Clin Exp Nephrol
DOI 10.1007/s10157-014-1019-5

ORIGINAL ARTICLE

Underestimating chronic kidney disease by urine dipstick without serum creatinine as a screening tool in the general Japanese population

Daisuke Uchida · Hiroo Kawarazaki · Yugo Shibagaki · Takashi Yasuda · Naoto Tominaga · Tsuyoshi Watanabe · Koichi Asahi · Kunitoshi Iseki · Chiho Iseki · Kazuhiko Tsuruya · Kunihiro Yamagata · Toshiki Moriyama · Ichiei Narita · Shoichi Fujimoto · Tsuneo Konta · Masahide Kondo · Masato Kasahara · Kenjiro Kimura

Received: 26 June 2014 / Accepted: 29 July 2014

Abstract
Background It is not known if urine dipstick alone can identify chronic kidney disease (CKD) in the general Japanese population.
Methods We designed a cross-sectional study using data obtained in 2008 from a nationwide community-based health examination program for adults aged 40–74. The data consisted of blood tests, urine tests and questionnaire related to metabolic disorders. Those who had both serum creatinine measured and urine dipstick tested were analyzed.
Results Data were obtained from 538,846 people with a mean age of 62.8 years, consisting of 41.6 % males. Our study showed that 14.4 % had an eGFR below 60 mL/min/1.73 m^2, 5.2 % had proteinuria and 18.1 % had CKD. Within the population with CKD, non-proteinuric CKD accounted for 71.4 %. The proportion of non-proteinuric CKD was highest in stage G3a (91.8 %) followed by G3b (77.0 %) disease, and was greater in the more elderly and in females. The proportion of non-proteinuric CKD was 47.9 % in diabetes mellitus, 69.3 % in dyslipidemia, 66.8 % in hypertension and 57.1 % in metabolic syndrome. Furthermore, non-proteinuric CKD accounted for 78.1 % of the population without these lifestyle diseases, suggesting that even in the population without apparent risk, CKD is still prevalent and can be missed when urine dipstick is the only screening method used.

T. Watanabe, K. Asahi, K. Iseki, C. Iseki, K. Tsuruya, K. Yamagata, T. Moriyama, I. Narita, S. Fujimoto, T. Konta, M. Kondo, M. Kasahara and K. Kimura are the members of Steering Committee for Design of the Comprehensive Health Care System for Chronic Kidney Disease (CKD) Based On Individual Risk Assessments at Specific Health Check.

D. Uchida and H. Kawarazaki have contributed equally to this manuscript.

D. Uchida (✉) · H. Kawarazaki · Y. Shibagaki · T. Yasuda · N. Tominaga · K. Kimura
Department of Nephrology and Hypertension, St. Marianna University School of Medicine, 2-16-1 Sugao, Miyamae-ku, Kawasaki, Kanagawa 216-8511, Japan
e-mail: uchidadaiske@gmail.com

T. Watanabe · K. Asahi
Division of Nephrology and Hypertension, Fukushima Medical University, 1 Hikariga-oka, Fukushima 960-1295, Japan

K. Iseki · C. Iseki
Dialysis Unit, University Hospital of The Ryukyus, 207 Uehara, Okinawa, Nishihara 903-0215, Japan

K. Tsuruya
Department of Integrated Therapy for Chronic Kidney Disease, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Fukuoka, Higashi-ku 812-8582, Japan

K. Yamagata
Department of Nephrology, Graduate School of Comprehensive Human Sciences, University of Tsukuba, 1-1-1 Tennoudai, Tsukuba, Ibaraki 305-8575, Japan

T. Moriyama
Health Care Center, Osaka University, 1-17 Machikaneyama-cho, Osaka, Toyonaka 560-0043, Japan

I. Narita
Division of Clinical Nephrology and Rheumatology, Graduate School of Medical and Dental Sciences, Niigata University, 1-757 Chuo-ku Niigata, Niigata 951-8510, Japan

S. Fujimoto
Department of Hemovascular Medicine and Artificial Organs, Faculty of Medicine, University of Miyazaki, 5200 Kihara, Kiyotake, Miyazaki 889-1692, Japan

Published online: 24 August 2014

Conclusions This study showed that a considerable population of CKD might be overlooked when only dipstick proteinuria is assessed for CKD screening. Hence, we strongly recommend that both urinalysis and serum creatinine measurement should be a part of the nationwide CKD screening system.

Keywords Chronic kidney disease · Screening · Urine dipstick test

Introduction

The current epidemic of chronic kidney disease (CKD) is a health problem worldwide. Individuals with CKD are at a significantly increased risk of both cardiovascular disease (CVD) and end-stage kidney disease (ESKD). In Japan, urinalysis by urine dipstick for CKD screening in schoolchildren, working adults and non-workers older than 40 years has been a mandatory and routine part of annual medical check-ups since 1983. Concurrently, there has been a drastic decrease in ESKD caused by glomerulonephritis and an increase in the mean age of those treated for ESKD [1]. In 1992, measurement of serum creatinine was added to both the company-based and community-based annual health examination program in adults aged 40 or more, for early detection of CKD. The combination of urinalysis and measurement of serum creatinine has contributed to better detection of early-stage CKD in Japanese adults aged 40 years or more [1].

In 2000, the Ministry of Health, Labour and Welfare devised the "Healthy Japan 21" policy, to maintain and improve the health of the Japanese public in the 21st century. The primary focus of this policy was prevention of CVD, malignancy, diabetes mellitus and metabolic syndrome (MS), by advocating an improvement in diet, exercise, mental health, smoking, alcohol and dental health. In 2008, the Ministry of Health, Labour and Welfare started a new surveillance project to prevent and reduce the number of people with MS, the prevalence of which is 25 % among Japanese men aged 40 years or more [2]. This specific health check, consists of a physical check-up, including height, weight, waist circumference, blood pressure, and blood tests related to metabolic disorders, such as those of glucose, lipids, hepatic enzymes and urine. Questionnaire surveys for a past history of stroke, cardiac disease, kidney disease, lifestyles such as smoking, alcohol intake, exercise, etc., and treatment for hypertension, diabetes mellitus and dyslipidemia are also performed. However, serum creatinine measurement was deleted from the list of mandatory tests for adults aged 40 years or more because urinalysis by urine dipstick was previously thought to be superior to measurement of serum creatinine level for early detection of CKD. This was also due to the political aim of reducing the cost of disease screening, which was based on the assumption that detecting high-risk people, such as those with hypertension or metabolic disorders, may be enough to identify those with CKD. However, this may overlook a certain number of people with CKD who do not have proteinuria. Furthermore, there remains a concern that limiting screening to people with hypertension or MS may not sufficiently decrease the incidence of new ESKD in Japanese people, because glomerulonephritis, the second leading cause of ESKD, is not associated with hypertension or MS [1].

The aim of this study was to clarify the accuracy and validity of CKD screening only by dipstick assessment of urine proteinuria without measurement of serum creatinine in the Japanese general population.

Subjects and methods

This study was a cross-sectional study using data obtained in 2008 from a nationwide community-based health examination program for adults aged 40–74 years. The data of those in whom both urine dipstick and serum creatinine had been measured were analyzed. Proteinuria was diagnosed by a dipstick test result of 1+ or more and CKD was diagnosed by an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m^2 or positive dipstick proteinuria. Diabetes mellitus was defined as fasting plasma glucose of at least 126 mg/dL, hemoglobin A1c (National Glycohemoglobin Standardization Program; NGSP) of at least 6.5 % or a history of anti-diabetic medication. Dyslipidemia was defined as fasting triglyceride levels of at least 150 mg/dL, high-density lipoprotein (HDL) cholesterol levels below 40 mg/dL, low-density lipoprotein (LDL) cholesterol levels of at least 140 mg/dL or history of anti-dyslipidemic medication. Hypertension was defined as a systolic blood pressure of 140 mmHg and above, diastolic

T. Konta
Department of Cardiology, Pulmonology, and Nephrology, Yamagata University School of Medicine, 2-2-2 Iida-Nishi, Yamagata 990-9585, Japan

M. Kondo
Department of Health Care Policy and Management, Graduate School of Comprehensive Sciences, University of Tsukuba, 1-1-1 Tennoudai, Ibaraki 305-8577, Tsukuba, Japan

M. Kasahara
Department of EBM Research, Institute for Advancement of Clinical and Translational Science, Kyoto University Hospital, Kyoto, Japan

blood pressure of 90 mmHg and above, or a history of antihypertensive medication. MS was defined in accordance with the current Japanese definition [3]. That is a waist size of at least 85 cm in males and 90 cm in females, and 2 or more of the following: blood pressure of at least 130/85 mmHg, fasting triglyceride levels of at least 150 mg/dL or HDL cholesterol below 40 mg/dL, and fasting plasma glucose of at least 110 mg/dL. Estimated GFR was calculated by the equation for Japanese adults [194 × serum Cre − 1.094 × Age − 0.287 (×0.739 in females)] [4]. Comorbidities included diabetes, dyslipidemia, hypertension and MS.

The data are presented as average ± standard deviation (SD) or percentages. All analyses were performed with SPSS version 17.0 (IBM, Chicago, IL).

The study was conducted according to the guidelines of the Declaration of Helsinki and the Ethical Guidelines for Epidemiological Research (December 1, 2008, Ministry of Education, Culture, Sports, Science and Technology and Ministry of Health, Labour and Welfare of Japan). Ethical

Table 1 Characteristics of the whole cohort

	Total $n = 538,846$	Non-CKD $n = 441,550$	CKD without proteinuria $n = 69,506$	CKD with proteinuria $n = 27,790$
Age, years	62.8 ± 8.7	62.3 ± 8.9	65.6 ± 7.2	63.9 ± 8.6
Males, *n* (%)	223,881 (41.6)	176,754 (40.0)	30,982 (44.6)	16,145 (58.1)
Diabetes mellitus, *n* (%)	44,255 (8.2)	32,500 (7.4)	5,629 (8.1)	6,126 (22.0)
Dyslipidemia, *n* (%)	238,096 (44.2)	191,110 (43.3)	32,584 (46.9)	14,402 (51.8)
Hypertension, *n* (%)	216,639 (40.2)	167,499 (37.9)	32,825 (47.2)	16,315 (58.7)
Metabolic syndrome, *n* (%)	48,544 (9.0)	35,266 (8.0)	7,584 (10.9)	5,693 (20.5)
Chronic kidney disease, *n* (%)	97,296 (18.1)	–	69,506 (100)	27,790 (100)
Body height (cm)	157.5 ± 8.6	157.4 ± 8.6	157.6 ± 8.3	159.0 ± 8.7
Body weight (kg)	57.9 ± 10.7	57.5 ± 10.6	58.8 ± 10.3	61.9 ± 11.9
Body mass index ($kg/m^{2)}$	23.2 ± 3.3	23.1 ± 3.3	23.6 ± 3.2	24.4 ± 3.9
Waist size (cm)	83.8 ± 9.3	83.4 ± 9.2	84.8 ± 9.0	86.8 ± 10.1
Systolic blood pressure (mmHg)	129.1 ± 17.8	128.5 ± 17.6	130.0 ± 17.6	136.0 ± 19.3
Diastolic blood pressure (mmHg)	76.5 ± 10.9	76.3 ± 10.8	76.7 ± 10.7	79.6 ± 11.6
Pulse/min	52.6 ± 12.8	52.2 ± 12.7	53.2 ± 12.9	56.4 ± 14.5
Fasting plasma glucose (mg/dL)	97.7 ± 20.8	97.1 ± 19.8	97.1 ± 17.3	109.5 ± 35.9
HbA1c (NGSP) (%)	5.3 ± 0.69	5.3 ± 0.66	5.3 ± 0.57	5.7 ± 1.2
Triglycerides (mg/dL)	121.3 ± 82.3	118.9 ± 81.0	127.1 ± 76.6	144.3 ± 107.5
HDL cholesterol (mg/dL)	62.0 ± 16.2	62.6 ± 16.1	59.5 ± 15.8	58.3 ± 16.3
LDL cholesterol (mg/dL)	125.4 ± 30.6	125.3 ± 30.5	126.3 ± 30.3	124.5 ± 32.8
AST, IU/L	24.4 ± 11.3	24.2 ± 11.0	24.6 ± 10.0	27.1 ± 16.5
ALT, IU/L	22.0 ± 14.4	21.9 ± 14.2	21.5 ± 13.0	25.5 ± 18.8
GGTP, IU/L	37.0 ± 48.7	36.3 ± 47.1	35.6 ± 44.0	52.8 ± 75.4
Hemoglobin (g/dL)	13.5 ± 2.1	13.4 ± 2.1	13.7 ± 2.1	13.8 ± 2.2
Uric acid (mg/dL)	5.2 ± 1.4	5.1 ± 1.3	6.0 ± 1.4	5.8 ± 1.5
Creatinine (mg/dL)	0.72 ± 0.25	0.67 ± 0.13	0.97 ± 0.38	0.87 ± 0.58
eGFR categories, mL/min/1.73 m^2, *n* (%)				
G1, ≥90	107,085 (19.9)	102,921 (23.3)	–	4,164 (15.0)
G2, 60–89	354,118 (65.7)	338,629 (76.7)	–	15,489 (55.7)
G3a, 45–59	68,906 (12.8)	–	63,279 (91.0)	5,627 (20.2)
G3b, 30–44	7,320 (1.4)	–	5,637 (8.1)	1,683 (6.1)
G4, 15–29	996 (0.18)	–	404 (0.6)	592 (2.1)
G5, <15	421 (0.08)	–	186 (0.3)	235 (0.8)
G3a–G5, <60	77,643 (14.4)	–	69,506 (100)	8,137 (29.3)
Proteinuria, *n* (%)				
Negative or trace	511,056 (94.8)	441,550 (100)	69,506 (100)	–
1+ or more	27,790 (5.2)	–	–	27,790 (100)

Expressed as Mean ± SD unless noted otherwise

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *eGFR* estimated glomerular filtration rate, *GGTP* gamma-glutamyl transpeptidase, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *NGSP* national glycohemoglobin standardization program

approval was also obtained from the respective institutional review boards.

