Table 5 Multivariate analysis of the relationship between weight gain after 20 years of age and the prevalence of chronic kidney disease in subgroups

Gender and subgroup	Number of participants	Odds ratio (95% CI)	*p* value
Women			
Body mass index (kg/m^2)			
<25	22,363	1.13 (0.99–1.27)	0.06
25+	5,788	1.08 (0.88–1.33)	0.44
Waist circumference (cm)			
<90	23,656	1.15 (1.03–1.29)	0.01
90+	4,495	1.23 (0.97–1.55)	0.08
Metabolic syndrome[a]			
No	26,218	1.15 (1.03–1.28)	<0.0001
Yes	1,933	1.55 (1.04–2.31)	0.03
Men			
Body mass index (kg/m^2)			
<25	13,500	1.00 (0.87–1.14)	0.98
25+	7,610	0.90 (0.76–1.07)	0.24
Waist circumference (cm)			
<85	10,247	0.94 (0.79–1.12)	0.50
85+	10,863	1.05 (0.91–1.20)	0.50
Metabolic syndrome[a]			
No	10,979	1.24 (1.07–1.43)	0.01
Yes	10,131	1.04 (0.92–1.18)	0.50

Models adjusted for age, smoking, regular exercise, alcohol intake, history of kidney disease, place of residence, hypertension, diabetes, and hypercholesterolemia

[a] Defined as abdominal obesity (waist circumference ≥90 cm for women and ≥85 cm for men) plus any two of the following three categories: (1) fasting blood glucose ≥100 mg/dl, and/or hemoglobin A_{1c} ≥ 5.2%, and/or the use of insulin, and/or oral antidiabetic medication; (2) triglycerides ≥150 mg/dl, and/or high-density lipoprotein cholesterol <40 mg/dl, and/or cholesterol-lowering medication; and (3) blood pressure ≥130/85 mmHg, and/or use of antihypertensive medication

Table 6 Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of three weight indicators for detecting chronic kidney disease

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Women				
Weight gain after 20 years	0.38 (0.36–0.40)	0.71 (0.70–0.71)	0.12 (0.11–0.13)	0.92 (0.91–0.92)
Body mass index	0.29 (0.27–0.31)	0.80 (0.80–0.81)	0.13 (0.12–0.14)	0.92 (0.91–0.92)
Waist circumference	0.23 (0.22–0.25)	0.85 (0.84–0.85)	0.14 (0.13–0.15)	0.91 (0.91–0.92)
Men				
Weight gain after 20 years	0.57 (0.55–0.59)	0.51 (0.51–0.52)	0.12 (0.12–0.13)	0.91 (0.90–0.91)
Body mass index	0.49 (0.47–0.52)	0.66 (0.65–0.66)	0.15 (0.14–0.16)	0.92 (0.91–0.92)
Waist circumference	0.63 (0.61–0.65)	0.50 (0.49–0.51)	0.13 (0.13–0.14)	0.92 (0.91–0.92)

CI confidence interval

Our study had several limitations. First, the actual body weight gain could not be confirmed, but bias resulting from this factor is not likely because body weight gain is easy to measure. Second, CKD was defined from a single creatinine value and measurements of creatinine can vary among different laboratories. In addition, a single measurement of urinary protein was used because of the nature of an annual health check program. Therefore, it is not possible in this study to confirm whether participants fulfilled CKD criteria for at least a 3-month period. Finally, this was a cross-

sectional study, which makes it difficult to establish causal relationships. Further longitudinal investigations will be needed to clarify whether weight gain after maturity is an independent factor in the development of CKD.

Despite these limitations, there were several strengths to our study. As far as we know, this is the first report about weight gain after maturity and CKD among women from the general population. Our study also had a large sample size, which allowed us to perform stratified subgroup analyses.

Conclusions

Weight gain ≥10 kg after maturity was independently associated with the prevalence of CKD among the Japanese population, even those without metabolic syndrome. Because weight gain is more easily understood by the general population than BMI and can be more accurately measured than waist circumference, advice to limit weight gain to <10 kg after 20 years of age is recommended to avoid an obesity-related increase in the risk of CKD, particularly for women.

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Conflict of interest The authors have declared that no conflict of interest exists.

Appendix

When the participants with a history of kidney disease were excluded, weight gain was independently associated with CKD in both genders (Tables 7 and 8).

Table 7 Multivariate analysis of the relationship between weight gain after 20 years of age and the prevalence of chronic kidney disease among women without history of kidney disease (n = 28,026)

Variable	Age-adjusted (95% CI)	Model 1[a] Odds ratio (95% CI)	Model 2[b] Odds ratio (95% CI)
Weight gain after 20 years			
<10 kg (ref)	1.00	1.00	1.00
≥10 kg	1.43 (1.31–1.55)	1.42 (1.30–1.54)	1.25 (1.14–1.36)
Age			
40–44 (ref)	1.00	1.00	1.00
45–49	1.21 (1.01–1.45)	1.20 (1.00–1.43)	1.14 (0.95–1.36)
50–54	2.04 (1.74–2.40)	2.04 (1.74–2.39)	1.81 (1.53–2.12)
55–59	2.39 (2.06–2.76)	2.38 (2.05–2.76)	1.99 (1.70–2.32)
Current smoker			
No (ref)		1.00	1.00
Yes		1.05 (0.92–1.19)	1.06 (0.93–1.20)
Regular exercise			
No (ref)		1.00	1.00
Yes		1.14 (1.04–1.25)	1.13 (1.04–1.24)
Alcohol intake			
Every day (ref)		1.00	1.00
Sometimes		1.05 (0.91–1.22)	1.06 (0.91–1.22)
Little or never		1.15 (1.01–1.31)	1.14 (1.00–1.30)
Hypertension[c]			
No (ref)			1.00
Yes			1.54 (1.29–1.75)
Diabetes mellitus[d]			
No (ref)			1.00
Yes			1.50 (1.40–1.69)
Hypercholesterolemia[e]			
No (ref)			1.00
Yes			1.16 (1.06–1.26)

