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【 ORIGINAL ARTICLE 】

Healthy Lifestyle and Incident Hypertension and Diabetes in Participants with and without Chronic Kidney Disease: The Japan Specific Health Checkups (J-SHC) Study

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Abstract:

Objective Whether or not combined lifestyle factors are associated with similar decreases in risks of incident hypertension and diabetes among individuals with and without chronic kidney disease (CKD) remains unclear.

Methods This population-based prospective cohort study included participants 40-74 years old who were free from heart disease, stroke, renal failure, hypertension, diabetes, and hypercholesterolemia at baseline (n =60,234). Healthy lifestyle scores (HLSs) were calculated by adding the total number of 5 healthy lifestyle factors (non-smoking, body mass index <25 kg/m^2, regular exercise, healthy eating habits, and moderate or less alcohol consumption). Cox proportional hazards models were used to examine associations between the HLS and incident hypertension or type 2 diabetes and whether or not CKD modified these associations.

Results During a median of 4 years, there were 2,773 incident hypertension cases (30.1 cases per 1,000 person-years) and 263 incident diabetes cases (2.4 cases per 1,000 person-years). The risk of developing hypertension and diabetes decreased linearly as participants adhered to more HLS components. Compared with adhering to 0, 1, or 2 components, adherence to all 5 HLS components was associated with a nearly one-half reduction in the risk of hypertension [hazard ratio (HR) =0.52; 95% confidence interval (CI), 0.45-0.60] and diabetes (HR=0.51; 95% CI, 0.32-0.81) in fully adjusted models. CKD did not have a modifying effect on associations between the HLS and incident hypertension ($P_{interaction}$=0.6) or diabetes ($P_{interaction}$=0.3).

Conclusion Adherence to HLS components was associated with reduced risks of incident hypertension and diabetes, regardless of CKD status.

Key words: CKD, diabetes mellitus, hypertension, obesity, physical activity

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Introduction

Adherence to healthy lifestyle factors is associated with a reduced risk of incident type 2 diabetes and hypertension in the general population (1-6). A systematic review and meta-analysis of prospective cohort studies summarized the relationship between combined lifestyle factors (including, but not limited to, smoking, alcohol drinking, physical activity, diet, and being overweight or obese) and incident type 2 diabetes (1). Compared with participants considered to have the least-healthy lifestyle, those with the healthiest lifestyle had a 75% lower risk of incident diabetes (1). A dose-dependent relationship between combined lifestyle factors

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and incident hypertension has also been reported (2-6). Furthermore, a population-based cohort study using data from the United Kingdom (UK) Biobank found no significant interaction between lifestyle factors and genetic risk, indicating that adherence to multiple ideal health behaviors effectively prevents diabetes and hypertension, even in individuals with a high genetic risk (6).

It remains unclear, however, whether or not combined lifestyle factors are associated with similar decreases in risks of incident hypertension and diabetes among individuals with and without chronic kidney disease (CKD). This information is clinically relevant because individuals with CKD may be at high risk of developing type 2 diabetes and hypertension. The rate of incident type 2 diabetes among individuals with CKD is markedly higher than in the general population (7, 8). The prevalence of hypertension is also high among patients with CKD (ranging from 60-90%, depending on the stage of CKD and its cause) (9). Furthermore, higher blood pressure levels are associated with a higher risk for incident CKD (10) as well as CKD progression (11). Thus, establishing the effect of combined lifestyle factors on preventing hypertension would be of clinical importance for both individuals with and without CKD.

Against this backdrop, the present study aimed to use data from a Japanese nation-wide prospective cohort study to calculate a healthy lifestyle score (HLS) from five lifestyle risk factors that are largely modifiable [smoking, body mass index (BMI), physical activity, eating habits, and alcohol consumption] (12-15) and to examine the prospective association between the HLS and incident hypertension and diabetes. Our goals were to (i) evaluate the association between the HLS and incident hypertension and diabetes in the total cohort (including participants with and without CKD), (ii) examine whether the associations varied by the presence of CKD, and (iii) estimate the population attributable fractions (PAFs) of HLS for incident hypertension and diabetes. As a secondary objective, the present study aimed to explore the independent association between each HLS component and incident hypertension and diabetes.

Materials and Methods

Data source and study design

This is a longitudinal study of individuals who participated in the nationwide Specific Health Checkup program in Japan between 2008 and 2014 [the Japan Specific Health Checkups (J-SHC) study] (16-19). Details of this cohort study and the program have been published previously (20), and more recent data have been added since that report (16-19). In brief, the Japanese government initiated the program in 2008 to support the early diagnosis of and intervention for metabolic syndrome for all insured persons and their dependents 40-74 years old throughout Japan. The databases used in this study were based in Fukushima, Ibaraki, Niigata, Osaka, Fukuoka, Miyazaki, and Okinawa Prefectures. Participants in the program answer a self-administered questionnaire that covers their medical history, smoking habits, alcohol intake, exercise habits, and eating habits. Trained staff members measure the height, weight, and blood pressure of each participant. Serum and spot urine samples are collected to measure chemical data.

This study was conducted according to the principles of the Declaration of Helsinki, as well as the Ethical Guidelines for Medical and Health Research Involving Human Subjects published by the Ministry of Education, Science, and Culture and the Ministry of Health, Labour and Welfare in 2015. The study protocol was approved by the Ethics Committee of Fukushima Medical University. The need for informed consent was waived due to the use of de-identified information.