Results

The health examination data were obtained from 20 prefectures around Japan. A total of 538,846 people had both urine dipstick tested and serum creatinine measured, together with other mandatory tests. The average age of the study population was 62.8 ± 8.7 years and males constituted 41.6 % of the population.

Prevalence of CKD

The characteristics of the entire cohort are shown in Table 1. Estimated GFR below 60 mL/min/1.73 m^2 was found in 14.4 % (n = 77,643) of the population and proteinuria was found in 5.2 % (n = 27,790). CKD (either or both low eGFR and proteinuria) was identified in 18.1 % (n = 97,296) of the population.

Proportion of CKD without proteinuria

Of the 97,296 people with CKD, 69,506 (71.4 %) had no proteinuria, indicating the possibility that 71.4 % of people with CKD (91.8 % with stage G3a, 77.0 % with stage G3b, 40.6 % with stage G4, and 44.2 % with stage G5 disease) might be overlooked when only the urine dipstick method is used for CKD screening (Table 2). With advancing age, the population with CKD increased, especially those without proteinuria (Fig. 1). Thus, we are more likely to overlook CKD in the elderly when CKD screening only involves urine dipstick tests. The proportion of CKD without proteinuria was greater in females than in males (76.5 vs. 65.7 %, $p < 0.001$).

Table 2 Distribution of GFR category and proteinuria in subjects with CKD

CKD	Proteinuria		Total
	Negative or trace	1+ or more	
GFR category, *n* (%)			
G1	–	4,164 (100)	4,164
G2	–	15,489 (100)	15,489
G3a	63,279 (91.8)	5,627 (8.17)	68,906
G3b	5,637 (77.0)	1,683 (23.0)	7,320
G4	404 (40.6)	592 (59.4)	996
G5	186 (44.2)	235 (55.8)	421
G3a–G5	69,506 (89.5)	8,137 (10.5)	77,643
Total	69,506 (71.4)	27,790 (28.6)	97,296

CKD chronic kidney disease

Proportion of those with eGFR below 60 mL/min/1.73 m^2 and without proteinuria

Of the 77,643 people who had an eGFR below 60 mL/min/1.73 m^2, as many as 69,506 (89.5 %) subjects showed no proteinuria (Table 2). Moreover, among the 511,056 people who did not have proteinuria, 69,506 (13.6 %) were found to have an eGFR below 60 mL/min/1.73 m^2.

Proportion of CKD with/without comorbidities and no proteinuria

Table 3 shows the prevalence of CKD according to eGFR categories, proteinuria and comorbidities. The main purpose of the Japanese specific health check is to reveal those who may have MS and to give lifestyle guidance to prevent disease onset. Indeed, among those with MS (n = 48,544), 19.5 % had an eGFR below 60 mL/min/1.73 m^2, 11.7 % had proteinuria, and 27.4 % had CKD. This also indicates the possibility of overlooking CKD in 57.1 % of the people

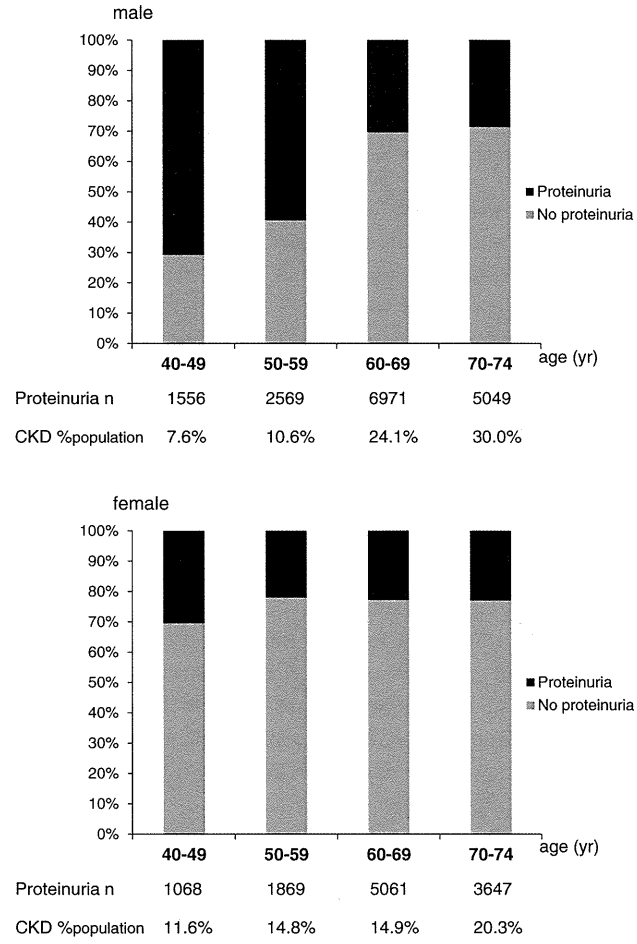

Fig. 1 Distribution of proteinuria according to age in those with CKD

Table 3 Comparison of age, gender, GFR category, proteinuria and coexisting morbidities in subjects grouped according to the comorbidities of diabetes mellitus (DM), dyslipidemia (DL), hypertension (HTN) and metabolic syndrome (MS)

	DM $n = 44,255$	DL $n = 238,096$	HTN $n = 216,639$	MS $n = 48,543$	No. comorbidities $n = 72,297$
Age, years	65.22 ± 7.22	63.43 ± 8.02	65.07 ± 7.36	64.12 ± 8.00	60.58 ± 9.55
Males, *n* (%)	25,494 (57.6)	100,405 (42.2)	100,387 (46.3)	33,325 (68.6)	26,084 (36.0)
eGFR, mL/min/1.73 m^2					
G1, ≥90	9,886 (22.3)	43,678 (18.3)	37,683 (17.4)	7,458 (15.4)	14,452 (20.0)
G2, 60–89	26,826 (60.6)	157,429 (66.1)	140,680 (64.9)	33,634 (69.3)	50,462 (69.8)
G3a, 45–59	6,045 (13.7)	32,540 (13.7)	32,902 (15.2)	8,053 (16.6)	6,968 (9.6)
G3b, 30–44	1,148 (2.6)	3,714 (1.6)	4,397 (2.0)	1,134 (2.3)	381 (0.53)
G4, 15–29	277 (0.63)	534 (0.22)	726 (0.34)	220 (0.45)	21 (0.029)
G5, <15	73 (0.16)	201 (0.084)	251 (0.12)	44 (0.091)	13 (0.018)
G3a–G5, <59	7,543 (17.0)	36,989 (15.5)	38,276 (17.7)	9,451 (19.5)	7,383 (10.2)
Proteinuria					
Negative to trace	38,129 (86.2)	223,694 (94.0)	200,324 (92.5)	42,850 (88.3)	70,330 (97.3)
1 + to more	6,126 (13.8)	14,402 (6.0)	16,315 (7.5)	5,693 (11.7)	1,967 (2.7)
DM, *n* (%)	–	22,501 (9.5)	18,662 (8.6)	12,763 (26.3)	–
DL, *n* (%)	22,501 (50.8)	–	102,595 (47.4)	42,250 (87.0)	–
HTN, *n* (%)	18,662 (42.2)	102,595 (43.1)	–	35,383 (72.9)	–
MS, *n* (%)	12,763 (28.8)	42,250 (17.7)	35,383 (16.3)	–	–
CKD, *n* (%)	11,755 (26.7)	46,986 (19.7)	49,140 (22.7)	13,277 (27.4)	9,000 (12.4)
Within those w CKD					
CKD w/o UProt, *n* (%)	5,629 (47.9)	32,584 (69.3)	32,825 (66.8)	7,584 (57.1)	7,033 (78.1)
CKD w UProt, *n* (%)	6,126 (52.1)	14,402 (30.7)	16,315 (33.2)	5,693 (42.9)	1,967 (21.9)

CKD chronic kidney disease, *UProt* proteinuria, *w* with, *w/o* without

($n = 7,584$) who have CKD and no proteinuria if serum creatinine is not measured. Furthermore, among the people without MS, the frequency of CKD patients with no proteinuria was estimated to be 56.3 %, which means a considerable number of people with CKD may be overlooked by the current specific health check. The proportion of the population of CKD patients without proteinuria who will be overlooked by having only urine dipstick screening for CKD is 47.9 % in patients with diabetes mellitus, 69.3 % of those with dyslipidemia, and 66.8 % in hypertensive patients, indicating that even in those with a high risk, CKD may be overlooked if screening does not include serum creatinine assessments.

It is also important to note that non-proteinuric CKD accounted for 78.1 % of the CKD population without comorbidities. This suggests that even in the population without apparent risk, CKD is still prevalent and that we will miss these people when CKD screening is only done by the urine dipstick test.

Discussion

From this large cross-sectional study of the general Japanese population, we found that a significant portion of people with CKD would have been overlooked if screened only by the urine dipstick test without measurement of serum creatinine. This study shows that as many as 71.4 % of people with CKD would have been missed if they had been screened using only the urine dipstick test and when limited to people with an eGFR below 60 mL/min/1.73 m^2, 89.5 % may have been overlooked. And the proportion of overlooking is the highest in people without comorbidities such as MS, diabetes, dyslipidemia, or hypertension.

Previous studies showed that proteinuria is independent of eGFR as a predictor of mortality and is also the strongest risk factor for CKD progression, with its associated risks of cardiovascular (CV) morbidity and mortality [5–7]. Along with proteinuria, Matsushita et al. [6] have shown in a meta-analysis of worldwide general population cohorts that, indeed, CV mortality and all-cause mortality increase when eGFR is about 70 mL/min/1.73 m^2 and lower. It has been shown that independent of proteinuria, the risk of ESKD is prominently higher in people with a lower eGFR [8]. Our study showed that the probability of overlooking CKD by screening only with urine dipstick is highest in stage G3a followed by G3b disease, and, in general, from these early stages, CVD, renal failure and mortality risk significantly increase, suggesting the need for detection of CKD at this early stage. The risk of such outcomes was

independent of proteinuria, and, more importantly, showed a multiplicatively associated risk of mortality with the existence of proteinuria along with low eGFR [9].

Detection of CKD would be even more important in a population possessing other risk factors for CV events. Muntner et al. have reported that compared to a non-CKD population, people with CKD (defined by eGFR below 60 mL/min/1.73 m^2) possessing other risk factors, such as hypertension, diabetes or dyslipidemia, had a threefold greater risk of CVD [9]. Nakayama et al. [10] have shown in a Japanese cohort that compared to patients with primary renal disease, patients with diabetic and hypertensive nephropathy are at a 3–5 times higher risk of CV events. Present Japanese health screening tests focus mainly on the detection of MS, thereby aiming to prevent CV mortality and morbidity. Our study showed that 27.4 % of those with MS had associated CKD, which strongly suggests that MS is a high-risk factor for CKD. On the other hand, our study also revealed that as many as 57.1 % of MS subjects with CKD might have been overlooked if serum creatinine had not been measured along with urine dipstick, indicating that even in high-risk patients, we cannot recognize CKD without measuring serum creatinine. Furthermore, within the population with CKD, 69.3 % with dyslipidemia, 66.8 % with hypertension and 47.9 % with diabetes could not be diagnosed as CKD only with urine dipstick.