[a] Model 1 is adjusted for age, current smoking, regular exercise, alcohol intake, and place of residence

[b] Model 2 is adjusted for the variables in model 1 plus hypertension, diabetes, and hypercholesterolemia

[c] Defined as the use of antihypertensive medication, a systolic blood pressure of ≥140 mmHg, and/or a diastolic blood pressure ≥90 mmHg, or both

[d] Defined as the use of insulin or oral antidiabetic medication, a fasting serum glucose level ≥126 mg/dl, or both

[e] Defined as the use of cholesterol-lowering medication, a low-density lipoprotein cholesterol level ≥140 mg/dl, or both

Table 8 Multivariate analysis of the relationship between weight gain after 20 years of age and the prevalence of chronic kidney disease among men without history of kidney disease ($n = 21,027$)

Variable	Age-adjusted (95% CI)	Model 1[a] Odds ratio (95% CI)	Model 2[b] Odds ratio (95% CI)
Weight gain after 20 years			
<10 kg (ref)	1.00	1.00	1.00
≥10 kg	1.37 (1.25–1.50)	1.34 (1.23–1.47)	1.15 (1.05–1.26)
Age			
40–44 (ref)	1.00	1.00	1.00
45–49	1.29 (1.11–1.51)	1.31 (1.12–1.53)	1.20 (1.03–1.41)
50–54	1.41 (1.22–1.64)	1.47 (1.26–1.71)	1.22 (1.05–1.42)
55–59	1.80 (1.57–2.06)	1.86 (1.62–2.14)	1.43 (1.24–1.64)
Current smoker			
No (ref)		1.00	1.00
Yes		1.06 (0.96–1.16)	1.05 (0.96–1.16)
Regular exercise			
No (ref)		1.00	1.00
Yes		1.05 (0.95–1.15)	1.03 (0.93–1.14)
Alcohol intake			
Every day (ref)		1.00	1.00
Sometimes		1.20 (1.08–1.35)	1.24 (1.10–1.39)
Little or never		1.40 (1.26–1.56)	1.48 (1.32–1.65)
Hypertension[c]			
No (ref)			1.00
Yes			2.04 (1.85–2.24)
Diabetes mellitus[d]			
No (ref)			1.00
Yes			2.00 (1.78–2.25)
Hypercholesterolemia[e]			
No (ref)			1.00
Yes			1.24 (1.13–1.36)

[a] Model 1 is adjusted for age, current smoking, regular exercise, alcohol intake, and place of residence

[b] Model 2 is adjusted for the variables in model 1 plus hypertension, diabetes, and hypercholesterolemia

[c] Defined as the use of antihypertensive medication, a systolic blood pressure ≥140 mmHg, and/or a diastolic blood pressure ≥90 mmHg, or both

[d] Defined as the use of insulin or oral antidiabetic medication, a fasting serum glucose level ≥126 mg/dl, or both

[e] Defined as the use of cholesterol-lowering medication, a low-density lipoprotein cholesterol level ≥140 mg/dl, or both

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●一般演題 1-5

慢性腎臓病(CKD)におけるメタボリックシンドローム(MetS)・脂質異常症の実態と意義
―特定健診受診者コホートにおける横断的解析―

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1 背　景

これまでのコホート研究結果から，メタボリックシンドローム(MetS)は慢性腎臓病(CKD)の発症要因であること，CKDではMetSに類似の脂質異常(高中性脂肪(TG)血症，低HDL-コレステロール(HDL-C)血症，small dense LDLやレムナントなど質的に異常なリポ蛋白の増加)が存在し，心血管イベント(CVD)発症(心腎連関)との関連が示唆されている。しかし，全国的規模の一般住民レベルでのCKDにおけるMetSと脂質異常の実態およびそれらの相互関連の研究はない。

2 方　法

全国69自治体国保・3健保組合のコホート群から平成20年度の約58万人分の特定健康診査(特定健診)データを収集，血清Cr値が測定された332,174名について日本人の推定GFR推算式[1]に基づくeGFRと試験紙法による尿蛋白レベルで層別化し，血清脂質異常との関連を横断的に解析した。また，各保険者(国保)において特定健診データに基づいてMetS(該当群，予備群，非該当群)ならびに特定保健指導レベルが判定された65,476名につき，CKDステージとの関連を検討した。

MetSの判定は内臓脂肪蓄積(腹囲：男性85cm，女性90cm以上)を満たし，追加リスクすなわち①血糖(空腹時血糖値110mg/dL以上，HbA1c(JDS)5.5%以上，糖尿病に対する薬剤治療中のいずれかに該当)，②脂質(TG 150mg/dL以上，HDL-C 40mg/dL未満，脂質異常症に対する薬剤治療中のいずれかに該当)，③血圧(収縮期血圧130mmHg以上，拡張期血圧85mmHg以上，高血圧症に対する薬剤治療中のいずれかに該当)のうち2項目以上満たす者を該当者，1項目を満たす者を予備群，いずれも当てはまらない者ならびに追加リスクに当てはまっても内臓脂肪蓄積のない者を非該当者とした。

特定保健指導レベルは，標準的な健診・保健指導プログラム(確定版)(平成19年4月厚生労働省健康局http://www.mhlw.go.jp/bunya/shakaihosho/iryouseido01/info03a. html)に基づき，内臓脂肪蓄積(腹囲：男性85cm，女性90cm以上または上記以外でBMI 25kg/m^{2}以上)，追加リスク①血糖(空腹時血糖値100mg/dL以上，HbA1c(JDS)5.2%以上，糖尿病に対す

Koichi Asahi, *et al.*：Metabolic syndrome and dyslipidemia in a population with chronic kidney disease: a cross-sectional study among participants of the Specific Health Check and Guidance System in Japan