Study population

Participants who underwent the Specific Health Checkup in 2008 with available lifestyle factors; who were free from heart disease, stroke, renal failure, hypertension (blood pressure ≥140/90 mmHg or the use of antihypertensive drugs), diabetes [hemoglobin A1c (HbA1c) ≥6.5%, fasting blood sugar level ≥126 mg/dL, or the use of anti-hyperglycemic drugs], and hypercholesterolemia [low-density lipoprotein (LDL) cholesterol level ≥140 mg/dL or the use of cholesterol-lowering medication]; and who underwent the Specific Health Checkup at least once between 2009 and 2014 were eligible. Exclusion criteria were participants with missing information on baseline serum creatinine and urinalysis. Participants with a prevalent prediabetic state (HbA1c >5.6% and/or fasting blood sugar ≥110 mg/dL) or prehypertension (blood pressure ≥120/80 mmHg) were also excluded per outcome.

HLS

We assigned scores for individual HLS components as previously described (Table 1) (12-15). The HLS was calculated as the sum of the score from each component and ranged from 0 (least healthy) to 5 (healthiest), in accordance with previous studies (12-15, 21-31). The HLS was the primary exposure, and its individual components were secondary exposures.

For smoking, a low risk was defined as not currently smoking (12-15). Optimal body weight was defined as a BMI <25 kg/m^2, the standard World Health Organization cut-off for healthy weight, in agreement with previous studies (12-15, 21-23). For exercise habits, those who answered 'Yes' to both questions were considered to be at low risk (12-15) based on current Japanese guidelines (32). Healthy eating habits were defined as eating breakfast and not eating snacks after dinner because our dataset did not include specific nutrition or food data. Those who answered 'No' to both skipping breakfast and eating snacks after dinner were considered to be at low risk (12-15). For alcohol consumption, low risk was defined as an average daily alcohol consumption <20 g (12-15).

Table 1. Components and Definitions of Healthy Lifestyle Score (HLS).

Component	Unhealthy (0 point)	Healthy (1 point)
Smoking	Current smoker	Never or ex-smoker
Body mass index	≥25 kg/m^2	<25 kg/m^2
Regular exercise		
Two questions were posed:		
Are you in the habit of exercising to light sweat for more than 30 minutes at a time, 2 times weekly, for over a year?	'No' to one or two questions	'Yes' to both questions
In your daily life, do you walk or do any equivalent amount of physical activity for longer than one hour a day?		
Eating habits		
Two questions were posed:		
Do you skip breakfast more than 3 times per week?	'Yes' to one or two questions	'No' to both questions
Do you eat snacks after supper more than 3 times a week?		
Alcohol intake	≥20 g/day	<20 g/day

HLS is the sum of each component, ranging from 0 (least healthy) to 5 (healthiest).

Baseline covariates

Estimated glomerular filtration rate (eGFR) was calculated using the eGFR formula for Japanese individuals (33). Proteinuria was defined as a dipstick urinalysis score of 1+ or greater (equivalent to ≥30 mg/dL). CKD was defined as the presence of proteinuria, an eGFR <60 mL/min/1.73 m^2, or both at baseline (34). Absence of proteinuria with an eGFR ≥60 mL/min/1.73 m^2 was defined as "non-CKD."

Outcome measurement

Study outcomes were incident hypertension or diabetes at the annual medical checkup program during the follow-up period (2009-2014). New-onset hypertension was defined as blood pressure ≥140/90 mmHg or the use of antihypertensive medication. New-onset diabetes was defined as HbA1c ≥6.5%, fasting blood sugar level ≥126 mg/dL, or the use of anti-hyperglycemic drugs (35). The date of participation in the Specific Health Checkup in 2008 was used as the index date. The date of the annual medical checkup program when fulfilling the above criteria was defined as the date of onset.

Statistical analyses

We first examined the association between the HLS and incident hypertension or diabetes, adjusted for CKD status, in the total cohort (including participants with and without CKD). Baseline HLSs of 0, 1, and 2 were combined into a single category due to the limited number of cases. Associations of the baseline HLS (primary exposure) and its individual components (secondary exposures) with incident events of hypertension or diabetes were assessed in univariable and multivariable Cox proportional hazards regression analyses. The assumption of proportional hazards was checked using Schoenfeld residuals and evaluated graphically and found to not be in violation. All models were analyzed unadjusted and adjusted for potential covariates identified *a priori*. The initial model tested the main effect of HLS as a categorical variable on incident events of hypertension or diabetes, after adjusting for age and sex. The second, fully adjusted model added terms for systolic blood pressure, HbA1c, LDL cholesterol, and CKD status.

Several analyses were performed to test the robustness of the data. First, the analysis was repeated after excluding early events (<2 years) to rule out reverse causality. Second, the analysis was repeated after adjusting for the eGFR and proteinuria, rather than the CKD status. Third, the analysis was repeated after adjusting for fasting blood sugar levels, rather than HbA1c. Fourth, the analysis was repeated using the average HLS during the study period, instead of the baseline HLS. The HLS was calculated for each visit, and the visit-specific HLS was then averaged across all non-missing visits to yield the average HLS. Stratified analyses were also conducted to test the consistency of results by sex and age (≤60 and >60 years).