Intriguingly, 56.5 % of people with CKD had no proteinuria and no MS, which means that even in a low risk population, CKD is very common but can be overlooked. Furthermore, 12.4 % of those without apparent comorbidities had CKD and 78.1 % of these people had no proteinuria. Since those without apparent risks would have significantly fewer opportunities to get further medical work-up, their CKD has a much higher risk of being overlooked compared to those with risk factors. Thus, screening by serum creatinine measurement is extremely important in detecting CKD.

This study also brought to light the fact that the elderly population is more inclined to have non-proteinuric CKD. The Japanese society is aging rapidly. Considering the increasing proportion of elderly people in the general population and the increasing age of those on dialysis and initializing dialysis, screening for CKD in this at-risk population is anticipated to result in appropriate treatment at an early stage. Kondo et al. [11] have reported that the use of urine dipstick and serum creatinine is each cost effective as a screening tool for CKD and combination of the two would be even more cost effective. Thus, both urinalysis and serum creatinine measurement in the specific health check are necessary not only for early detection of CKD but also for the reduction of medical cost.

A limitation of this study is that it was not a longitudinal study following up the eGFR of each individual for an extended period of time, but a cross-sectional study. Further, diagnosis of CKD was based on a single test, which may have misestimated renal function. However, the large number of data collected from a nationwide screening test seems adequate to prove its validity. Measuring the urinary protein excretion was analyzed by urine dipstick alone that was a quantitation method which cannot detect microalbuminuria.

Chronic kidney disease is fully established as an independent and powerful risk for CV events. In this regard, early detection of CKD is thought to be important, and this study highlights the fact that this population-based screening test is an ideal opportunity to detect CKD simultaneously with evaluation of other metabolic risk factors. However, there is concern that the current specific health check for CKD will be inadequate without serum creatinine measurement. Hence, we strongly recommend that both urinalysis and serum creatinine measurement should be a part of the nationwide health examination program.

Acknowledgments This study was supported by a Health and Labor Sciences Research Grant for "Design of the specific health check for chronic kidney disease (CKD) based on individual risk assessment at Specific Health Checks" from the Ministry of Health, Labor and Welfare of Japan.

Conflict of interest All authors declare that they have no competing interests.

References

1. Imai E, Yamagata K, Iseki K, et al. Kidney disease screening program in Japan: history, outcome, and perspectives. Clin J Am Soc Nephrol. 2007;2:1360–6.
2. Takeuchi H, Saitoh S, Takagi S, et al. Metabolic syndrome and cardiac disease in Japanese men: applicability of the concept of metabolic syndrome defined by the National Cholesterol Education Program-Adult Treatment Panel III to Japanese men–the Tanno and Sobetsu Study. Hypertens Res Off J Jpn Soc Hypertens. 2005;28:203–8.
3. Matsuzawa Y. Metabolic syndrome–definition and diagnostic criteria in Japan. J Atheroscler Thromb. 2005;12:301.
4. Matsuo S, Imai E, Horio M, et al. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis Off J Natl Kidney Found. 2009;53:982–92.
5. Hemmelgarn BR, Manns BJ, Lloyd A, et al. Relation between kidney function, proteinuria, and adverse outcomes. JAMA J Am Med Assoc. 2010;303:423–9.
6. Chronic Kidney Disease Prognosis Consortium, Matsushita K, van der Velde M et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet 2010; 375:2073–2081.
7. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. JAMA J Am Med Assoc. 2007;298:2038–47.

8. Levey AS, de Jong PE, Coresh J, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO controversies conference report. Kidney Int. 2010;80:17–28.
9. Muntner P. Traditional and nontraditional risk factors predict coronary heart disease in chronic kidney disease: results from the atherosclerosis risk in communities study. J Am Soc Nephrol. 2005;16:529–38.
10. Nakayama M, Sato T, Miyazaki M, et al. Increased risk of cardiovascular events and mortality among non-diabetic chronic kidney disease patients with hypertensive nephropathy: the Gonryo study. Hypertens Res Off J Jpn Soc Hypertens. 2011;34:1106–10.
11. Kondo M, Yamagata K, Hoshi S-L, et al. Cost-effectiveness of chronic kidney disease mass screening test in Japan. Clin Exp Nephrol. 2011;16:279–91.

OPEN ACCESS Freely available online

PLOS ONE

Association between Combined Lifestyle Factors and Non-Restorative Sleep in Japan: A Cross-Sectional Study Based on a Japanese Health Database

Minako Wakasugi[1]*, Junichiro James Kazama[2], Ichiei Narita[3], Kunitoshi Iseki[3], Toshiki Moriyama[3], Kunihiro Yamagata[3], Shouichi Fujimoto[3], Kazuhiko Tsuruya[3], Koichi Asahi[3], Tsuneo Konta[3], Kenjiro Kimura[3], Masahide Kondo[3], Issei Kurahashi[4], Yasuo Ohashi[5], Tsuyoshi Watanabe[3]

1 Center for Inter-organ Communication Research, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan, **2** Department of Clinical Nephrology and Rheumatology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan, **3** Steering Committee for "Design of the comprehensive health care system for chronic kidney disease (CKD) based on the individual risk assessment by Specific Health Checkups," Fukushima, Japan, **4** iAnalysis LLC, Tokyo, Japan, **5** Department of Integrated Science and Engineering for Sustainable Society, Chuo University, Tokyo, Japan

Abstract

Background: Although lifestyle factors such as cigarette smoking, excessive drinking, obesity, low or no exercise, and unhealthy dietary habits have each been associated with inadequate sleep, little is known about their combined effect. The aim of this study was to quantify the overall impact of lifestyle-related factors on non-restorative sleep in the general Japanese population.

Methods and Findings: A cross-sectional study of 243,767 participants (men, 39.8%) was performed using the Specific Health Check and Guidance System in Japan. A healthy lifestyle score was calculated by adding up the number of low-risk lifestyle factors for each participant. Low risk was defined as (1) not smoking, (2) body mass index$<$25 kg/m^2, (3) moderate or less alcohol consumption, (4) regular exercise, and (5) better eating patterns. Logistic regression analysis was used to examine the relationship between the score and the prevalence of non-restorative sleep, which was determined from questionnaire responses. Among 97,062 men (mean age, 63.9 years) and 146,705 women (mean age, 63.7 years), 18,678 (19.2%) and 38,539 (26.3%) reported non-restorative sleep, respectively. The prevalence of non-restorative sleep decreased with age for both sexes. Compared to participants with a healthy lifestyle score of 5 (most healthy), those with a score of 0 (least healthy) had a higher prevalence of non-restorative sleep (odds ratio, 1.59 [95% confidence interval, 1.29–1.97] for men and 2.88 [1.74–4.76] for women), independently of hypertension, hypercholesterolemia, diabetes, and chronic kidney disease. The main limitation of the study was the cross-sectional design, which limited causal inferences for the identified associations.

Conclusions: A combination of several unhealthy lifestyle factors was associated with non-restorative sleep among the general Japanese population. Further studies are needed to establish whether general lifestyle modification improves restorative sleep.

Citation: Wakasugi M, Kazama JJ, Narita I, Iseki K, Moriyama T, et al. (2014) Association between Combined Lifestyle Factors and Non-Restorative Sleep in Japan: A Cross-Sectional Study Based on a Japanese Health Database. PLoS ONE 9(9): e108718. doi:10.1371/journal.pone.0108718

Editor: Mathias Basner, University of Pennsylvania Perelman School of Medicine, United States of America

Received February 24, 2014; **Accepted** September 2, 2014; **Published** September 30, 2014

Funding: This study was supported by a Health and Labor Sciences Research Grant for "Design of a comprehensive health care system for chronic kidney disease (CKD) based on individual risk assessment by Specific Health Checkups" (H24-intractible(renal)-ippan-006) from the Ministry of Health, Labor, and Welfare of Japan. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

* Email: minakowa@med.niigata-u.ac.jp

Introduction

A combination of healthy lifestyle factors, such as abstaining from smoking, maintaining a body mass index (BMI) of less than 25 kg/m^2, consuming alcohol moderately, exercising regularly, and having a healthy diet, is reportedly associated with a significantly reduced risk of developing several diseases, such as coronary heart disease [1–2], type 2 diabetes mellitus [3], stroke [4], sudden cardiac death [5], chronic kidney disease [6], cancer [7–9], and total mortality [10]. A clear linear relationship was observed in these studies between risk reduction and the number of healthy lifestyle factors, suggesting that an analysis of combined lifestyle factors may demonstrate their influence better than analyses based on single factors due to the complexity and multiple dimensions of habitual health behaviors. In addition, maintaining an overall healthy lifestyle throughout young adulthood was strongly associated with a low cardiovascular disease risk profile in middle age regardless of sex, race, or a parental history of myocardial infarction, suggesting that genetic factors may not be very important in determining a low risk profile [11]. Most of these studies were conducted in non-Japanese populations except for a few studies [6,9]; however, a combination of healthy lifestyle

factors may play a prominent role regardless of sex, race, or genetics.

Little is known about the impact of combined lifestyle factors on inadequate sleep. There is growing evidence that inadequate sleep, which includes short sleep duration and poor sleep quality, is associated with lifestyle factors that include obesity, insufficient physical exercise, and consumption of substances such as caffeine, alcohol, and nicotine [12]. Inadequate sleep may also modify eating patterns, thereby mediating or contributing to the observed relationship between sleep disturbance and obesity [13].

Inadequate sleep is associated with several chronic diseases. Epidemiological studies have shown that short sleep duration is associated with a higher risk of lifestyle-related diseases such as obesity [14–17], type 2 diabetes mellitus [18–19], hypertension [20], dyslipidemia [21], coronary heart disease [22], and chronic kidney disease [23]. Sleep quality is important in modifying the association between sleep duration and these diseases [24–26].

We hypothesized that a combination of unhealthy lifestyle factors is associated with inadequate sleep. Evidence of a relationship could have important clinical and public health implications. If a combination of unhealthy behaviors is associated with inadequate sleep, lifestyle interventions have the potential to reduce its occurrence. We present the results of a large cross-sectional study on the prevalence of non-restorative sleep (NRS), typically defined as subjectively feeling unrefreshed upon waking [27], and its association with a combination of lifestyle factors in the general Japanese population.

Methods

Study population and design

This cross-sectional study used baseline data from a prospective cohort study of 667,218 participants, aged 40 to 74 years, obtained from the Japanese Specific Health Check and Guidance System (SHC) created in 2008. Twenty-four of the prefectures participating in this nationwide project (Hokkaido, Miyagi, Yamagata, Fukushima, Ibaraki, Tochigi, Tokyo, Saitama, Kanagawa, Niigata, Nagano, Ishikawa, Gifu, Osaka, Okayama, Tokushima, Kochi, Fukuoka, Saga, Nagasaki, Oita, Kumamoto, Miyazaki, and Okinawa) agreed to participate in our study and were included in the present analysis. Data were sent to and verified by an independent data center, the NPO Japan Clinical Research Support Unit (Tokyo, Japan). All participants remained anonymous, and the study was conducted according to Japanese privacy protection laws and ethical guidelines for epidemiological studies published by the Ministry of Education, Science, and Culture and the Ministry of Health, Labor, and Welfare. The study protocol was approved by the ethics committee in Fukushima Medical University (No. 1485).