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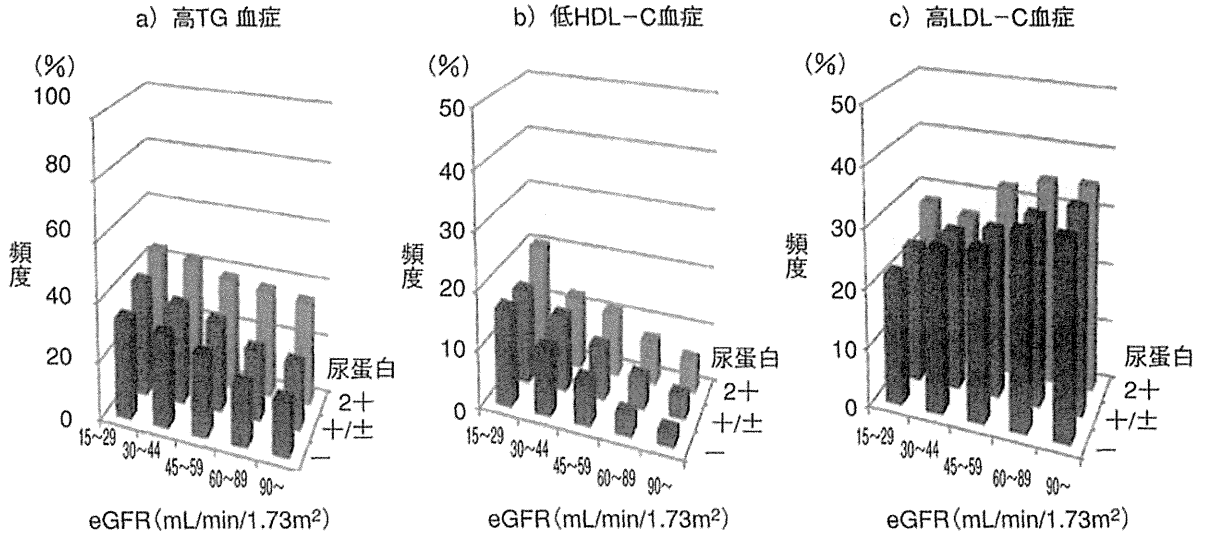

図1　特定健診における脂質異常症の頻度とCKD(eGFRと尿蛋白)の関連

る薬剤治療中のいずれかに該当)，②脂質(TG 150mg/dL以上，HDL−C 40mg/dL未満，脂質異常症に対する薬剤治療中のいずれかに該当)，③血圧(収縮期血圧130mmHg以上，拡張期血圧85mmHg以上，高血圧症に対する薬剤治療中のいずれかに該当)に加え，喫煙歴(6ヵ月以上かつ最近1ヵ月)，年齢に基づき「積極的支援」，「動機付け支援」，「情報提供のみ」の各保健指導レベルに階層化された。すなわち，内臓脂肪蓄積(腹囲：男性85cm，女性90cm以上：腹囲条項)ありで追加リスク2項目以上該当，または追加リスク1項目該当かつ喫煙歴ありは「積極的支援」，追加リスク1項目該当かつ喫煙歴なしは「動機付け支援」，内臓脂肪蓄積(腹囲条項非該当だがBMI 25kg/m^{2}以上)ありで追加リスク3項目該当または2項目該当かつ喫煙歴ありは「積極的支援」，追加リスク2項目該当かつ喫煙歴なしまたは1項目該当は「動機付け支援」と判定された。この判定で「積極的支援」と判定される者のうち65歳以上の者は「動機付け支援」にdown gradeされ，糖尿病，高血圧症または脂質異常症(高脂血症)の治療にかかわる薬剤を服用している者は支援対象から除外された。

3　結　　果

尿蛋白(定性：試験紙法)と腎機能低下(eGFR)はそれぞれ独立して，その程度が進行するとともにCVDの既往歴ならびに肥満(BMI 25kg/m^{2}以上)を有する割合(頻度)が増加(正相関)した。また，尿蛋白と腎機能低下はその程度が進行するとともに，高TG血症，低HDL−C血症を有する割合(頻度)が増加(正相関)し，高LDL−C血症を有する割合が減少(負相関)した(**図1**)。

MetS該当者またはMetS予備群の割合は，CKDでない者が27.3%であるのに対し，CKDステージ1または2で40.2%，CKDステージ3以上かつ尿蛋白陰性の者で36.4%，CKDステージ3以上かつ尿蛋白陽性の者で51.1%であった。また，保健指導レベルが「積極的支援」または「動機付け支援」レベルと判定された者の割合は，CKDのない者が12.9%であるのに対し，CKDステージ1または2で11.4%，CKDステージ3以上かつ尿蛋白陰性の者で12.4%，CKDステージ3以上かつ尿蛋白陽性の者で8.5%であった(**表1**)。

4　考　　察

日本人の一般住民においてCKDにおける脂質異常症の特徴は，MetS類似の高TG血症，低HDL−C血症の頻度の増加であり，高LDL−C血症についてはCKDの進行に伴いその頻度が

表1　特定健診におけるメタボリックシンドロームならびに特定保健指導レベルとCKDの関連

1）メタボリックシンドロームとCKD

MetS判定（国保）	CKDなし	CKDステージ1, 2（eGFR≧60, 尿蛋白陽性）	CKDステージ3以上（eGFR＜60, 尿蛋白陰性）	CKDステージ3以上（eGFR＜60, 尿蛋白陽性）	合　計
MetS該当（%）	8505（15.9）	1323（27.7）	1380（23.4）	456（39.1）	11664（17.8）
MetS予備群（%）	6114（11.4）	598（12.5）	763（13.0）	140（12.0）	7615（11.6）
MetS非該当（%）	38572（71.9）	2792（58.4）	3715（63.1）	562（48.2）	45641（69.7）
判定不能（%）	447（0.8）	69（1.4）	32（0.5）	8（0.7）	556（0.9）
合計（%）	53638（100.0）	4782（100.0）	5890（100.0）	1166（100.0）	65476（100.0）

