individual effects of each factor might be weak or insignificant.

The present study also demonstrated that the population-attributable risk fraction was 47%, suggesting that nearly half of the cases of *de novo* proteinuria might be prevented by comprehensive lifestyle modification. In addition, the present study showed that the participants who were at low risk for the five lifestyle factors had a significant risk reduction, nearly the same as those without hypertension or diabetes. Much effort has been focused on the pharmacologic management of hypertension, diabetes mellitus and hypercholesterolemia for preventing CKD. Although these treatments have been proven to have benefits, they are costly and may have adverse effects. In general, modification of lifestyle is not costly and may not be associated with adverse effects. Therefore, a healthy lifestyle could play a central part in the global war against CKD.

This study has several strengths. To the best of our knowledge, this is the first report about the combined effects of health-related behaviors on the risk of CKD. Because all the participants lived on one small island, the relatively homogenous nature of the cohort would reduce confounding. However, the generalizability to other populations may be limited. Further investigations in other populations are necessary to confirm the present findings. In addition, the population-attributable risk fraction, which provided potentially valuable information regarding the community-level effect of healthy lifestyle factors, was also calculated.

Study limitation

The present study had several limitations. First, the lifestyle factors other than BMI were determined based on information obtained through self-reporting and may not have been accurate. In addition, the duration of maintaining a healthy lifestyle and the nutritive content of the diet were not evaluated because of a lack of information. Second, despite adjustments for potential confounding factors, residual confounding remains plausible. For example, socioeconomic status was not adjusted for because there was no information. Third, CKD was defined from a single creatinine value and a single measurement of urinary protein because of the nature of an annual health check program. Therefore, it is not possible in this study to confirm whether participants fulfilled CKD criteria for at least a 3-month period. However, the incidence of proteinuria was similar to that in the previous study.[8] Fourth, the relationship between the healthy lifestyle score and the incidence of proteinuria is influenced by the weight given to each component of the score. We chose to give equal weight to each healthy lifestyle factor, in accordance with previous studies,[1–4] and this would make the study a clear-cut message for the prevention of coronary heart disease, type 2 diabetes mellitus, stroke and CKD; it provides a simple strategy to minimize the overall incidence of these chronic diseases. However, because the use of equal weights is an imperfect approximation of the underlying biological relationships between lifestyle and CKD, future analyses should examine this issue. Fifth, the present study contained

small numbers of outcome events and participants, which may explain the wide CIs. Sixth, there may have been selection bias in the study population, because the subjects included in the study received annual physical checks for the second consecutive year; subjects with severe disorders or signs or symptoms tended to attend clinics and hospitals, and thus they did not receive annual physical checks. Finally, the follow-up duration was relatively short. However, as the Specific Health Checkups and Guidance System are ongoing all over Japan, the reproducibility of this study could be assessed by studies with larger sample sizes and longer observation periods if many local governments would work cooperatively. Further research is also needed to assess the relationship between improving the healthy lifestyle factors and the incidence of proteinuria.

In conclusion, a healthy lifestyle was associated with a significant reduction in the risk of CKD, independent of having diabetes mellitus, hypertension and hypercholesterolemia. The present data indicate the possibility that a substantial number of cases of CKD could be prevented by the adoption of a healthier lifestyle. Further investigations in other populations and with longer observation periods are necessary to confirm the present findings.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on Hypertension Research website (http://www.nature.com/hr)