Associations stratified by the CKD status were then examined to determine whether or not associations between the HLS and outcomes varied by the presence of CKD. Interactions were tested by including a cross-product term along with the main effect terms in the models. To investigate the combined impact of the HLS and CKD status on outcomes, multivariable-adjusted hazard ratios (HRs) and 95% confidence interval (CIs) of participants with and without CKD with a higher HLS were estimated, as well as for participants with CKD with a lower HLS, and compared to those without CKD and with the lowest HLS as the reference category.

Finally, adjusted PAFs and 95% CIs were calculated to estimate the proportion of incident cases that would not have occurred if all participants had been in the healthiest lifestyle group, assuming that the observed associations represent causal effects. All reported p values were two-sided, and values <0.05 were considered statistically significant except for tests of interaction. All statistical analyses were performed using Stata 16 (StataCorp., College Station, USA).

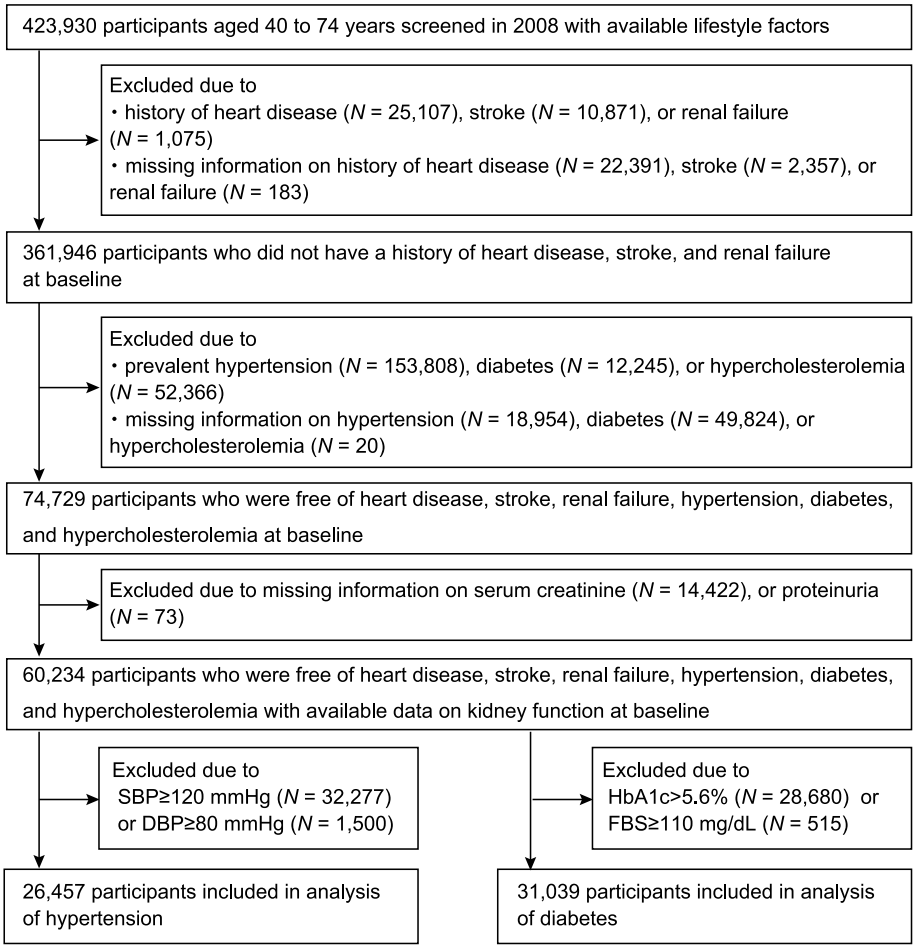

Figure 1. Flowchart for the selection of the analyzed study sample.

Results

Participant flow and characteristics

Of the 423,930 individuals 40-74 years old with available lifestyle factors who participated in the Specific Health Checkup program in 2008, 74,729 were free from heart disease, stroke, renal failure, hypertension, diabetes, and hypercholesterolemia at baseline (Fig. 1). Among these participants, 60,234 with baseline serum creatinine and urinalysis data were included in the analyses. Characteristics of participants with and without baseline data on the kidney function were similar (Supplementary material 1). Participants with advanced CKD stage were more likely to be excluded due to the high prevalence of comorbidities (Supplementary material 2). Participants with prevalent prehypertension or prediabetic status were excluded per outcome, leaving 26,457 participants for the analysis for hypertension and 31,039 for diabetes.

Hypertension

Among the 26,457 participants who were free from prehypertension at baseline, those with a higher HLS at baseline were more likely to be older, have CKD, and less likely to be male (Table 2). Among the included participants, 2,975 (11.2%) had CKD, of which the majority (79.5%) had an eGFR in the range of 45-59 mL/min/1.73 m^2 (Supplementary material 3). During a median follow-up of 4 years (25th percentile: 2; 75th percentile: 5), we identified 2,773 incident hypertension cases (30.1 cases per 1,000 person-years). Both the HLS and CKD were significantly associated with incident hypertension (Table 3). In unadjusted and adjusted models, a higher HLS was monotonically associated with a lower risk of incident hypertension. Compared with the lowest category of HLS (0-2), participants in the healthiest group exhibited a 48% relative reduction in the risk of developing hypertension (HR: 0.52; 95% CI: 0.45-0.60) in the fully adjusted model. The PAF was 22.4% (95% CI: 15.7-28.6%), suggesting that nearly one-fifth of hypertension cases in this cohort might have been prevented if all participants had been in the low-risk group.