2）特定保健指導レベルとCKD

保健指導レベル判定（国保）	CKDなし	CKDステージ1, 2（eGFR≧60, 尿蛋白陽性）	CKDステージ3以上（eGFR＜60, 尿蛋白陰性）	CKDステージ3以上（eGFR＜60, 尿蛋白陽性）	合　計
積極的支援（%）	2104（3.9）	197（4.1）	125（2.1）	14（1.2）	2440（3.7）
動機付け支援（%）	4833（9.0）	347（7.3）	607（10.3）	85（7.3）	5872（9.0）
情報提供のみ（%）	45943（85.7）	4132（86.4）	5095（86.5）	1049（90.0）	56219（85.9）
判定不能（%）	758（1.4）	106（2.2）	63（1.1）	18（1.5）	945（1.4）
合計（%）	53638（100.0）	4782（100.0）	5890（100.0）	1166（100.0）	65476（100.0）

低下することが確認された。少なくとも低HDL血症は腎機能低下の要因である可能性があるが，今後この特徴と心腎連関の因果関係を検討するとともに，それを踏まえた治療が望まれる。

また今回の検討でCKDステージの進行に伴いMetSと判定される者の割合は増加するが，全体としては一般住民のCKDのおおむね半数以上はMetS該当者およびその予備群とは判定されないことも明らかになった。さらに，内臓脂肪蓄積と追加リスクに加え喫煙習慣，年齢，服薬状況を加味した保健指導レベル判定では，CKDステージの進行とともに「積極的支援」レベルまたは「動機付け支援」レベルの保健指導の対象となる者はむしろ減少し，よりCVDリスクの高いCKDステージ3以上かつ尿蛋白陽性の者でもこれに該当する者が10%に満たなかった。

CKD進行例ではすでに何らかの薬物治療中であるために，特定保健指導における支援対象から除外されたことが考えられるが，特定健診受診者における腎疾患の既往に関する検討では，特定健診問診項目「医師から，慢性の腎不全にかかっているといわれたり，治療（人工透析）を受けたことがありますか。」に対し「はい」と回答したものは，ステージ1以上の全CKDの1.57%であり，CKDステージ3以上でeGFR 45mL/min/1.73m^{2}未満の者に限ってもその8.9%にすぎないことが判明している[2)]。このことは受診者のみならず医療機関におけるCKDの認知度も極めて低いことを予想させる成績であり，薬物治療中のため特定保健指導で支援対象とならない者に対するCVD予防のための啓蒙の実態の把握も必要と考えられる。

以上よりMetSに視点をおいた現行の特定健診・保健指導では，CKDが盲点となる可能性が示唆され，CVD高危険群の効率的な把握の観点からは制度改善の余地があると考えられる。今後は血清Cr値の特定健診検査項目への採用と蛋白尿を含めた受診勧奨基準の設定ならびにCKD発症・進展予防のための保健指導プログラムの策定が必要となると考えられる。

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AJKD
Original Investigation

Self-reported Sleep Duration and Prediction of Proteinuria: A Retrospective Cohort Study

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Background: Although multiple studies have shown that sleep duration is a predictor of cardiovascular diseases and mortality, few studies have reported an association between sleep duration and chronic kidney disease.

Study Design: Retrospective cohort study.

Setting & Participants: 6,834 employees of Osaka University aged 20-65 years who visited Osaka University Healthcare Center for their mandatory annual health examinations between April 2006 and March 2010 and did not have estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, proteinuria, or treatment for self-reported kidney disease.

Predictor: Self-reported questionnaires about life style, including sleep duration, and blood and urine testing at the first examinations during the study period. An association between sleep duration and outcome was assessed using multivariate Poisson regression models adjusting for clinically relevant factors.

Outcome: Time to the development of proteinuria defined as 1+ or higher by dipstick test.

Results: Self-reported baseline sleep duration was 6.0 ± 0.9 hours, which reflected the mean sleep duration during a median of 2.5 (25th-75th percentile, 1.4-3.9) years of the observational period. Development of proteinuria was observed in 550 employees (8.0%). A multivariate Poisson regression model clarified that shorter sleep duration, especially 5 or fewer hours, was associated with the development of proteinuria in a stepwise fashion (vs 7 hours; incidence rate ratios of 1.07 [95% CI, 0.87-1.33; $P = 0.5$], 1.28 [95% CI, 1.00-1.62; $P = 0.05$], and 1.72 [95% CI, 1.16-2.53; $P = 0.007$] for 6, 5, and ≤4 hours, respectively), along with younger age, heavier current smoking, trace urinary protein by dipstick test, higher eGFR, higher serum hemoglobin A_{1c} level, and current treatment for heart disease. A stepwise association between shorter sleep duration and the development of proteinuria also was verified in 4,061 employees who did not work the night shift.

Limitations: Self-reported sleep duration might be biased. Results in a single center should be confirmed in the larger cohort including different occupations.

Conclusion: Short sleep duration, especially 5 or fewer hours, was a predictor of proteinuria.

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INDEX WORDS: Sleep duration; sleep deprivation; chronic kidney disease; proteinuria; Osaka University Healthcare Center.

Editorial, p. 325

Although sleep is one of the vital factors contributing to health, sleep duration has become shorter in modern societies in recent decades and the prevalence of sleep deprivation has increased, irrespective of socioeconomic status.[1] This trend is a major public health concern because multiple studies have shown that shorter sleep duration is associated with obesity,[2-4] hypertension,[5] diabetes,[6-8] cardiovascular diseases (CVDs),[9-12] and even death.[10,13,14] Most of these studies showed that the population with 5 or fewer hours of sleep duration was at significantly higher risk, whereas those with 7 hours of sleep duration were at lowest risk. More interestingly, a British cohort study showed that a decrease in sleep duration was associated significantly with cardiovascular mortality.[15] These results strongly suggest that sleep duration is a modifiable target of treatment modalities for CVD, such as smoking[16] and obesity.[17]

The modifiable lifestyle factors of smoking and obesity also have been studied as a potential target for the treatment of chronic kidney disease (CKD) charac-

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terized by proteinuria and decrease in glomerular filtration rate (GFR). Multiple studies have shown that smoking and obesity are risk factors for CKD[18] and that weight loss[19] and smoking cessation[20] are associated with improved renal outcomes. However, to our knowledge, no cohort study has reported an association between sleep duration and CKD.