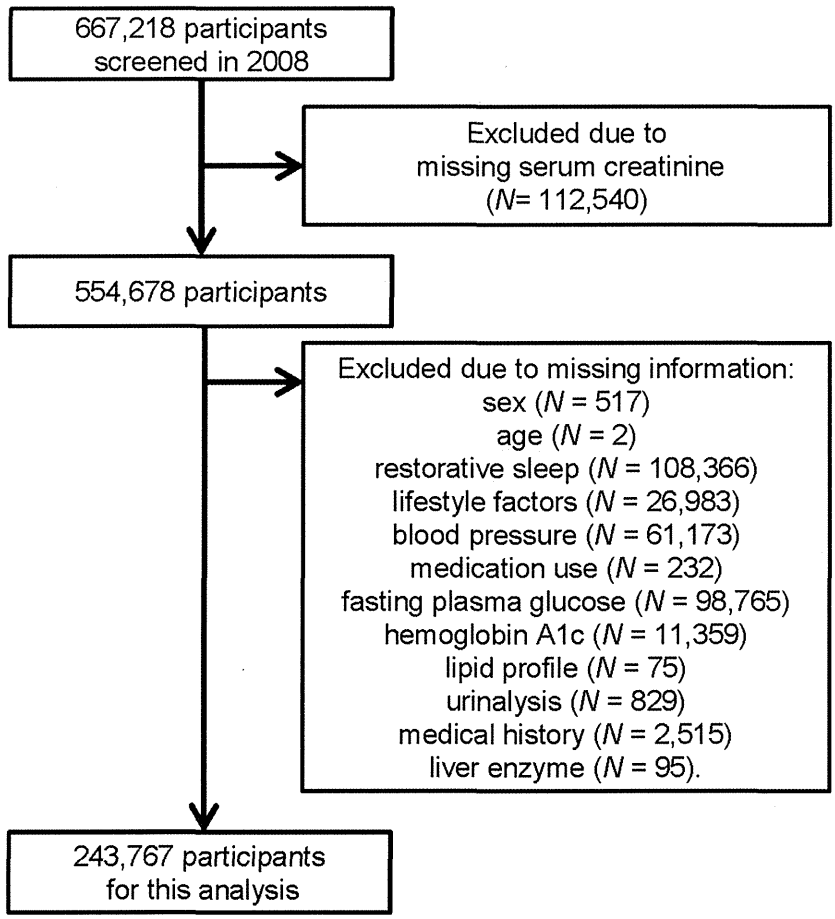

Figure 1. Flow chart of participant selection. Of the 667,218 SHC participants screened in 2008, we excluded anyone with missing information, resulting in a final sample size of 243,767.
doi:10.1371/journal.pone.0108718.g001

Table 1. Clinical characteristics of male participants by restorative sleep achievement.

Characteristics	Total (*N*= 97,062)	Restorative sleep (*N*= 78,384 [80.8%])	Non-restorative sleep (*N*= 18,678 [19.2%])	*P* value
Age, years	63.9 (8.5)	64.4 (8.2)	61.7 (9.5)	<0.0001
Healthy lifestyle score, *n* (%)				<0.0001
0	484 (0.5)	360 (0.5)	124 (0.7)	
1	5,049 (5.2)	3,715 (4.7)	1,334 (7.1)	
2	16,986 (17.5)	13,140 (16.8)	3,846 (20.6)	
3	30,331 (31.3)	24,326 (31.0)	6,005 (32.2)	
4	31,355 (32.3)	25,735 (32.8)	5,620 (30.1)	
5	12,857 (13.3)	11,108 (14.2)	1,749 (9.4)	
Components of the healthy lifestyle score				
Current smoker, *n* (%)	25,359 (26.1)	20,214 (25.8)	5,145 (27.5)	<0.0001
Body mass index, kg/m^2	23.6 (3.0)	23.6 (2.9)	23.7 (3.2)	0.05
Alcohol<20 g/day, *n* (%)	67,556 (69.6)	53,924 (68.8)	13,632 (73.0)	<0.0001
Regular exercise				
Exercise to sweat lightly, *n* (%)	46,069 (47.5)	39,055 (49.8)	7,014 (37.6)	<0.0001
Walking>1 hour/day, *n* (%)	53,950 (55.6)	45,253 (57.7)	8,697 (46.6)	<0.0001
Eating pattern				
Snacks after supper, *n* (%)	12,000 (12.4)	8,775 (11.2)	3,225 (17.3)	<0.0001
Skipping breakfast, *n* (%)	11,060 (11.4)	7,818 (10.0)	3,242 (17.4)	<0.0001
Past history, *n* (%)				
Stroke	4.938 (5.1)	4,003 (5.1)	935 (5.0)	0.59
Heart disease	7,964 (8.2)	6,285 (8.0)	1,679 (9.0)	<0.0001
Renal disease	552 (0.6)	417 (0.5)	135 (0.7)	0.002
Comorbidities, *n* (%)				
Hypertension	49,135 (50.6)	40,406 (51.5)	8,729 (46.7)	<0.0001
Diabetes	14,596 (15.0)	11,965 (15.3)	2,631 (14.1)	<0.0001
Hypercholesterolemia	33, 258 (34.3)	26,878 (34.3)	6,380 (34.2)	0.74
Chronic kidney disease	22,570 (23.3)	18,481 (23.6)	4,089 (21.9)	<0.0001
Medication, *n* (%)				
Antihypertensive drugs	30,756 (31.7)	25,382 (32.4)	5,374 (28.8)	<0.0001
Antidiabetic medication	6,649 (6.9)	5,457 (7.0)	1,192 (6.4)	0.005
Cholesterol-lowering drugs	10,779 (11.1)	8,856 (11.3)	1,923 (10.3)	<0.0001
Systolic pressure, mmHg	131 (17)	132 (17)	130 (17)	<0.0001
Diastolic pressure, mmHg	78 (11)	78 (11)	78 (11)	0.001
Fasting plasma glucose, mg per 100 mL	102 (25)	102 (24)	102 (26)	0.66
Hemoglobin A_{1c}, %	5.79 (0.79)	5.79 (0.77)	5.78 (0.85)	0.02
LDL cholesterol, mg per 100 mL	120.9 (30.0)	120.8 (29.9)	121.1 (30.4)	0.21
Triglycerides, mg per 100 mL	107 (77, 154)	107 (77, 153)	107 (76, 155)	0.58
HDL cholesterol, mg per 100 mL	57 (15)	57 (15)	57 (15)	0.96
Creatinine, mg per 100 mL	0.85 (0.23)	0.85 (0.23)	0.84 (0.23)	0.03
eGFR, mL min^{-1} per 1.73 m^2	74.4 (16.4)	74.2 (16.3)	75.6 (16.9)	<0.0001
Proteinuria, *n* (%)	7,670 (7.9)	6,157 (7.9)	1,513 (8.1)	0.26

Numbers in the table are means (standard deviation) for continuous variables except triglycerides (median and interquartile range) or numbers (percentages) for categorical variables.
LDL, low-density lipoprotein; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate.
doi:10.1371/journal.pone.0108718.t001

The SHC has been previously described [6,28]. Briefly, it is a new healthcare strategy initiated by the Japanese Government in 2008 for the early diagnosis and intervention of metabolic syndrome. The proportion of men to women in the SHC does not necessarily reflect the national population. This is because the SHC is designed for people who have National Health Insurance, or dependents (e.g., spouse) of salaried workers who have health insurance. In this system, participants answer a self-administered questionnaire that covers medical history, smoking habits, alcohol intake, exercise habits, and eating patterns. Trained staff then

Table 2. Clinical characteristics of female participants by restorative sleep achievement.

Characteristics	Total (*N* = 146,705)	Restorative sleep (*N* = 108,166 [73.7%])	Non-restorative Sleep (*N* = 38,539 [26.3%])	*P* value
Age, years	63.7 (7.9)	64.2 (7.7)	62.6 (8.5)	<0.0001
Healthy lifestyle score, *n* (%)				<0.0001
0	63 (0.0)	35 (0.0)	28 (0.1)	
1	1,283 (0.9)	765 (0.7)	518 (1.3)	
2	9,909 (6.8)	6,502 (6.0)	3,407 (8.8)	
3	35,999 (24.5)	25,208 (23.3)	10,791 (28.0)	
4	71,637 (48.8)	53,100 (49.1)	18,537 (48.1)	
5	27,814 (19.0)	22,556 (20.9)	5,258 (13.6)	
Components of the healthy lifestyle score				
Current smoker, *n* (%)	9,763 (6.7)	6,655 (6.2)	3,108 (8.1)	<0.0001
Body mass index, kg/m^2	22.7 (3.4)	22.7 (3.3)	22.6 (3.5)	<0.0001
Alcohol<20 g/day, *n* (%)	142,216 (96.9)	105,038 (97.1)	37,178 (96.5)	<0.0001
Regular exercise				
Exercise to sweat lightly, *n* (%)	58,932 (40.2)	46,404 (42.9)	12,528 (32.5)	<0.0001
Walking>1 hour/day, *n* (%)	76,043 (51.8)	58,492 (54.1)	17,551 (45.5)	<0.0001
Eating pattern				
Snacks after supper, *n* (%)	20,361 (13.9)	13,630 (12.6)	6,731 (17.5)	<0.0001
Skipping breakfast, *n* (%)	11,791 (8.0)	7,429 (6.9)	4,362 (11.3)	<0.0001
Past history, *n* (%)				
Stroke	3.902 (2.7)	2,813 (2.6)	1,089 (2.8)	0.02
Heart disease	7,606 (5.2)	5,271 (4.9)	2,335 (6.1)	<0.0001
Renal disease	632 (0.4)	436 (0.4)	196 (0.5)	0.007
Comorbidities, *n* (%)				
Hypertension	62,034 (42.3)	46,822 (43.3)	15,212 (39.5)	<0.0001
Diabetes	11,623 (7.9)	8,625 (8.0)	2,998 (7.8)	<0.0001
Hypercholesterolemia	74,371 (50.7)	55,682 (51.5)	18,689 (48.5)	<0.0001
Chronic kidney disease	21,762 (14.8)	16,146 (14.9)	5,616 (14.6)	<0.0001
Medication, *n* (%)				
Antihypertensive drugs	39,592 (27.0)	29,884 (27.6)	9,708 (25.2)	<0.0001
Antidiabetic medication	5,373 (3.7)	3,960 (3.7)	1,413 (3.7)	0.96
Cholesterol-lowering drugs	28,802 (19.6)	21,771 (20.1)	7,031 (18.2)	<0.0001
Systolic pressure, mmHg	128 (18)	129 (18)	130 (18)	<0.0001
Diastolic pressure, mmHg	75 (11)	75 (11)	75 (11)	<0.0001
Fasting plasma glucose, mg per 100 mL	95 (18)	95 (17)	95 (19)	0.03
Hemoglobin A_{1c}, %	5.71 (0.59)	5.72 (0.58)	5.70 (0.60)	<0.0001
LDL cholesterol, mg per 100 mL	130.0 (30.3)	130.2 (30.2)	129.2 (30.8)	<0.0001
Triglycerides, mg per 100 mL	92 (68, 127)	92 (69, 127)	91 (67, 126)	<0.0001
HDL cholesterol, mg per 100 mL	65.7 (16.0)	65.5 (16.0)	66.3 (16.2)	<0.0001
Creatinine, mg per 100 mL	0.63 (0.15)	0.63 (0.15)	0.63 (0.16)	0.005
eGFR, mL min^{-1} per 1.73 m^2	75.6 (15.9)	75.4 (15.9)	76.3 (16.1)	<0.0001
Proteinuria, *n* (%)	5,777 (3.9)	4,169 (3.9)	1,608 (4.2)	0.006

Numbers in the table are means (standard deviation) for continuous variables except triglycerides (median and interquartile range) or numbers (percentages) for categorical variables.
LDL, low-density lipoprotein; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate.
doi:10.1371/journal.pone.0108718.t002

measure the height, weight, blood pressure, and waist circumference of each participant, after which serum and spot urine samples are collected. BMI is calculated by dividing body weight in kilograms by the square of height in meters. Blood samples are analyzed using an automated clinical chemical analyzer within 24 h of sampling. All blood analyses are conducted at a local, rather than a central, laboratory. Although the methods used for blood analyses are not calibrated between laboratories, analyses

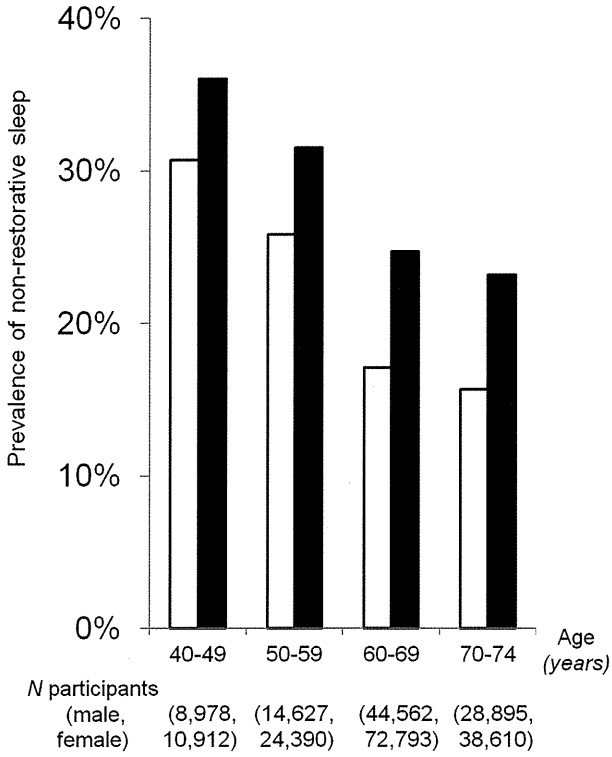

Figure 2. Prevalence of non-restorative sleep by sex and age. Trends were significant for both males (□; $P<0.0001$) and females (■; $P<0.0001$).
doi:10.1371/journal.pone.0108718.g002