Results from the sensitivity analyses were consistent with the primary analyses (Supplementary material 4). Excluding early events (<2 years), adjusting for the eGFR and proteinuria instead of CKD status, and adjusting for fasting blood sugar levels instead of HbA1c produced similar results. The results were also similar when using the average HLS instead of the baseline HLS. The average HLS was highly correlated with the baseline HLS (Supplementary material

Table 2. Baseline Characteristics of 26,457 Participants Included in the Analysis of Hypertension According to Healthy Lifestyle Score.

Characteristics	Healthy lifestyle score at baseline						p for trend
	0 [n=27 (0.1%)]	1 [n=555 (2.1%)]	2 [n=2,338 (8.8%)]	3 [n=6,531 (24.7%)]	4 [n=12,449 (47.1%)]	5 [n=4,557 (17.2%)]	
Age, years	52±9	52±9	55±10	57±10	59±9	63±8	<0.001
Males (%)	74.1	70.6	60.8	41.6	24.6	27.3	<0.001
Current smoker (%)	100.0	92.1	67.8	25.5	3.0	0.0	<0.001
Body mass index, kg/m^2	26.3±0.9	23.4±3.6	22.7±3.4	22.0±3.1	20.9±2.4	20.9±2.1	<0.001
Alcohol >20 g/day (%)	100.0	75.0	43.4	18.0	3.9	0.0	<0.001
Exercise habit							
Exercise to light sweat (%)	25.9	13.0	17.6	22.1	29.2	100.0	<0.001
Walking >1 h per day (%)	29.6	28.6	35.8	38.3	43.6	100.0	<0.001
Eating habit							
Snacks after supper (%)	48.1	43.8	37.8	34.7	5.5	0.0	<0.001
Skipping breakfast (%)	70.4	66.3	37.5	18.8	2.4	0.0	<0.001
Systolic BP, mmHg	110±7	109±7	108±8	107±8	107±8	108±8	<0.001
Diastolic BP, mmHg	66±7	68±7	67±7	66±7	65±7	66±7	<0.001
Fasting blood sugar, mg/dL	94±10	92±10	91±10	90±9	89±9	90±9	<0.001
Hemoglobin A1c, %	5.4±0.4	5.4±0.3	5.5±0.3	5.5±0.3	5.5±0.3	5.6±0.3	<0.001
LDL cholesterol, mg/dL	109±22	104±22	109±21	110±19	111±19	112±18	<0.001
CKD (%)	7.4	6.8	10.1	9.8	11.2	14.6	<0.001
Stage 1-2 (%)	3.7	3.2	3.3	1.9	1.8	1.4	<0.001
G3a (%)	3.7	3.6	6.5	7.7	9.0	12.6	
G3b-5 (%)	0.0	0.0	0.3	0.2	0.4	0.7	
Proteinuria (%)	3.7	3.4	3.8	2.2	2.1	1.6	<0.001
Serum Cr, mg/dL	0.78±0.16	0.73±0.14	0.73±0.16	0.69±0.16	0.67±0.16	0.70±0.29	<0.001
eGFR, mL/min/1.73 m^2	79±15	84±15	81±15	80±16	78±16	74±14	<0.001

Data are presented as mean±standard deviation or percentage.

BP: blood pressure, CKD: chronic kidney disease, Cr: creatinine, eGFR: estimated glomerular filtration rate, LDL: low-density lipoprotein

Table 3. Number, Crude Incidence Rate, and Hazard Ratio (95% CI) of Incident Hypertension According to Healthy Lifestyle Score.

	No. of incident hypertension	Rate (95% CI)[a]	HR (95% CI)		
			Unadjusted	Age/sex adjusted	Multivariable adjusted[b]
HLS					
0-2	386	38.6 (34.9-42.7)	1 (ref.)	1 (ref.)	1 (ref.)
3	743	33.1 (30.8-35.6)	0.86 (0.76-0.97)	0.78 (0.69-0.88)	0.80 (0.70-0.90)
4	1,204	27.5 (26.0-29.1)	0.71 (0.63-0.80)	0.59 (0.53-0.67)	0.62 (0.54-0.69)
5	440	27.7 (25.2-30.4)	0.72 (0.62-0.82)	0.50 (0.44-0.58)	0.52 (0.45-0.60)
HR for trend[c]			0.88 (0.84-0.92)	0.79 (0.75-0.83)	0.80 (0.76-0.84)
CKD status					
Non-CKD	2,345	28.5 (27.4-29.7)	1 (ref.)	1 (ref.)	1 (ref.)
CKD	428	43.5 (39.6-47.8)	1.56 (1.41-1.73)	1.37 (1.27-1.48)	1.29 (1.17-1.44)

[a]per 1,000 person-years.

[b]Adjusted for sex, age, systolic blood pressure, hemoglobin A1c, LDL cholesterol, and CKD status.

[c]HR for trend was calculated by entering the exposure categories as a continuous term in the Cox model.