The purpose of the present study was to investigate whether there is an association between the modifiable lifestyle factor of sleep duration and urinary protein, a key prognostic factor of CKD.[21] Results of the present study provide novel insight into the treatment strategy against CKD.

METHODS

Study Population

Candidate participants in the present retrospective cohort study were 10,445 employees of Osaka University aged 20-65 years who visited Osaka University Healthcare Center for their annual health examinations during the entry period between April 2006 and March 2010. In Japan, annual health examinations are mandatory for all employees by the Labor Standards Act.[22] Osaka University is located in a suburb of Osaka city, the third largest city in Japan, with a population of ~2.5 million. Of 9,697 (92.8%) employees with an estimated GFR (eGFR) ≥60 mL/min/1.73 m^2, negative or trace urinary protein by dipstick test, and no current treatment for self-reported kidney disease, we excluded 160 employees (1.5%) with missing baseline data, including 40 employees with missing baseline information about sleep duration (0.4%). After excluding 2,703 (25.9%) employees with a single visit during the observational period between April 2006 and March 2011, the present study finally included 6,834 employees (65.4%). Because of the retrospective nature of the present study, sample size was determined by the number of the employees of Osaka University who visited Osaka Healthcare Center during the entry period. The study protocol was approved by the ethics committee in Osaka University Healthcare Center.

Measurements

At the first visit during the entry period between April 2006 and March 2010, baseline data for the employees were measured. Demographic, physical, and laboratory data included age, sex, occupation, body mass index (BMI; body weight in kilograms divided by height in meters squared), and mean arterial pressure [MAP (mm Hg) = diastolic blood pressure + (systolic blood pressure − diastolic blood pressure)/3)], urinary protein and hematuria by dipstick test, hemoglobin A_{1c} level, and serum concentrations of creatinine, total cholesterol, triglycerides, and uric acid. Urinary protein and hematuria were examined using Uropaper III Eiken (Eiken Chemical, www.eiken.co.jp/en/index.html). The employees brought their first-void urine in the morning. Results of urine dipstick tests were interpreted by well-trained nurses and recorded as negative, trace, 1+, 2+, 3+, and 4+. Occupations were classified into clerical workers, academic researchers, engineers and technical assistants, health care workers in university hospitals, and other occupations.

Information about life style and current treatments for comorbid conditions was based exclusively on self-reported standard questionnaires, which all employees were required to fill out at every visit for their annual health examinations. Sleep duration was ascertained by the question "How long do you sleep?" There were 6 possible answers: 3 or fewer, 4, 5, 6, 7, or 8 or more hours. Excessive daytime somnolence was determined according to a positive answer to the question "Are you very sleepy during daytime?" The frequency of night shift was based on the question "How often do you work at night between 10:00 PM and 5:00 AM per month?", for which the possible responses were none, 1-5, 5-9, 10-14, or 15 or more nights. Smoking status was classified into non-, past, and current smokers, according to the question; "Do you smoke?", with possible answers I do not smoke, I quit smoking, or I smoke. If current smokers, the number of cigarettes smoked per day was ascertained by the question "How many cigarettes do you smoke per day?", with choices of 10 or fewer, 11-20, 21-40, 41-60, and 61 or more cigarettes. Frequency of drinking alcohol was asked by the question "How often do you drink per a week?", with responses of rarely, 1-3 days, 4-6 days, or every day. Diagnosis of comorbid conditions, including hypertension, diabetes, dyslipidemia, hyperuricemia, and heart disease, was made according to positive answers to the questions "Are you being treated for hypertension, diabetes, dyslipidemia, hyperuricemia, and/or heart disease?"

Mean sleep duration of each employee during the observational period was calculated based on all answers during the follow-up period, excluding baseline sleep duration. To calculate mean sleep duration during the observational period, 3 or fewer and 8 or more hours of sleep duration were regarded as 3 and 8 hours, respectively. Because of small numbers of employees with 3 or fewer hours of baseline sleep duration (n = 12 [0.2%]), employees with 3 or fewer and 4 hours of baseline sleep duration were categorized into a single group with 4 or fewer hours of baseline sleep duration. Similarly, employees with 8 or more hours of baseline sleep duration (n = 115 [1.7%]) were categorized into 7 or more hours of baseline sleep duration.

The outcome measure of the present study was the development of proteinuria, defined as urinary protein (≥1+) by dipstick test. The observational period was defined as time from the first visit during the entry period between April 2006 and March 2010 to (1) development of proteinuria or (2) last measurement of urinary protein before the end of March 2011, whichever came first. All date were retrieved from the electronic database in Osaka University Healthcare Center.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation or median and interquartile range, as appropriate, and categorical variables were expressed as number and proportion. Statistical significance was set at $P < 0.05$. For employees not immediately excluded on the basis of eGFR, proteinuria, or self-reported kidney disease, differences in baseline characteristics between employees included and excluded were compared using χ^2 test, t test, and Wilcoxon rank-sum test, as appropriate. Stepwise associations between baseline sleep duration and other clinical characteristics were compared using Cochran-Armitage test for trend and Jonckheere-Terpstra test for trend, as appropriate. Cumulative probability of proteinuria was calculated using the Kaplan-Meier method. Predictors of proteinuria were identified using log-rank test for trend and/or Poisson regression models adjusting for clinically relevant factors. The appropriateness of Poisson regression models was tested with a goodness-of-fit test using deviance statistic. Interactions between sleep duration and other covariates were assessed incorporating their interaction terms into multivariate models. Because night shift might affect sleep duration, as a sensitivity analysis, the association between sleep duration and the development of proteinuria was assessed in those who did not report working the night shift. Statistical analyses were performed using Stata, version 11.2 (Stata Corp, www.stata.com) and R, version 2.13.1 (The R Foundation for Statistical Computing, www.r-project.org/).