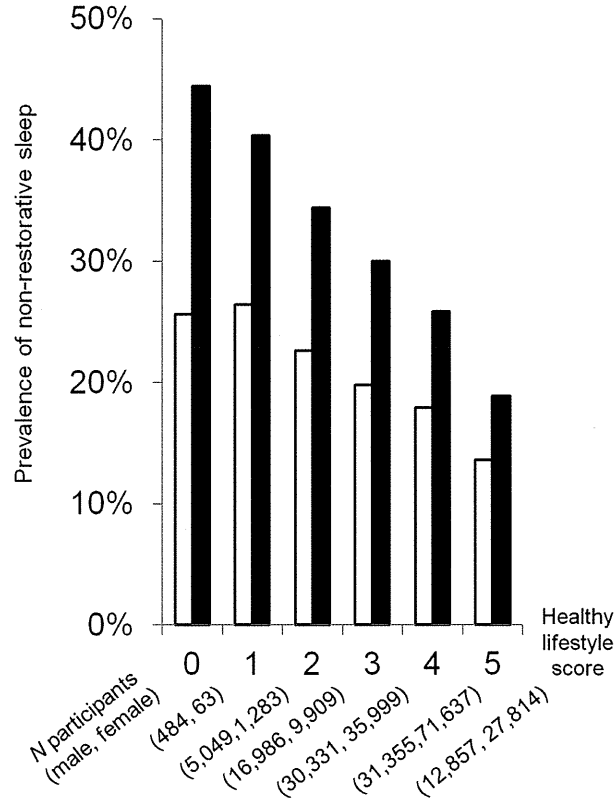

Figure 3. Prevalence of non-restorative sleep by healthy lifestyle score. Trends were significant for both males (□; $P<0.0001$) and females (■; $P<0.0001$).
doi:10.1371/journal.pone.0108718.g003

are performed according to the Japan Society of Clinical Chemistry-recommended methods for laboratory tests, which have been widely adopted by laboratories across Japan [29]. Participants diagnosed with metabolic syndrome are obligated to receive repeated lifestyle guidance over a six-month period after an annual health examination.

Participants from 40 to 74 years of age without missing information were included in this study. The complete selection process is presented in Figure 1.

Primary outcome

The primary outcome was NRS, which was assessed using this question from the self-administered questionnaire: 'Do you feel refreshed after a night's sleep?' Participants answered either yes or no. NRS was considered present when the answer was 'no'.

Lifestyle factors and covariates

For each lifestyle factor (smoking, BMI, alcohol intake, exercise habits, and eating patterns), we created a binary low-risk variable in which participants were given a score of 1 if they met the criteria for low risk or a score of 0 if otherwise, based on previous research [6]. The a priori definition of low risk was based on current literature, recommended guidelines, and realistically obtainable levels within the general population. We calculated a healthy lifestyle score by adding the total number of lifestyle factors for which each participant was at low risk. The score ranged from 0 (least healthy) to 5 (most healthy).

For smoking, we defined low risk as currently not smoking. Optimal body weight was defined as a BMI of <25 kg/m^2, the standard World Health Organization cutoff for healthy weight. For alcohol, average daily consumption over 20 g was considered high risk. Alcohol consumption was assessed by the following questions: "How often do you drink alcohol (sake, shochu [distilled spirits], beer, liquor, etc.)?" to which participants responded by selecting (1) every day, (2) sometimes, or (3) rarely (can't drink); and "How much do you drink a day, in terms of glasses of refined sake? (A glass [180 mL] of refined sake is equivalent to a medium bottle [500 mL] of beer, 80 mL of shochu (alcohol content 35 percent), a glass [double, 60 mL] of whiskey, and 2 glasses [240 mL] of wine)," to which participants responded by selecting (1) <1 drink per day, (2) 1–2 drinks per day, (3) 2–3 drinks per day, or (4) ≥ 3 drinks per day'. The ethanol content per drink was calculated to be equivalent to 20 g. For exercise habits, two questions were asked: 'Are you in the habit of exercising to sweat lightly for over 30 minutes each time, two times weekly, for over a year?' and 'In your daily life, do you walk or do any equivalent amount of physical activity for more than one hour a day?' Low risk patients were defined as those who answered 'yes' to both questions on the basis of a current Japanese guideline [30]. For eating patterns, two questions were asked: 'Do you skip breakfast more than three times a week?' and 'Do you eat snacks after supper more than three times a week?' Low risk patients were defined as those who answered 'no' to both questions.

Hemoglobin A1c (HbA1c) was estimated as a National Glycohemoglobin Standardization Program equivalent value using the following equation [31]: HbA1c (%) = HbA1c (Japan Diabetes Society) (%)+0.4%. Diabetes was defined in accordance with American Diabetes Association guidelines [32] as a fasting plasma glucose concentration of 126 mg/dL or higher, HbA1c of

Table 3. Multivariate analysis of the relationship between categories from the healthy lifestyle score and prevalence of non-restorative sleep ($N = 243,767$).

Variable	Male ($N = 97,062$)		Female ($N = 146,705$)	
	Age-adjusted odds ratio (95%CI)	Multivariate odds ratio[a] (95%CI)	Age-adjusted odds ratio (95%CI)	Multivariate odds ratio[a] (95%CI)
Categories				
Current smoker				
No (ref)	1.00	1.00	1.00	1.00
Yes	0.90 (0.87–0.93)****	0.90 (0.87–0.93)****	1.09 (1.04–1.14)****	1.09 (1.04–1.14)****
Body mass index				
<25 m/kg^2 (ref)	1.00	1.00	1.00	1.00
≥25 m/kg^2	0.97 (0.93–1.00)	0.97 (0.94–1.01)	0.98 (0.95–1.00)	0.99 (0.96–1.02)
Alcohol consumption				
<20 g/day (ref)	1.00	1.00	1.00	1.00
≥20 g/day	0.83 (0.80–0.86)****	0.83 (0.80–0.86)****	1.03 (0.96–1.10)	1.03 (0.96–1.10)
Regular exercise				
Yes (ref)	1.00	1.00	1.00	1.00
No	1.57 (1.51–1.62)****	1.57 (1.51–1.63)****	1.52 (1.47–1.58)****	1.52 (1.48–1.56)****
Eating pattern				
Healthy (ref)	1.00	1.00	1.00	1.00
Less healthy	1.54 (1.48–1.60)****	1.54 (1.48–1.60)****	1.44 (1.40–1.48)****	1.44 (1.40–1.48)****
Age				
40–49 years	1.96 (1.85–2.08)****	1.95 (1.84–2.07)****	1.56 (1.48–1.63)****	1.50 (1.43–1.57)****
50–59 years	1.63 (1.55–1.71)****	1.62 (1.54–1.71)****	1.35 (1.30–1.40)****	1.32 (1.27–1.37)****
60–69 years	1.09 (1.04–1.13)****	1.09 (1.04–1.13)****	1.06 (1.03–1.09)****	1.05 (1.02–1.09)**
70–74 years (ref)	1.00	1.00	1.00	1.00
Hypertension		0.96 (0.93–1.00)*		0.94 (0.91–0.96)****
Diabetes mellitus		0.99 (0.95–1.04)		1.06 (1.02–1.11)**
Hypercholesterolemia		0.97 (0.93–1.00)		0.95 (0.92–0.97)****
Chronic kidney disease		1.04 (1.00–1.08)		1.04 (1.00–1.08)*

[a] Adjusted for age (years), sex, hypertension, diabetes, hypercholesterolemia, and chronic kidney disease.
Definitions of these factors are described in the text.
*$P<0.05$,
**$P<0.01$,
***$P<0.001$,
****$P<0.0001$.
doi:10.1371/journal.pone.0108718.t003

6.5% or higher, or self-reported use of anti-hyperglycemic drugs. Hypertension was defined as using antihypertensive medications, a systolic blood pressure ≥140 mmHg, a diastolic blood pressure ≥ 90 mmHg, or both. Hypercholesterolemia was defined as using cholesterol-lowering medications, a low-density lipoprotein (LDL) cholesterol level ≥140 mg/dL, or both. Chronic kidney disease was defined as proteinuria in urinalysis, a glomerular filtration rate (GFR) less than 60 mL/min/1.73 m^2, or both [33]. Proteinuria was defined as a dipstick urinalysis score of 1+ or greater (equivalent to ≥30 mg/dL) because of poor discrimination between negative and trace positive dipstick readings [34]. Estimated GFR was calculated using the Japanese equation [35].

Statistical analysis

Data were analyzed separately by sex. First, we calculated the prevalence of NRS stratified by age categories. Age was categorized as 40–49, 50–59, 60–69, and 70–74 years. Second, we analyzed clinical and laboratory parameters stratified by the presence or absence of NRS. The chi-square test, Student's t-test, and Mann-Whitney U test were used to assess differences among participant characteristics in relation to NRS. Spearman and Pearson correlation coefficients were calculated to evaluate the relationship among each independent variable. To evaluate the association between prevalent NRS and each variable of the healthy lifestyle score, multivariable-adjusted odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were calculated using the category conventionally believed to be most healthy as the reference group. Data were initially adjusted for age. Next, we added age, hypertension, diabetes, hypercholesterolemia, and chronic kidney disease to multivariate models (Model 1). Finally, we added history of stroke, heart disease, and renal failure to Model 1 (Model 2).

To assess the robustness of the main results, we conducted several subsidiary analyses. First, subgroup analyses were stratified by age categories because age is associated with NRS. Healthy lifestyle scores from 0 (least healthy) to 1 (second-least healthy)

were combined into one category because there were few cases. Age was also added as a continuous variable. Second, subgroup analyses were conducted among nonusers of medications to avoid variations in results due to medications. Nonusers of medications were defined as individuals who took no medications for diabetes, hypertension, and hypercholesterolemia. Finally, the analyses were repeated after excluding participants with obesity (BMI≥25 kg/m^2) to enhance the association between healthy lifestyle and NRS, as obese participants could modify their lifestyle to lose weight. Because increased BMI may be a consequence rather than a component of an unhealthy lifestyle, another healthy lifestyle score was created to incorporate all variables except BMI. This score ranged from 0 to 4 points.

P<0.05 was considered statistically significant, and all tests were two-tailed. All analyses were performed with the SPSS for Windows statistical package (Version 18.0; SPSS, Chicago, IL, USA) and Stata/MP software (Version 12.1; Stata Corp, College Station, TX, USA).

Results

Participant flow

Of the 667,218 SHC participants screened in 2008, we excluded those who did not have serum creatinine levels measured (n = 112,540) because it is not mandatory for the SHC but is included independently in some areas. We also excluded anyone with missing information (n = 310,911), resulting in a final sample size of 243,767 (Figure 1). There were no substantial differences between included and excluded participants for characteristics such as prevalence of NRS, sex, age, and healthy lifestyle score (Table S1).

Demographic characteristics of participants

Among 97,062 men and 146,705 women, 18,678 (19.2%) and 38,539 (26.3%) were identified as having NRS, respectively. Tables 1 and 2 present the associations between various clinical characteristics and NRS. Both male and female participants with NRS were younger, had higher prevalence of current smokers, higher BMI, lower prevalence of exercise habits, and higher prevalence of less healthy eating patterns. They were also more likely to have a history of heart or renal disease and less likely to have hypertension, diabetes, and chronic kidney disease. Some differences were observed between sexes. Women with NRS were less likely to have an adequate intake of daily alcohol, while this was more likely in men with NRS compared to those without NRS. In addition, the proportion of those with a history of stroke was significantly higher in women with NRS, but not in men with NRS.

Associations between the healthy lifestyle score and NRS

The prevalence of NRS decreased with increasing age for both men and women (P for trend <0.0001, Figure 2), and was lower among men than women for all age groups. An inverse, dose-response relationship was observed between healthy lifestyle scores and prevalence of NRS for both male and female participants (P for trend <0.0001, Figure 3).