CI: confidence interval, HLS: healthy lifestyle score, HR: hazard ratio

5A). The results were also similar when stratified by sex ($P_{interaction}$=0.5; Supplementary material 6) or age ($P_{interaction}$=0.1; Supplementary material 7).

No effect modification was observed by the presence of CKD ($P_{interaction}$=0.6; Supplementary material 8). When all groups were compared to a single combined non-CKD group with unhealthy lifestyle category as the reference, the CKD group with HLSs of 4 and 5 had a significantly lower risk of hypertension than the reference (Fig. 2A).

Each HLS component showed significant inverse associa-

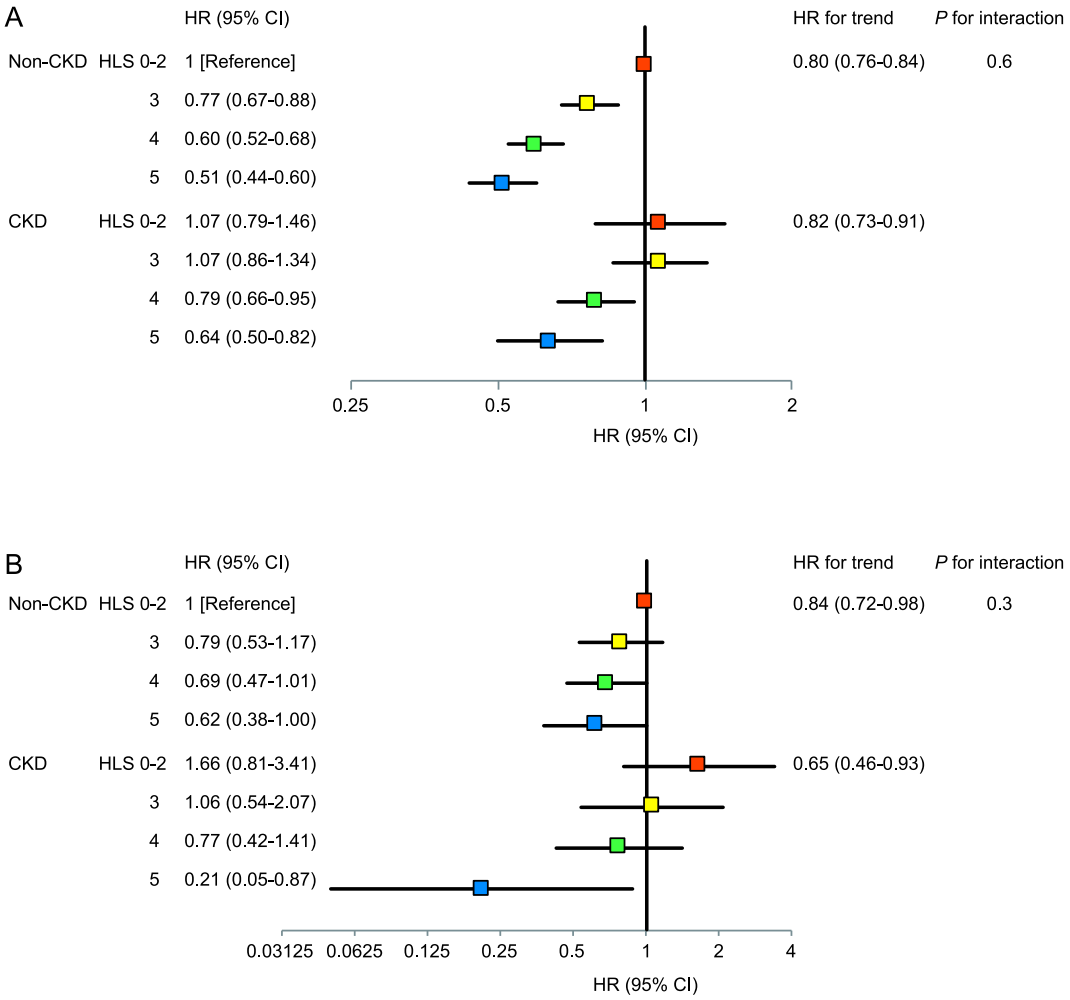

Figure 2. Associations of the baseline HLS with incident hypertension (A) and diabetes (B) by CKD status. The least healthy, non-CKD group is the reference group. Adjusted for age, sex, systolic blood pressure, HbA1c, and LDL cholesterol. The HR for trend indicates the change in the HR by changing one lifestyle category in a healthy direction. Error bars indicate 95% CIs. CI: confidence interval, CKD: chronic kidney disease, HLS: healthy lifestyle score, HR: hazard ratio

tions with hypertension for all five components after taking the remaining lifestyle factors into account (Supplementary material 9). When stratified by CKD, only smoking status was modified by CKD status ($P_{interaction}$=0.02; Fig. 3A). Non-smoking was associated with a significantly reduced risk of incident hypertension (HR: 0.58; 95% CI: 0.45-0.75), with a PAF of 8.0% (95% CI: 5.0-10.8%) in participants with CKD (Supplementary material 10).