Table 1. Clinical Characteristics of Those Excluded and Included in the Study

	Excluded Employees	Included Employees				
		Total	Night Shift		P^a	P^b
			No	Yes		
No. of employees	2,703	6,834	4,061	2,773		
Demographic and physical data						
Age (y)	32 (28-38)	34 (29-42)	35 (29-44)	32 (28-38)	<0.001	<0.001
Men	1,405 (52.0)	3,445 (50.4)	1,723 (42.4)	1,722 (62.1)	0.2	<0.001
Occupation					<0.001	<0.001
Clerical workers	568 (21.0)	1,909 (27.9)	1,848 (45.5)	61 (2.2)		
Academic researchers	1,016 (37.6)	2,641 (38.6)	1,262 (31.1)	1,379 (49.7)		
Engineers and technical assistants	171 (6.3)	473 (6.9)	441 (10.9)	32 (1.2)		
Health care workers	922 (34.1)	1,736 (25.4)	447 (11.0)	1,289 (46.5)		
Other employees	26 (1.0)	75 (1.1)	63 (1.6)	12 (0.4)		
BMI (kg/m^2)	21.8 ± 3.2	21.8 ± 3.2	21.5 ± 3.2	22.2 ± 3.2	0.5	<0.001
MAP (mm Hg)	84 ± 12	85 ± 12	85 ± 13	85 ± 12	<0.001	0.3
Lifestyle data						
Smoking status					0.001	0.02
Nonsmokers	2,182 (80.7)	5,508 (80.6)	3,314 (81.6)	2,194 (79.1)		
Past smokers	193 (7.1)	589 (8.6)	327 (8.1)	262 (9,4)		
Current smokers						
1-10 cigarettes/d	147 (5.4)	259 (3.8)	139 (3.4)	120 (4.3)		
11-20 cigarettes/d	143 (5.3)	377 (5.5)	214 (5.3)	163 (5.9)		
≥21 cigarettes/d	38 (1.4)	101 (1.5)	67 (1.6)	34 (1.2)		
Alcohol consumption					0.03	<0.001
Rarely	1,425 (52.7)	3,625 (53.0)	2,234 (55.0)	1,391 (50.2)		
1-3 d/wk	807 (29.9)	1,880 (27.5)	1,057 (26.0)	823 (29.7)		
4-6 d/wk	211 (7.8)	560 (8.2)	304 (7.5)	256 (9.2)		
7 d/wk	260 (9.6)	769 (11.3)	466 (11.5)	303 (10.9)		
Sleep duration	6.0 ± 0.9	6.0 ± 0.9	6.1 ± 0.9	5.8 ± 0.8	0.5	<0.001
≥8 h	94 (3.5)	188 (2.8)	148 (3.6)	40 (1.4)		
7 h	684 (25.3)	1,682 (24.6)	1,170 (28.8)	512 (18.5)		
6 h	1,206 (44.6)	3,155 (46.2)	1,864 (45.9)	1,291 (46.6)		
5 h	597 (22.1)	1,543 (22.6)	749 (18.4)	794 (28.6)		
4 h	111 (4.1)	245 (3.6)	120 (3.0)	125 (4.5)		
≤3 h	11 (0.4)	21 (0.3)	10 (0.2)	11 (0.4)		
Excessive daytime somnolence	111 (4.1)	248 (3.6)	151 (3.7)	97 (3.5)	0.3	0.6
Laboratory data						
Urinary protein by dipstick test					<0.001	<0.001
Negative	2,522 (93.3)	6,535 (95.6)	3,923 (96.6)	2,612 (94.2)		
Trace	181 (6.7)	299 (4.4)	138 (3.4)	161 (5.8)		
Hematuria by dipstick test					0.001	<0.001
Negative	2,354 (87.1)	5,810 (85.0)	3,365 (82.9)	2,445 (88.2)		
Trace	50 (1.8)	134 (2.0)	84 (2.1)	50 (1.8)		
1+	186 (6.9)	642 (9.4)	450 (11.1)	192 (6.9)		
≥2+	113 (4.2)	248 (3.6)	162 (4.0)	86 (3.1)		
eGFR (mL/min/1.73 m^2)	91 ± 15	90 ± 15	90 ± 16	91 ± 15	0.009	0.008
Hemoglobin A_{1c} (%)	4.9 ± 0.4	4.9 ± 0.4	4.9 ± 0.4	4.9 ± 0.4	0.01	<0.001
Total cholesterol (mg/dL)	189 ± 32	192 ± 33	193 ± 33	190 ± 32	<0.001	<0.001
Triglycerides (mg/dL)	64 (45-96)	64 (45-95)	62 (44-91)	66 (46-101)	0.8	<0.001
Uric acid (mg/dL)	5.1 ± 1.4	5.1 ± 1.4	4.9 ± 1.4	5.3 ± 1.4	0.7	<0.001
Treatments for comorbid conditions						
Hypertension	52 (1.9)	145 (2.1)	100 (2.5)	45 (1.6)	0.5	0.02
Diabetes	9 (0.3)	38 (0.6)	25 (0.6)	13 (0.5)	0.2	0.4
Dyslipidemia	25 (0.9)	86 (1.3)	56 (1.4)	30 (1.1)	0.2	0.3
Hyperuricemia	15 (0.6)	42 (0.6)	27 (0.7)	15 (0.5)	0.7	0.5
Heart diseases	5 (0.2)	13 (0.2)	10 (0.2)	3 (0.1)	0.9	0.2

Note: Comprises 9,537 employees who did not have eGFR <60 mL/min/1.73 m^2, proteinuria, or treatment for self-reported kidney disease and were not missing baseline data. The 2,703 excluded employees were those who had a single visit during the study period. Continuous variables are shown as mean ± standard deviation or median (25th-75th percentile); categorical variables are given as number (percentage).

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; MAP, mean arterial pressure.

[a]Excluded employees versus included employees.