When each variable of the healthy lifestyle score was considered individually, less healthy eating patterns and no regular exercise were associated with a higher prevalence of NRS (Table 3), but there were no apparent associations between BMI and the prevalence of NRS. Some differences were observed between men and women. Current smokers were associated with a higher prevalence of NRS in women and a lower prevalence in men. In addition, alcohol consumption was not associated with NRS in women but was associated with a lower prevalence in men.

Tables 4 and 5 show that participants with a score of 0 (least healthy) had an age-adjusted OR of 1.56 (95% CI, 1.26–1.93) for men and 2.76 (95% CI, 1.68–4.56) for women, compared to those with a score of 5 (most healthy). Additional adjustments for potential consequences of an unhealthy lifestyle (i.e., hypertension, diabetes mellitus, hypercholesterolemia, and chronic kidney disease) only partially changed risk (OR for men: 1.59, 95% CI, 1.29–1.97; OR for women: 2.88, 95% CI, 1.74–4.76). This association was not changed by additional adjustments for history of stroke, heart disease, and renal failure (Model 2).

When stratified by age categories, the association between a healthy lifestyle score and prevalence of NRS was similar when compared with the entire study population for both men and women (Figure 4). Among participants who currently took no medications for diabetes, hypertension, or hypercholesterolemia, a similar association was also observed for both sexes. Furthermore, the associations were consistent among obese and non-obese participants.

Discussion

Our findings support the hypothesis that a combination of unhealthy lifestyle factors is associated with inadequate sleep. A

Table 4. Odds ratios for the association between the healthy lifestyle score and prevalent non-restorative sleep in men (N = 97,062).

Healthy lifestyle score	Unadjusted	Age-adjusted	Model 1	Model 2
0	2.19 (1.77–2.70)****	1.56 (1.26–1.93)****	1.59 (1.29–1.97)****	1.60 (1.29–1.98)****
1	2.28 (2.10–2.47)****	1.73 (1.59–1.88)****	1.76 (1.62–1.91)****	1.77 (1.63–1.92)****
2	1.86 (1.75–1.98)****	1.54 (1.44–1.64)****	1.56 (1.46–1.66)****	1.56 (1.46–1.66)****
3	1.57 (1.48–1.66)****	1.40 (1.32–1.48)****	1.41 (1.33–1.49)****	1.41 (1.33–1.50)****
4	1.39 (1.31–1.47)****	1.31 (1.24–1.39)****	1.32 (1.24–1.40)****	1.32 (1.24–1.40)****
5 (ref)	1.00	1.00	1.00	1.00

Model 1: adjusted for age (years), hypertension, diabetes, hypercholesterolemia, and chronic kidney disease.
Model 2: adjusted Model 1 plus history of stroke, heart disease, and renal failure.
*P<0.05,
**P<0.01,
***P<0.001,
****P<0.0001.
doi:10.1371/journal.pone.0108718.t004

Table 5. Odds ratios for the association between the healthy lifestyle score and prevalent non-restorative sleep in women ($N = 146,705$).

Healthy lifestyle score	Unadjusted	Age-adjusted	Model 1	Model 2
0	3.43 (2.09–5.65)****	2.76 (1.68–4.56)****	2.88 (1.74–4.76)****	2.88 (1.74–4.75)****
1	2.91 (2.59–2.26)****	2.43 (2.16–2.73)****	2.48 (2.21–2.79)****	2.47 (2.20–2.78)****
2	2.25 (2.14–2.37)****	2.00 (1.90–2.11)****	2.04 (1.94–2.15)****	2.03 (1.93–2.14)****
3	1.84 (1.77–1.91)****	1.71 (1.65–1.78)****	1.74 (1.67–1.81)****	1.73 (1.67–1.80)****
4	1.50 (1.45–1.55)****	1.44 (1.39–1.49)****	1.45 (1.40–1.50)****	1.44 (1.39–1.49)****
5 (ref)	1.00	1.00	1.00	1.00

Model 1: adjusted for age (years), hypertension, diabetes, hypercholesterolemia, and chronic kidney disease.
Model 2: adjusted Model 1 plus history of stroke, heart disease, and renal failure.
*$P<0.05$,
**$P<0.01$,
***$P<0.001$,
****$P<0.0001$.
doi:10.1371/journal.pone.0108718.t005

combination of healthy lifestyle factors was associated with a decreased prevalence of NRS in both men and women of any age, even after adjusting for comorbidities such as hypertension, diabetes mellitus, hypercholesterolemia, chronic kidney disease, and history of stroke, heart disease, and renal failure. Although further study is needed to strengthen the association between the combined lifestyle factors and inadequate sleep, these findings raise the possibility that a healthy lifestyle could not only reduce the risk of developing several diseases but also improve sleep quality. If healthy lifestyle factors can provide restorative sleep, gaining satisfying rest would be a strong motivator for lifestyle modification.

Insomnia is an important public health issue [36] characterized by nighttime sleep problems. These may be manifest as difficulties in initiating or maintaining sleep, NRS, a combination of these complaints, or daytime symptoms [37]. Although there is a lack of consistency in the definition of NRS, and reports on NRS have been less extensive compared with other symptoms of primary insomnia (i.e., sleep latency and total sleep time), mounting evidence suggests that NRS is a frequent symptom observed in the general population. NRS prevalence was reported to be 10.8% in the non-institutionalized general population in seven European countries (France, the United Kingdom, Germany, Italy, Portugal, Spain, and Finland) [38], 35% in the participants of the Atherosclerosis Risk in Community Study in the United States [39], and 14.8% in the general South Korean population [40]. Although our methodology and questionnaire were not the same as those used in these studies, our findings were consistent in that NRS is frequently observed in the general Japanese population. The prevalence of NRS was higher in women than in men and decreased with age in our study. These results are in line with previous studies from Europe [38], the United States [36,39], South Korea [40], as well as an international survey conducted in Finland, Greece, Jordan and Lebanon, Morocco, Mexico, the Philippines, Portugal, Sweden, and Switzerland [41]. Although the prevalence of insomnia differs from one country to another [40], a decrease in NRS prevalence with age is commonly observed. This suggests that some common risk factors may be shared among young people with different racial, ethnic, cultural, and environmental background.

With regard to individual lifestyle factors, we found associations between NRS and physical inactivity or unhealthy eating patterns. Both physical activity and a healthy diet are known to be associated with sleep quality. A high level of exercise is related to better sleep patterns such as higher sleep quality, shortened sleep latency, and fewer awakenings during the night [42], while lack of habitual exercise is associated with more reported sleep complaints [43–44]. Meanwhile, skipping breakfast and a regular habit of snacking are more common in individuals with short sleep duration than in those with normal sleep duration [45]. A randomized crossover study showed that skipping breakfast in a nocturnal lifestyle, i.e., sleeping at 1:30 a.m. and waking at 8:30 a.m., was associated with decreased secretion of melatonin and leptin [46], suggesting that those lifestyle factors might be both a cause and a consequence of inadequate sleep. Although information is limited about NRS and physical inactivity or eating patterns, our findings are in line with these studies.

We found no association between NRS and BMI. Although obesity is associated with sleep apnea, little is known about its connection to NRS. Previous literature has shown that BMI is not associated with the prevalence of NRS, except in underweight individuals (BMI<20 kg/m^2) who had a higher prevalence of NRS than those with normal BMI (20–24 kg/m^2) [40]. A possible reason for this discrepancy is that use of a binary variable in our analysis did not detect an association between being underweight and having NRS that might only be observed when analyzed quantitatively.

Notably, sex differences were observed for smoking and alcohol consumption. Although smoking was associated with increases in NRS in women, the opposite relationship was observed in men, and adequate alcohol consumption was associated with increases in NRS among only male participants. It has generally been found that both alcohol consumption and smoking are associated with increases in sleep disorders [47–49], but associations between NRS and alcohol consumption or smoking are still controversial. Smoking has been associated with NRS in some studies [40,48] but not in another [39]. While alcohol consumption is not associated with NRS [39], some studies have found that alcohol abuse [50] and alcohol dependence [40] are connected to NRS. These inconsistencies may be primarily due to the different definitions of NRS, which only represents a single dimension or item of sleep symptoms [36]. It is also possible that using the binary variable in our study influenced results. Although associations between NRS and alcohol or smoking differed between men and women, the combined effect of healthy lifestyle factors on NRS were similar for both, suggesting that lifestyle factors cooperate with one another and are important for restorative sleep. Furthermore, a comprehensive analysis of

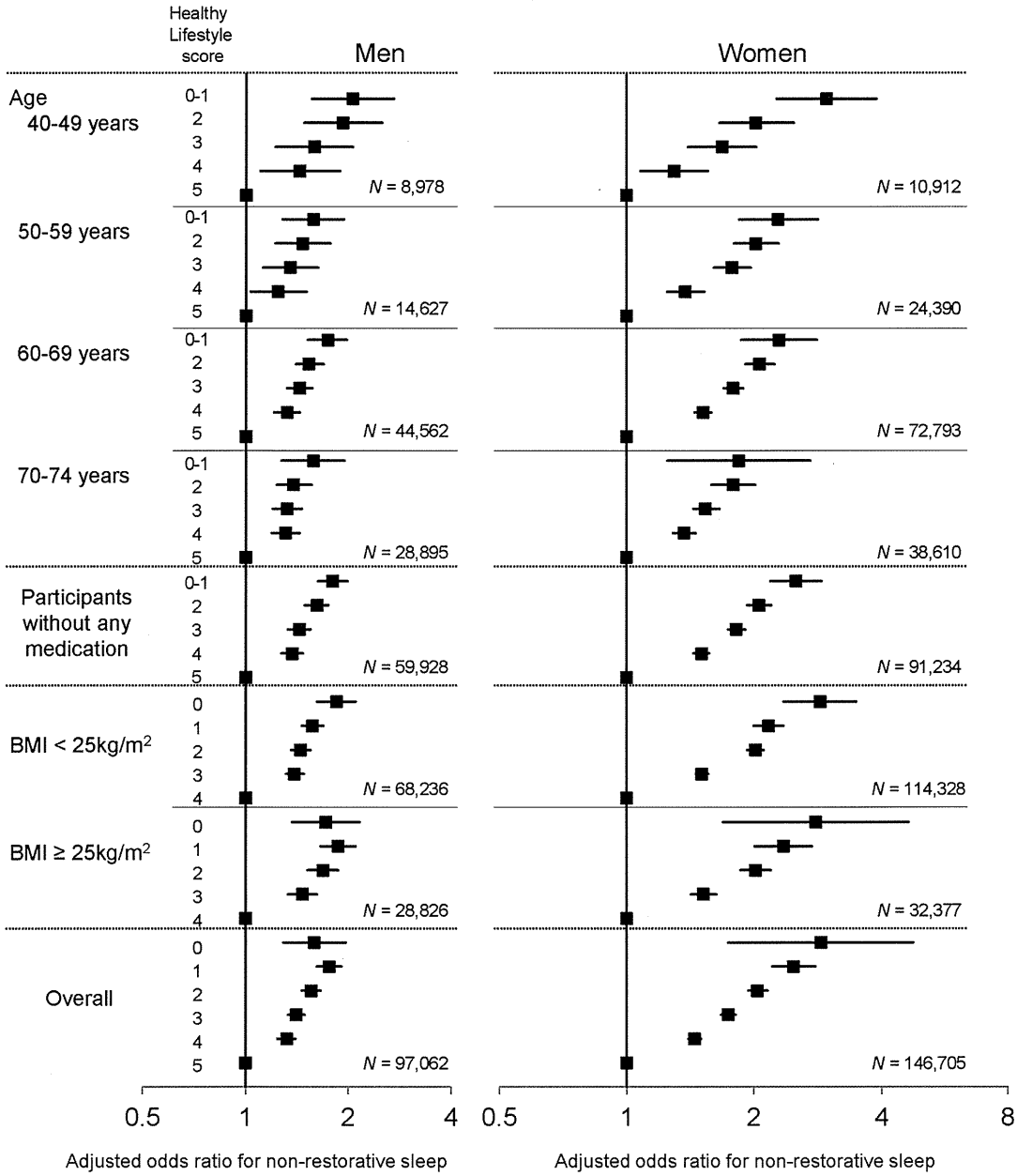

Figure 4. Subgroup analysis. Forest plot shows odds ratio with 95% confidence interval for the association between a healthy lifestyle score and prevalent non-restorative sleep in subgroups and in the entire study population. All analyses were adjusted for the following covariates: age (in years), hypertension, diabetes, hypercholesterolemia, and chronic kidney disease.
doi:10.1371/journal.pone.0108718.g004

healthy lifestyle may capture influence of individual factors better than analyses based on a single factor, given the complexity and multiple dimensions of habitual health behaviors. Further investigation is needed to determine whether critical thresholds exist for each lifestyle factor and to establish combined effects and interaction effects as well as individual effects.