Diabetes

Among the 31,039 included participants who were free from prediabetic status at baseline, those with a higher HLS at baseline were more likely to be older, have CKD, and less likely to be male (Table 4). Among the included participants, 3,552 (11.4%) had CKD, of which the majority (76.9%) had an eGFR in the range of 45-59 mL/min/1.73 m^2 (Supplementary material 11). During a median follow-up of 4 years (25th percentile: 2; 75th percentile: 5), we identified 263 incident diabetes cases (2.4 cases per 1,000 person-years). HLS, but not CKD, was significantly associated with incident diabetes (Table 5). In unadjusted and adjusted models, a higher HLS was monotonically associated with a lower risk of incident diabetes. Compared with the lowest category of HLS (0-2), participants in the healthiest group exhibited a 49% relative reduction in the risk of developing diabetes (HR: 0.51; 95% CI: 0.32-0.81) in the fully adjusted model. The PAF was 27.4% (95% CI: 1.3-46.6%).

Results from sensitivity analyses were consistent with the primary analyses (Supplementary material 12). Excluding early events (<2 years), adjusting for the eGFR and proteinuria instead of CKD status, and adjusting for fasting blood sugar levels instead of HbA1c produced similar results. The results were also similar when using the average HLS instead of the baseline HLS. The average HLS was highly correlated with the baseline HLS (Supplementary material 5B). The results were also similar when stratified by sex ($P_{interaction}$=0.9; Supplementary material 13). Age ($P_{interaction}$= 0.01; Supplementary material 14) modified the association

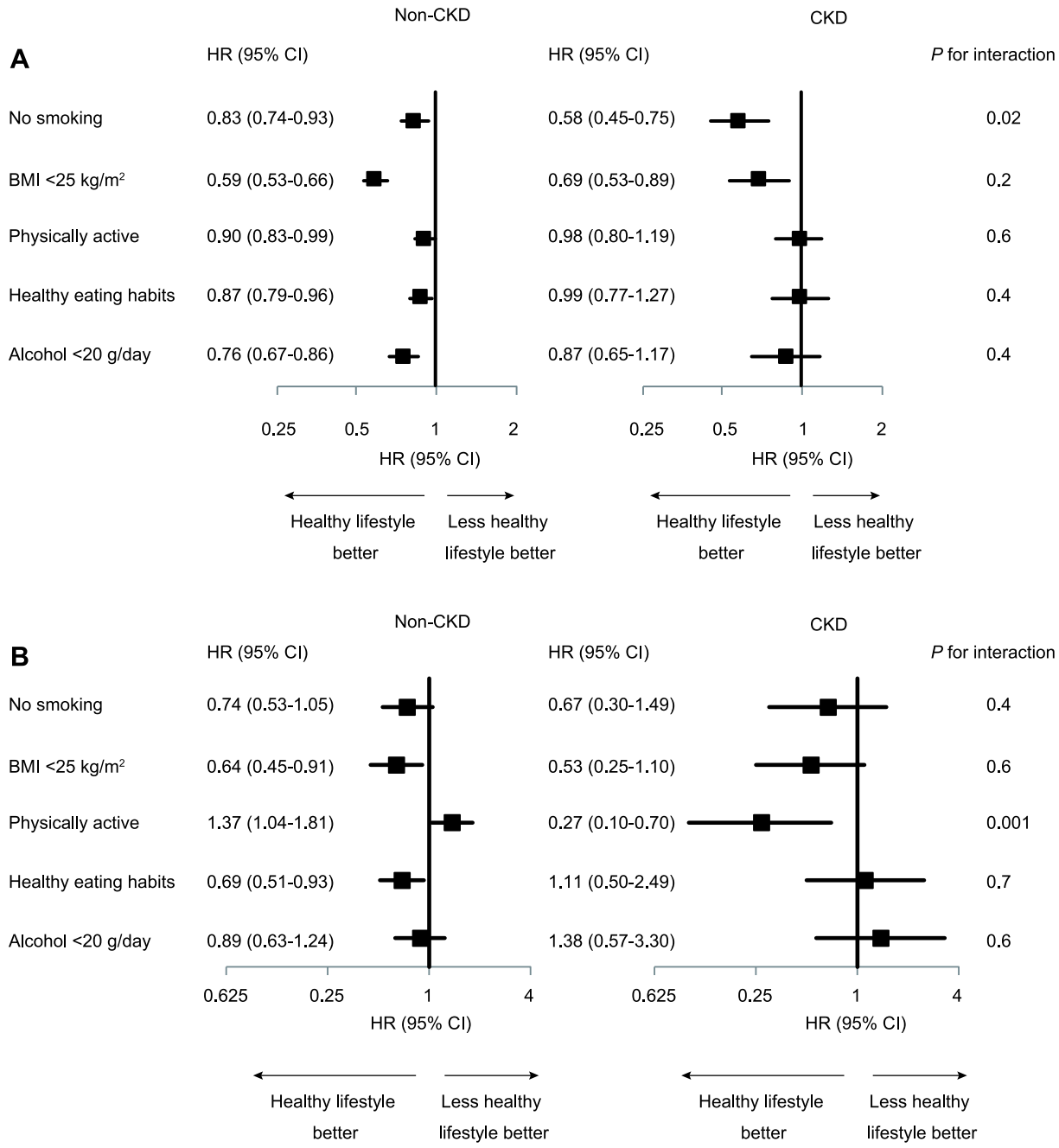

Figure 3. Associations between each HLS component and incident hypertension (A) and diabetes (B) by CKD status. Adjusted for age, sex, systolic blood pressure, HbA1c, LDL cholesterol, and other lifestyle factors. $P_{interaction}$ shows the results of fitting an interaction term between each HLS component and CKD (i.e. each HLS component ×CKD). BMI: body mass index, CI: confidence interval, HLS: healthy lifestyle score, HR: hazard ratio. Error bars indicate 95% CIs.

between the HLS and incident diabetes, with a non-significant association with the HLS in the older age group.