[b]Included employees without night shift versus included employees with night shift.

Table 2. Clinical Characteristics of Included Employees

	Baseline Sleep Duration				
	≤4 h	5 h	6 h	≥7 h	P_{trend}
No. of employees	266	1,543	3,155	1,870	
Mean sleep duration during observational period (h)	4.5 ± 0.7	5.3 ± 0.6	6.0 ± 0.5	6.7 ± 0.6	
Demographic and physical data					
Age (y)	34 (29-41)	34 (28-42)	34 (29-42)	34 (29-41)	0.5
Age category					
20-29 y	75 (28.2)	473 (30.7)	935 (29.6)	514 (27.5)	
30-39 y	111 (41.7)	598 (28.8)	1,269 (40.2)	811 (43.4)	
40-49 y	53 (19.9)	304 (19.7)	595 (18.9)	313 (16.7)	
50-59 y	24 (9.0)	151 (9.8)	317 (10.0)	195 (10.4)	
60-65 y	3 (1.1)	17 (1.1)	39 (1.2)	37 (2.0)	
Men	124 (46.6)	752 (48.7)	1,599 (50.7)	970 (51.9)	0.03
Occupations					
Clerical workers	60 (22.6)	371 (24.0)	917 (29.1)	561 (30.0)	<0.001[a]
Academic researchers	75 (28.2)	489 (31.7)	1,212 (38.4)	865 (46.3)	<0.001[a]
Engineers and technical assistants	22 (8.3)	113 (7.3)	216 (6.8)	122 (6.5)	0.2[a]
Health care workers	104 (39.1)	543 (35.2)	788 (25.0)	301 (16.1)	<0.001[a]
Other employees	5 (1.9)	27 (1.7)	22 (0.7)	21 (1.1)	0.05[a]
BMI (kg/m^2)	22.0 ± 3.4	22.1 ± 3.5	21.8 ± 3.2	21.6 ± 3.1	<0.001
MAP (mm Hg)	85 ± 13	85 ± 12	85 ± 12	85 ± 12	0.2
Lifestyle data					
Smoking status					
Nonsmokers	216 (81.2)	1,249 (80.9)	2,540 (80.5)	1,503 (80.4)	0.6[b]
Past smokers	19 (7.1)	121 (7.8)	282 (8.9)	167 (8.9)	
Current smokers					
1-10 cigarettes/d	11 (4.1)	62 (4.0)	111 (3.5)	75 (4.0)	
11-20 cigarettes/d	15 (5.6)	87 (5.6)	176 (5.6)	99 (5.3)	
≥21 cigarettes/d	5 (1.9)	24 (1.6)	46 (1.5)	26 (1.4)	
Alcohol consumption					
Rarely	165 (62.0)	836 (54.2)	1,649 (52.3)	975 (52.1)	0.01[c]
1-3 d/wk	64 (24.1)	443 (28.7)	885 (28.1)	488 (26.1)	
4-6 d/wk	20 (7.5)	118 (7.6)	268 (8.5)	154 (8.2)	
7 d/wk	17 (6.4)	146 (9.5)	353 (11.2)	253 (13.5)	
Excessive daytime somnolence	30 (11.3)	76 (4.9)	100 (3.2)	42 (2.2)	<0.001
Laboratory data					
Urinary protein by dipstick test					<0.001
Negative	242 (91.0)	1,463 (94.8)	3,024 (95.8)	1,806 (96.6)	
Trace	24 (9.0)	80 (5.2)	131 (4.2)	64 (3.4)	
Hematuria by dipstick test					
Negative	230 (86.5)	1,333 (86.4)	2,671 (84.7)	1,576 (84.3)	} 0.05[d]
Trace	8 (3.0)	27 (1.7)	63 (2.0)	36 (1.9)	
1+	19 (7.1)	129 (8.4)	307 (9.7)	187 (10.0)	
≥2+	9 (3.4)	54 (3.5)	114 (3.6)	71 (3.8)	
eGFR (mL/min/1.73 m^2)	89 ± 15	90 ± 15	90 ± 15	91 ± 16	0.05
eGFR category					
≥120 mL/min/1.73 m^2	8 (3.0)	55 (3.6)	128 (4.1)	98 (5.2)	
105-119 mL/min/1.73 m^2	26 (9.8)	175 (11.3)	374 (11.9)	239 (12.8)	
90-104 mL/min/1.73 m^2	81 (30.5)	493 (32.0)	984 (31.2)	558 (29.8)	
75-89 mL/min/1.73 m^2	112 (42.1)	584 (37.8)	1,181 (37.4)	713 (38.1)	
60-74 mL/min/1.73 m^2	39 (14.7)	236 (15.3)	488 (15.5)	262 (14.0)	
Hemoglobin A_{1c} (%)	5.0 ± 0.4	5.0 ± 0.4	4.9 ± 0.4	4.9 ± 0.4	<0.001
Total cholesterol (mg/dL)	189 ± 33	190 ± 32	192 ± 32	192 ± 34	0.08
Triglycerides (mg/dL)	59 (43-92)	62 (44-92)	63 (44-95)	65 (47-97)	<0.001
Uric acid (mg/dL)	5.0 ± 1.3	5.1 ± 1.4	5.1 ± 1.4	5.1 ± 1.4	0.03

(Continued)