Patients with NRS were recently reported to have higher C-reactive protein (CRP) levels, a marker for systemic inflammation, than those without NRS [51]. Elevated CRP has also been associated with lifestyle risk factors such as obesity [52], physical inactivity [53], cigarette smoking [54], and alcohol consumption [55,56]. These findings together suggest that participants with NRS have higher CRP levels due to unhealthy lifestyle behaviors, although no information about CRP was available in our study. It is possible that sleep deprivation [57,58] or stress [59] leads to increased CRP levels. Further investigation is warranted to clarify these aspects of the relationship between NRS and lifestyle factors.

Our study has several limitations. First, a selection bias of subjects might exist. Because participants in this cohort received annual physical checkups, they might be more health-conscious than the average Japanese population. Second, NRS was determined solely based on self-reported information and may

not be accurate. A single retrospective item has limitations that need to be addressed, such as recall bias and demand characteristics. In addition, frequency (i.e., more than three times per week) and sleep duration were not included in the questionnaire used to assess NRS. However, there is no reliable and well-validated patient-reported outcome instrument currently available for evaluating NRS [27]. Third, we cannot exclude the possibility that residual confounding factors exist, which were not measured in the present study, such as marital status [38], educational level [36,50], employment status [38], work schedule [50], level of stress [50], psychiatric disorders [38], and use of sleep medications. Whether these factors affect the relationship between lifestyle factors and NRS should be assessed in the future. Fourth, we gave equal weight to each lifestyle factor to achieve the main purpose of the study. That may have resulted in conservative estimates for multiple lifestyle factors. Fifth, the nutritive content in diet could not be evaluated due to lack of information. Evidence regarding the associations between diet and NRS is scarce, although a cross-sectional study using data from the National Health and Nutrition Examination Survey (NHANES) from the United States has shown that NRS is positively associated with butanoic acid, moisture, cholesterol, and negatively associated with calcium, vitamin C, and water [60]. Sixth, odds ratios do not approximate well to the relative risk when the effect sizes are large and the prevalence of the outcome of interest is high [61]. In our study, the prevalence of NRS was relatively high, whereas the effect sizes were not large. In addition, qualitative judgments based on interpreting odds ratios as though they were relative risks are unlikely to be seriously in error [61]. Therefore, we consider that our results demonstrate important effects. Finally, the cross-sectional study design limited our ability to determine the direction of the association or causality. NRS might be the cause, rather than the consequence, of one or more unhealthy lifestyle factors.

Our study also has several strengths. First, it was a large-scale cross-sectional study with participants from all over Japan. Second, this is the first report, to the best of our knowledge, to demonstrate the prevalence of NRS in the general Japanese population and assess the association between combined lifestyle factors and NRS.

In conclusion, a combination of healthy lifestyle factors was associated with an increase in restorative sleep independently of age, sex, and comorbidities in the general Japanese population. Further studies are needed to establish whether general lifestyle modification improves restorative sleep.

Supporting Information

Table S1 Clinical characteristics of participants included and excluded in the analysis. Numbers in the table are means (standard deviation) for continuous variables except triglycerides (median and interquartile range) or numbers (percentages) for categorical variables. Note that the percentages are computed based only on the total number of non-missing cases. LDL, low-density lipoprotein; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate.
(DOC)

Author Contributions

Conceived and designed the experiments: MW IN. Performed the experiments: MW JJK IN. Analyzed the data: MW. Wrote the first draft of the manuscript: MW. Contributed to drafting the manuscript: MW JJK IN. ICMJE criteria for authorship read and met: MW JJK IN KI TM KY SF KT KA TK KK MK IK YO TW. Agree with manuscript results and conclusions: MW JJK IN KI TM KY SF KT KA TK KK MK IK YO TW.

References

1. Stampfer MJ, Hu FB, Manson JE, Rimm EB, Willett WC (2000) Primary prevention of coronary heart disease in women through diet and lifestyle. N Engl J Med 343: 16–22.
2. Chiuve SE, McCullough ML, Sacks FM, Rimm EB (2006) Healthy lifestyle factors in the primary prevention of coronary heart disease among men: benefits among users and nonusers of lipid-lowering and antihypertensive medications. Circulation 114: 160–167.
3. Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, et al. (2001) Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. N Engl J Med 345: 790–797.
4. Kurth T, Moore SC, Gaziano JM, Kase CS, Stampfer MJ, et al. (2006) Healthy lifestyle and the risk of stroke in women. Arch Intern Med 166: 1403–1409.
5. Chiuve SE, Fung TT, Rexrode KM, Spiegelman D, Manson JE, et al. (2011) Adherence to a low-risk, healthy lifestyle and risk of sudden cardiac death among women. JAMA 306: 62–69.
6. Wakasugi M, Kazama JJ, Yamamoto S, Kawamura K, Narita I (2013) A combination of healthy lifestyle factors is associated with a decreased incidence of chronic kidney disease: a population-based cohort study. Hypertens Res 36: 328–333.
7. Platz EA, Willett WC, Colditz GA, Rimm EB, Spiegelman D, et al. (2000) Proportion of colon cancer risk that might be preventable in a cohort of middle-aged US men. Cancer Causes Control 11: 579–588.
8. Jiao L, Mitrou PN, Reedy J, Graubard BI, Hollenbeck AR, et al. (2009) A combined healthy lifestyle score and risk of pancreatic cancer in a large cohort study. Arch Intern Med 169: 764–770.
9. Sasazuki S, Inoue M, Iwasaki M, Sawada N, Shimazu T, et al. (2012) Combined impact of five lifestyle factors and subsequent risk of cancer: the Japan Public Health Center Study. Prev Med 54: 112–116.
10. van Dam RM, Li T, Spiegelman D, Franco OH, Hu FB (2008) Combined impact of lifestyle factors on mortality: prospective cohort study in US women. BMJ 337: a1440.
11. Liu K, Daviglus ML, Loria CM, Colangelo LA, Spring B, et al. (2012) Healthy lifestyle through young adulthood and the presence of low cardiovascular disease risk profile in middle age: the Coronary Artery Risk Development in (Young) Adults (CARDIA) study. Circulation 125: 996–1004.
12. Shochat T (2012) Impact of lifestyle and technology developments on sleep. Nature Science Sleep 4: 19–31.
13. Peuhkuri K, Sihvola N, Korpela R (2012) Diet promotes sleep duration and quality. Nutrition Research 32: 309–319.
14. Hasler G, Buysse DJ, Klaghofer R, Gamma A, Ajdacic V, et al. (2004) The association between short sleep duration and obesity in young adults: a 13-year prospective study. Sleep 27: 661–666.
15. Gangwisch JE, Malaspina D, Boden-Albala B, Heymsfield SB (2005) Inadequate sleep as a risk factor for obesity: analyses of the NHANES I. Sleep 28: 1289–1296.
16. Patel SR, Malhotra A, White DP, Gottlieb DJ, Hu FB (2006) Association between reduced sleep and weight gain in women. Am J Epidemiol 164: 947–954.
17. Chaput JP, Després JP, Bouchard C, Tremblay A (2008) The association between sleep duration and weight gain in adults: a 6-year prospective study from the Quebec Family Study. Sleep 31: 517–523.
18. Ayas NT, White DP, Al-Delaimy WK, Manson JE, Stampfer MJ, et al. (2003) A prospective study of self-reported sleep duration and incident diabetes in women. Diabetes Care 26: 380–384.
19. Gangwisch JE, Heymsfield SB, Boden-Albala B, Buijs RM, Kreier F, et al. (2007) Sleep duration as a risk factor for diabetes incidence in a large U.S. sample. Sleep 30: 1667–1673.
20. Gangwisch JE, Heymsfield SB, Boden-Albala B, Buijs RM, Kreier F, et al. (2006) Short sleep duration as a risk factor for hypertension: analyses of the first National Health and Nutrition Examination Survey. Hypertension 47: 833–839.
21. Kaneita Y, Uchiyama M, Yoshiike N, Ohida T (2008) Associations of usual sleep duration with serum lipid and lipoprotein levels. Sleep 31: 645–652.
22. Ayas NT, White DP, Manson JE, Stampfer MJ, Speizer FE, et al. (2003) A prospective study of sleep duration and coronary heart disease in women. Arch Intern Med 163: 205–209.
23. Yamamoto R, Nagasawa Y, Iwatani H, Shinzawa M, Obi Y, et al. (2012) Self-reported sleep duration and prediction of proteinuria: a retrospective cohort study. Am J Kidney Dis 59: 343–355.
24. Chang ET (2009) The impact of daytime naps on the relation between sleep duration and cardiovascular events. Arch Intern Med 169: 717. doi:10.1001/archinternmed.2009.29.
25. Chandola T, Ferrie JE, Perski A, Akbaraly T, Marmot MG (2010) The effect of short sleep duration on coronary heart disease risk is greatest among those with