No effect modification was observed by the presence of CKD ($P_{interaction}$=0.3; Supplementary material 15). Notably, the PAF in patients with CKD was 72.1% (95% CI: 11.2-91.2%). When all groups were compared to a single combined non-CKD group with the unhealthy lifestyle category as the reference, the CKD group with the healthiest lifestyle category had a significantly lower risk of diabetes than the reference (Fig. 2B).

When each HLS component was analyzed individually, we found significant inverse associations between the risk of incident diabetes and non-smokers (HR: 0.73; 95% CI: 0.53-0.99), BMI <25 kg/m^2 (HR: 0.62; 95% CI: 0.45-0.84), and healthy eating habits (HR: 0.73; 95% CI: 0.55-0.97) (Supplementary material 16). When stratified by CKD, only regular exercise was modified by CKD ($P_{interaction}$<0.001; Fig. 3B). Being physically active was associated with a significantly lower risk of incident diabetes (HR: 0.27; 95% CI: 0.10-0.70), with a PAF of 63.2% (95 % CI: 32.6-79.9%) in patients with CKD (Supplementary material 17).

Table 4. Baseline Characteristics of 31,039 Participants Included in the Analysis of Diabetes According to Healthy Lifestyle Score.

Characteristics	Healthy lifestyle score at baseline						p for trend
	0 [n=67 (0.2%)]	1 [n=822 (2.6%)]	2 [n=3,186 (10.3%)]	3 [n=7,921 (25.5%)]	4 [n=13,925 (44.9%)]	5 [n=5,118 (16.5%)]	
Age, years	51±9	53±9	56±10	58±10	60±10	64±8	<0.001
Males (%)	80.6	74.6	65.9	47.6	30.7	33.7	<0.001
Current smoker (%)	100.0	89.8	61.1	21.7	2.6	0.0	<0.001
Body mass index, kg/m^2	26.5±1.4	23.3±3.5	23.0±3.4	22.4±3.1	21.2±2.4	21.2±2.1	<0.001
Alcohol >20 g/day (%)	100.0	82.4	54.2	26.0	6.5	0.0	<0.001
Regular exercise							
Exercise to light sweat (%)	14.9	12.0	17.7	24.1	32.4	100.0	<0.001
Walking >1 h per day (%)	23.9	29.3	35.6	39.4	45.5	100.0	<0.001
Eating habit							
Snacks after supper (%)	44.8	39.9	33.1	30.2	4.9	0.0	<0.001
Skipping breakfast (%)	68.7	66.3	34.4	18.0	2.6	0.0	<0.001
Systolic BP, mmHg	122±10	119±12	119±12	117±12	117±13	118±12	0.04
Diastolic BP, mmHg	75±9	73±8	73±9	72±9	71±9	71±8	<0.001
Fasting blood sugar, mg/dL	94±8	91±8	90±8	89±8	88±8	88±7	<0.001
Hemoglobin A1c, %	5.3±0.2	5.2±0.2	5.3±0.2	5.3±0.2	5.3±0.2	5.3±0.2	<0.001
LDL cholesterol, mg/dL	105±22	100±23	106±21	109±20	110±19	111±19	<0.001
CKD (%)	7.5	8.0	10.4	10.2	11.3	15.0	<0.001
Stage 1-2 (%)	3.0	4.1	3.4	2.4	1.9	1.7	<0.001
G3a (%)	4.5	3.9	6.7	7.5	8.9	12.7	
G3b-5 (%)	0.0	0.0	0.3	0.3	0.5	0.6	
Proteinuria (%)	3.0	4.7	3.9	2.7	2.2	2.1	<0.001
Serum Cr, mg/dL	0.76±0.14	0.74±0.14	0.74±0.16	0.71±0.18	0.68±0.19	0.70±0.16	<0.001
eGFR, mL/min/1.73 m^2	84±16	84±16	81±16	80±16	78±16	75±15	<0.001

Data are presented as mean±standard deviation or percentage.

BP: blood pressure, CKD: chronic kidney disease, Cr: creatinine, eGFR: estimated glomerular filtration rate, LDL: low-density lipoprotein

Table 5. Number, Crude Incidence Rate, and Hazard Ratio (95% CI) of Incident Diabetes According to Healthy Lifestyle Score.

	No. of incident diabetes	Rate (95% CI)[a]	HR (95% CI)		
			Unadjusted	Age/sex adjusted	Multivariable adjusted[b]
HLS					
0-2	52	3.6 (2.7-4.7)	1 (ref.)	1 (ref.)	1 (ref.)
3	73	2.6 (2.1-3.3)	0.72 (0.51-1.03)	0.75 (0.52-1.08)	0.76 (0.53-1.09)
4	105	2.1 (1.7-2.6)	0.59 (0.42-0.82)	0.64 (0.45-0.91)	0.65 (0.45-0.92)
5	33	1.8 (1.3-2.6)	0.52 (0.33-0.80)	0.50 (0.32-0.79)	0.51 (0.32-0.81)
HR for trend[c]			0.80 (0.70-0.91)	0.80 (0.70-0.92)	0.81 (0.70-0.93)
CKD status					
Non-CKD	226	2.3 (2.0-2.6)	1 (ref.)	1 (ref.)	1 (ref.)
CKD	37	3.0 (2.2-4.1)	1.31 (0.93-1.86)	1.11 (0.78-1.58)	1.13 (0.80-1.61)

[a]per 1,000 person-years.

[b]Adjusted for sex, age, systolic blood pressure, hemoglobin A1c, LDL cholesterol, and CKD status.

[c]HR for trend was calculated by entering the exposure categories as a continuous term in the Cox model.

CI: confidence interval, HLS: healthy lifestyle score, HR: hazard ratio

Discussion

In this large-scale Japanese population-based cohort study, we confirmed the combined impact of healthy lifestyle factors on preventing incident hypertension and diabetes in a cohort that included participants with and without CKD. Our findings suggest the lack of a modifying effect of CKD on associations between the HLS and incident hypertension and diabetes. When each HLS component was analyzed in-

dividually, CKD modified the associations between smoking status and incident hypertension, and between regular exercise and incident diabetes. These findings suggest that adhering to an increasing number of HLS components effectively reduces the risk of both incident hypertension and diabetes, regardless of CKD status.

CKD was found to be significantly associated with incident hypertension but not diabetes, suggesting that CKD itself is not a risk factor for developing diabetes. This is in line with the results from a previous cohort study showing that neither of the two indicators of the kidney function and damage (eGFR and urinary albumin-creatinine ratio) was significantly associated with incident type 2 diabetes (8). Since type 2 diabetes and CKD share common lifestyle risk factors (8), the reported high incidence of type 2 diabetes among individuals with CKD (7, 8). might be explained by a lower adherence to a healthy lifestyle. This is supported by a previous study showing that the association between moderate-severe CKD and reduced insulin sensitivity was attenuated after adjusting for lifestyle factors and body composition (36).

We also found that CKD modified the association between smoking status and incident hypertension, and the effect was more pronounced among participants with CKD than among those without CKD. Considering the known correlations between the GFR and clearance of nicotine (37), one of the toxic components in tobacco that can cause an acute increase in blood pressure, the toxic effects of smoking may persist longer in patients with CKD than in individuals with a normal kidney function.

CKD also modified the association between regular exercise and incident diabetes. Being physically active was associated with a significantly lower risk of incident diabetes in participants with CKD, but not those without. Our latter finding is inconsistent with a previous systematic review and meta-analysis of cohort studies showing the protective effects of exercise on the development of diabetes (38, 39). This may be due to high-risk participants being more likely to engage in regular exercise habits than others. The present study included participants who fulfilled the following criteria: 1) HbA1c ≤5.6%, 2) fasting blood sugar <110 mg/dl, and 3) self-reported nonuse of anti-hyperglycemic drugs. These criteria, however, would encompass those with well-controlled diabetes who are not on medication. Such individuals are more likely to have regular exercise habits but still be at high risk of developing diabetes. For the same reason, a graded association between the HLS and incident diabetes may not be observed in the older group.

Our findings contribute to efforts to tackle the burden of CKD. The major worldwide risk factors for CKD and end-stage kidney disease (ESKD) are diabetes mellitus and hypertension (40). Preventing both diseases would lessen the burden of ESKD. Furthermore, we previously reported that incident proteinuria decreased as the number of HLS components adhered to increased (12-14). A recent cohort study of the Japanese general population also showed that subjects with a greater number of healthy lifestyle factors (noncurrent smoking, BMI <25, and healthy eating habits) showed a lower incidence of trace/positive proteinuria by dipstick test and rapid eGFR decline (eGFR decline ≥20%) than those with fewer factors (41). These findings strongly suggest that adherence to healthy lifestyle factors can reduce the risk of hypertension, diabetes, proteinuria, and rapid eGFR decline. Tackling multiple risk factors, rather than concentrating on one lifestyle factor, should be the cornerstone of efforts to reduce the global burden of CKD.

Strengths of the present study include the large sample size, large number of incident cases, use of a representative study population from throughout Japan, and detailed information on many lifestyle factors. However, this study also has several limitations that should be noted. First, the scores for HLS components, with the exception of BMI, were determined from self-reported questionnaires, raising the possibility of misclassification. Yet, in prospective studies, misclassification is typically considered nondifferential and therefore is expected to result in an underestimation of risk. Second, CKD was defined based on a single measurement of eGFR and proteinuria, which can also lead to misclassification. Furthermore, many participants, especially those with advanced CKD, were excluded due to comorbidities. This may have introduced selection bias. Third, despite adjusting for potential confounding factors, residual confounding is possible. Finally, this study was conducted in Japan, and thus the results might not be generalizable to other populations. However, the dose-dependent effect of adhering to multiple healthy lifestyle factors on incident hypertension and diabetes in the general population has been observed across different populations (1-6).

In conclusion, this large-scale Japanese population-based cohort study revealed that risks of incident hypertension and diabetes decreased as the number of HLS components adhered to increased, irrespective of CKD status. Our results strongly suggest that adherence to healthy lifestyle factors can reduce the development of incident hypertension and diabetes in individuals with and without CKD.

The authors state that they have no Conflict of Interest (COI).

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