sleep disturbance: a prospective study from the Whitehall II cohort. Sleep 33: 739–744.
26. Hoevenaar-Blom MP, Spijkerman AM, Kromhout D, van den Berg JF, Verschuren WM (2011) Sleep duration and sleep quality in relation to 12-year cardiovascular disease incidence: the MORGEN study. Sleep 34: 1487–1492.
27. Vernon MK, Dugar A, Revicki D, Treglia M, Buysse D (2010) Measurement of non-restorative sleep in insomnia: A review of the literature. Sleep Med Rev 14: 205–212.
28. Kohro T, Furui Y, Mitsutake N, Fujii R, Morita H, et al. (2008) The Japanese national health screening and intervention program aimed at preventing worsening of the metabolic syndrome. Int Heart J 49: 193–203.
29. Tsuruya K, Yoshida H, Nagata M, Kitazono T, Hirakata H, et al. (2014) Association of the triglycerides to high-density lipoprotein cholesterol ratio with the risk of chronic kidney disease: analysis in a large Japanese population. Atherosclerosis. 233: 260–267.
30. The Office for Lifestyle-Related Diseases Control, General Affairs Division, Health Service Bureau, Ministry of Health, Labour and Welfare of Japan (2006) Exercise and Physical Activity Guide for Health Promotion 2006 - To Prevent Lifestyle-related Diseases - <Exercise Guide 2006>Prepared in August, 2006. Available: http://www.nih.go.jp/eiken/programs/pdf/exercise_guide.pdf. Accessed 13 September 2011.
31. The Committee of Japan Diabetes Society on the diagnostic criteria of diabetes mellitus (2010) Report of the Committee on the classification and diagnostic criteria of diabetes mellitus. J Jpn Diabetes Soc 53: 450–467.
32. American Diabetes Association (2011) Diagnosis and classification of diabetes mellitus. Diabetes Care (Suppl 1): S62–S69.
33. National Kidney Foundation (2002) K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 39 (Suppl 1): S1–S266.
34. Harrison NA, Rainford DJ, White GA, Cullen SA, Strike PW (1989) Proteinuria: What value is the dipstick? Br J Urol 63: 202–208.
35. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, et al. (2009) Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis 53: 982–992.
36. Grandner MA, Petrov ME, Rattanaumpawan P, Jackson N, Platt A, et al. (2013) Sleep symptoms, race/ethnicity, and socioeconomic position. J Clin Sleep Med. 9: 897–905; 905A–905D.
37. Roth T, Zammit G, Lankford A, Mayleben D, Stern T, et al. (2010) Nonrestorative sleep as a distinct component of insomnia. Sleep 33: 449–458.
38. Ohayon MM (2005) Prevalence and correlates of nonrestorative sleep complaints. Arch Intern Med 165: 35–41.
39. Phillips B, Mannino D (2005) Correlates of sleep complaints in adults: the ARIC study. J Clin Sleep Med 1: 277–283.
40. Kim BS, Jeon HJ, Hong JP, Bae JN, Lee JY, et al. (2012) DSM-IV psychiatric comorbidity according to symptoms of insomnia: a nationwide sample of Korean adults. Soc Psychiatry Psychiatr Epidemiol 47: 2019–2033.
41. Léger D, Partinen M, Hirshkowitz M, Chokroverty S, EQUINOX (Evaluation of daytime QUality Impairment by Nocturnal awakenings in Outpatient's eXperience) Survey Investigators, et al. (2010) Characteristics of insomnia in a primary care setting: EQUINOX survey of 5293 insomniacs from 10 countries. Sleep Med. 11: 987–998.
42. Brand S, Gerber M, Beck J, Hatzinger M, Pühse U, et al. (2010) High exercise levels are related to favorable sleep patterns and psychological functioning in adolescents: a comparison of athletes and controls. J Adolesc Health 46: 133–141.
43. Kim K, Uchiyama M, Okawa M, Liu X, Ogihara R (2000) An epidemiological study of insomnia among the Japanese general population. Sleep 23: 41–47.
44. Morgan K (2003) Daytime activity and risk factors for late-life insomnia. J Sleep Res 12: 231–238.
45. Kim S, DeRoo LA, Sandler DP (2011) Eating patterns and nutritional characteristics associated with sleep duration. Public Health Nutr 14: 889–895.
46. Qin LQ, Li J, Wang Y, Wang J, Xu JY, et al. (2003) The effects of nocturnal life on endocrine circadian patterns in healthy adults. Life Sci 73: 2467–2475.
47. Phillips BA, Danner FJ (1995) Cigarette smoking and sleep disturbance. Arch Intern Med 155: 734–737.
48. Wetter DW, Young TB (1994) The relation between cigarette smoking and sleep disturbance. Prev Med 23: 328–334.
49. Brower KJ (2003) Insomnia, alcoholism and relapse. Sleep Med Rev 7: 523–539.
50. Ohayon MM, Hong SC (2002) Prevalence of insomnia and associated factors in South Korea. J Psychosom Res 53: 593–600.
51. Zhang J, Lamers F, Hickie IB, He JP, Feig E, et al. (2013) Differentiating nonrestorative sleep from nocturnal insomnia symptoms: demographic, clinical, inflammatory, and functional correlates. Sleep 36: 671–679.
52. Choi J, Joseph L, Pilote L (2013) Obesity and C-reactive protein in various populations: a systematic review and meta-analysis. Obes Rev 14: 232–244.
53. Kasapis C, Thompson PD (2005) The effects of physical activity on serum C-reactive protein and inflammatory markers: A systematic review. J Am Coll Cardiol 45: 1563–1569.
54. Bazzano LA, He J, Muntner P, Vupputuri S, Whelton PK (2003) Relationship between cigarette smoking and novel risk factors for cardiovascular disease in the United States. Ann Intern Med 138: 891–897.
55. Albert MA, Glynn RJ, Ridker PM (2003) Alcohol consumption and plasma concentration of C-reactive protein. Circulation 107: 443e7.
56. Averina M, Nilssen O, Arkhipovsky VL, Kalinin AG, Brox J (2006) C-reactive protein and alcohol consumption: Is there a U-shaped association? Results from a population-based study in Russia. The Arkhangelsk study. Atherosclerosis 188: 309–315.
57. van Leeuwen WM, Lehto M, Karisola P, Lindholm H, Luukkonen R, et al. (2009) Sleep restriction increases the risk of developing cardiovascular diseases by augmenting proinflammatory responses through IL-17 and CRP. PLoS One. 4: e4589.
58. Meier-Ewert HK, Ridker PM, Rifai N, Regan MM, Price NJ, et al. (2004) Effect of sleep loss on C-reactive protein, an inflammatory marker of cardiovascular risk. J Am Coll Cardiol. 43: 678–683.
59. Johnson TV, Abbasi A, Master VA (2013) Systematic review of the evidence of a relationship between chronic psychosocial stress and C-reactive protein. Mol Diagn Ther. 17: 147–164.
60. Grandner MA, Jackson N, Gerstner JR, Knutson KL (2014) Sleep symptoms associated with intake of specific dietary nutrients. J Sleep Res. 23: 22–34.
61. Davies HT, Crombie IK, Tavakoli M (1998) When can odds ratios mislead? BMJ. 316: 989–991.

Clin Exp Nephrol
DOI 10.1007/s10157-014-1062-2

ORIGINAL ARTICLE

Significance of estimated glomerular filtration rate in predicting brain or heart attacks in obese and non-obese populations

Yuji Sato · Shouichi Fujimoto · Tsuneo Konta · Kunitoshi Iseki · Toshiki Moriyama · Kunihiro Yamagata · Kazuhiko Tsuruya · Kenjiro Kimura · Ichiei Narita · Masahide Kondo · Koichi Asahi · Issei Kurahashi · Yasuo Ohashi · Tsuyoshi Watanabe

Received: 10 October 2014 / Accepted: 20 November 2014

Abstract
Background The Japanese Specific Health Checkup mainly focuses on metabolic syndrome for preventing cardiovascular events. Subjects are stratified by measuring waist circumference, body mass index, blood pressure, triglycerides, and fasting plasma glucose. However, estimated glomerular filtration rate (eGFR) is not considered essential.
Methods A longitudinal cohort study assessed the association of eGFR with new-onset brain or heart attacks in a large Japanese nationwide Specific Health Checkup database. A total of 109,349 Japanese subjects (mean age 63.2 years, 39.5 % men) were examined for the events 2 years later. The odds ratios were calculated for new events in the total and subgroup populations divided by BMI $<$ or $\geq$25 kg/m^2, obese and non-obese, respectively.
Results Obese subjects were more often male and had proteinuria (dipstick test $\geq$1+), lower eGFR, and higher systolic and diastolic BP, fasting plasma glucose, hemoglobin A1c, and triglycerides (TG). Rates of new-onset brain or heart attacks were 3.1 and 4.0 % in the groups of non-obese and obese subjects, respectively. In the total population, eGFR as well as higher BMI ($\geq$25 kg/m^2), higher BP (high-normal hypertension or greater), higher TG ($\geq$150 mg/dl), and proteinuria were significant risk factors for developing brain or heart attacks. The eGFR was significant in non-obese subjects, but not in the obese.
Conclusion As the ultimate aim of 'Specific Health Checkup' is to prevent cardiovascular events, our study suggests that eGFR should be evaluated in non-obese subjects.

Keywords Specific Health Checkup · Estimated GFR · Body mass index · Cardiovascular disease · Cerebrovascular disease

Y. Sato (✉)
Dialysis Division, University of Miyazaki Hospital, 5200 Kihara, Kiyotake, Miyazaki 889-1692, Japan
e-mail: ysato@med.miyazaki-u.ac.jp

S. Fujimoto
Department of Hemovascular Medicine and Artificial Organs, Faculty of Medicine, University of Miyazaki, Miyazaki, Japan

T. Konta · K. Iseki · T. Moriyama · K. Yamagata · K. Tsuruya · K. Kimura · I. Narita · M. Kondo · K. Asahi · T. Watanabe
Steering Committee for "Design of the comprehensive health care system for chronic kidney disease (CKD) based on the individual risk assessment by Specific Health Checkups", Fukushima, Japan

I. Kurahashi
iAnalysis LLC, Tokyo, Japan

Y. Ohashi
Department of Integrated Science and Engineering for Sustainable Society, Chuo University, Tokyo, Japan

Introduction

In Japan, lifestyle-related diseases account for 30 % of the national health expenditure and 60 % of the number of deaths from all causes [1]. The Japanese Ministry of Health, Labour and Welfare initiated the 'Specific Health Checkup' program in 2008, which focused on metabolic syndrome [2]. Its main purpose is to identify subjects at high risk of developing cardiovascular diseases, and then to intervene. Subjects requiring intervention are initially selected by their waist circumference, but the applied criterion is equivalent to a body mass index (BMI) of

Published online: 30 November 2014

approximately 25 kg/m^2. Subjects are advised by a health nurse, the advice is called 'Specific Counseling Guidance' if they have a BMI of ≥25 kg/m^2, which is associated with blood pressure (BP) abnormality (systolic BP ≥130 mmHg or diastolic BP ≥85 mmHg), glucose intolerance (fasting plasma glucose [FPG] ≥ 100 mg/dl or HbA1c ≥ 6.0 %), or dyslipidemia (triglycerides [TG] > 150 mg/dl or high-density lipoprotein [HDL] cholesterol < 40 mg/dl). Checking proteinuria is essential, but is not included in the specific counseling guidance criteria. Measurements of serum creatinine and the estimated glomerular filtration rate (eGFR) are not essential, but some local governments have adopted the serum creatinine measurement.

In a cross-sectional study [3], eGFR was significantly correlated with the presence of past cardiovascular events, and a longitudinal study [4] reported that the annual change of eGFR was a risk factor for the incidence of cardiovascular events. Using the Specific Health Checkup data including the eGFR and BMI, we aimed to demonstrate the usability of eGFR to predict cardiovascular diseases.

Materials and methods

Study design and population

A total of 667,139 subjects received a health checkup in both 2008 and 2010, but subjects in 2009 were not used for our data set. Overall, 330,246 subjects were excluded in 2008 because of missing laboratory data such as eGFR or FPG, and 36,061 subjects were also excluded because of missing BP, BMI, and waist circumference data. Other 157,002 subjects were excluded in 2010 because of missing data on eGFR or urine dipstick results. A further 10,819 with a past history of a cardiac event, stroke, or kidney disease and 23,662 subjects with an unknown past history of brain or heart events were excluded in 2008 or 2010. The remaining 109,349 subjects were used in a longitudinal study.

The study was performed as part of the prospective ongoing "Research on the Positioning of Chronic Kidney Disease in Specific Health Check and Guidance in Japan" project. A new annual health check program, "The Specific Health Checkup", was started by the Japanese government in 2008, targeting early diagnosis and intervention for metabolic syndrome. The target population comprised Japanese citizens between the ages of 40 and 74 years. Local governments called for citizens to attend this annual health check under their own volition. Details, such as the participants' area of residence, have been reported previously [5].

This study was conducted according to the guidelines of the Declaration of Helsinki and was granted ethical approval by the ethics committee in Fukushima Medical University (No. 1485). Informed consent was not obtained from participants because all data were anonymized [6].

Baseline measurements

Blood samples were collected after an overnight fast and were assayed within 24 h with an automated clinical chemistry analyzer. Dipstick urinalysis was performed manually and results recorded as (−), (±), (1+), (2+), and (3+). In Japan, the Japanese Committee for Clinical Laboratory Standards (http://jccls.org/) recommends that all urine dipstick results of 1+ correspond to a urinary protein level of 30 mg/dl. Proteinuria was defined as 1+ or more. Because the dipstick test sometimes indicates microalbuminuria in the general Japanese population [7], a changeable urine concentration or protein other than albumin in urine should be considered. Therefore, we adopted a dipstick test of 1+ or more as reflecting positive urine protein. Glucose tolerance was categorized as normal glucose tolerance, prediabetes, or diabetes according to the new American Diabetes Association criteria [8]. Normal glucose tolerance was defined as HbA1c 5.7 % and FPG 100 mg/dl, prediabetes as HbA1c between 5.7 and 6.5 % or FPG between 100 and 125 mg/dl, and diabetes as HbA1c ≥ 6.5 % or FPG ≥ 126 mg/dl or taking anti-diabetes medication. Estimated GFR was derived using the following equation [9]:

$$\text{eGFR}\left(\text{mL/min/1.73m}^2\right) = 194 \times \text{age (years)}^{-0.287} \times \text{serum creatinine (mg/dl)}^{-1.094} (\text{if female} \times 0.739).$$

In accordance with the recommendations of the Japanese Ministry of Health, Labour and Welfare (http://www.mhlw.go.jp/bunya/shakaihosho/iryouseido01/info03a.html), BP was measured on the right arm using a standard sphygmomanometer or an automated device after resting for 5 min in a seated position. BP data were categorized as normal (systolic BP < 130 mmHg and diastolic BP < 85 mmHg), high-normal (systolic BP 130–139 mmHg or diastolic BP 85–89 mmHg), or hypertensive (systolic BP ≥ 140 mmHg, diastolic BP ≥ 90 mmHg, or taking BP medication).

All subjects completed a self-administered questionnaire to document their medical history and current medications. Information obtained included brain attacks such as brain infarction and hemorrhage, and heart events which included myocardial infarction and cardiac angina. We identified the subjects with new-onset brain or heart attacks as those who had a positive record of these events in 2010 but a negative record of both events in 2008. The study physicians performed a physical examination of each subject and rechecked their medical history to confirm the precision of the information. Body height and weight were