Table 2 (Cont'd). Clinical Characteristics of Included Employees

	Baseline Sleep Duration				
	≤4 h	5 h	6 h	≥7 h	P_{trend}
Treatments for comorbid conditions					
Hypertension	5 (1.9)	37 (2.4)	61 (1.9)	42 (2.2)	0.9
Diabetes	0 (0.0)	14 (0.9)	15 (0.5)	9 (0.5)	0.4
Dyslipidemia	4 (1.5)	27 (1.7)	38 (1.2)	17 (0.9)	0.04
Hyperuricemia	2 (0.8)	7 (0.5)	22 (0.7)	11 (0.6)	0.8
Heart diseases	0 (0.0)	4 (0.3)	4 (0.1)	5 (0.3)	0.6
Outcome and follow-up data					
Observational period (y)	2.5 (1.2-4.0)	2.4 (1.4-3.9)	2.3 (1.3-3.9)	2.5 (1.5-3.9)	0.9
No. of examinations					0.4
1	81 (30.5)	463 (30.0)	1,016 (32.2)	592 (31.7)	
2	67 (25.2)	380 (24.6)	772 (24.5)	448 (24.0)	
3	44 (16.5)	285 (18.5)	566 (17.9)	340 (18.2)	
4	74 (27.8)	414 (26.8)	797 (25.3)	483 (25.8)	
5	0 (0.0)	1 (0.1)	4 (0.1)	7 (0.4)	
Development of proteinuria	33 (12.4)	142 (9.2)	240 (7.6)	135 (7.2)	0.002

Note: N = 6,834. Continuous variables are shown as mean ± standard deviation or median (25th-75th percentile); categorical variables given as number (percentage).

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; MAP, mean arterial pressure.

[a]Each occupation versus others (eg, clerical workers vs nonclerical workers).

[b]Nonsmokers versus others.

[c]Drinking rarely versus others.

[d]Negative or trace for hematuria by dipstick test versus 1+ or more.

RESULTS

After excluding 2,703 employees whose outcome was unavailable due to a single examination during the entire observational period, the present study enrolled 6,834 employees without eGFR <60 mL/min/1.73 m^2, proteinuria, or treatment for self-reported kidney disease at baseline. Of these 6,834 individuals, sleep durations of those excluded and included were not significantly different (6.0 ± 0.9 vs 6.0 ± 0.9 hours; $P = 0.5$; Table 1). Statistically significant differences were observed between the employees excluded and those included for age ($P < 0.001$), occupation ($P < 0.001$), MAP ($P < 0.001$), smoking status ($P = 0.001$), alcohol consumption ($P = 0.03$), urinary protein and hematuria by dipstick test ($P < 0.001$ and $P = 0.001$), eGFR ($P = 0.009$), hemoglobin A_{1c} level ($P = 0.01$), and total cholesterol level ($P < 0.001$). However, the differences did not reach a clinically meaningful level, suggesting that the characteristics were clinically similar and that the 2 groups were at approximately the same risk of developing proteinuria.

Clinical characteristics of 266 (3.9%), 1,543 (22.6%), 3,155 (46.2%), and 1,870 (27.4%) employees with 4 or fewer, 5, 6, and 7 or more hours of sleep duration are listed in Table 2. Shorter sleep duration was associated significantly with female sex ($P_{trend} = 0.03$), higher proportions of health care workers in the university hospitals ($P_{trend} < 0.001$) and other occupations ($P_{trend} = 0.05$), higher BMI ($P_{trend} < 0.001$), higher proportion of those who consumed alcohol rarely ($P_{trend} = 0.01$), higher prevalence of excessive daytime somnolence ($P_{trend} < 0.001$), trace urinary protein ($P_{trend} < 0.001$), negative/trace hematuria ($P_{trend} = 0.05$), lower eGFR ($P_{trend} = 0.05$), higher hemoglobin A_{1c} level ($P_{trend} < 0.001$), lower triglyceride level ($P_{trend} < 0.001$), lower uric acid level ($P_{trend} = 0.03$), and higher prevalence of current treatment for dyslipidemia ($P_{trend} = 0.04$). During a median of 2.5 (25th-75th percentile, 1.4-3.9) years of the observational period, mean sleep durations during the observational period of employees with 4 or fewer, 5, 6, and 7 or more hours of sleep duration were 4.5 ± 0.7, 5.3 ± 0.6, 6.0 ± 0.5, and 6.7 ± 0.6 hours, respectively. Of 6,586 employees without baseline excessive daytime somnolence, 6,338 (96.2%) never reported it during the observational period, whereas 113 (45.6%) of 248 employees with baseline excessive daytime somnolence had at least one positive answer to the same question after the baseline visit and 61 employees (24.6%) reported it in ≥50% of visits. These results strongly suggested that baseline sleep duration and excessive daytime somnolence reflected their subsequent conditions after the baseline visit.

During the observational period, 33 (12.4%), 142 (9.2%), 240 (7.6%), and 135 (7.2%) employees with 4 or fewer, 5, 6, and 7 or more hours of sleep duration developed proteinuria, respectively ($P_{trend} = 0.002$).

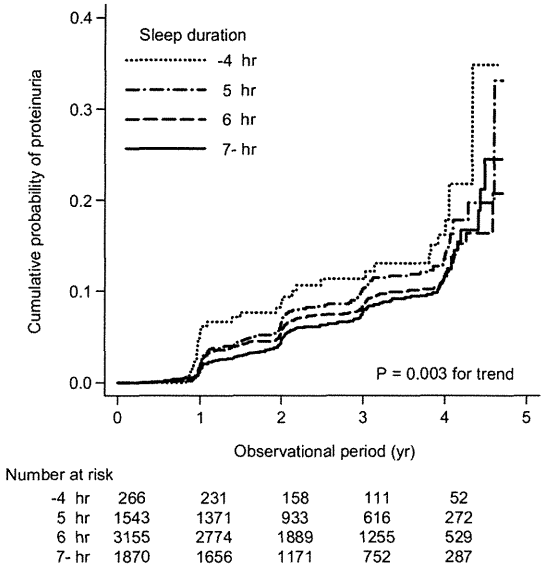

Figure 1. Estimated cumulative probability of the development of proteinuria in 6,834 included employees using the Kaplan-Meier method.

Cumulative probabilities of developing proteinuria at 1, 2, 3, and 4 years were 0.058, 0.088, 0.113, and 0.162 in employees with 4 or fewer hours of sleep duration; 0.020, 0.065, 0.102, and 0.139 in those with 5 hours; 0.020, 0.057, 0.084, and 0.116 in those with 6 hours; and 0.014, 0.047, 0.078, and 0.116 in those with 7 or more hours, showing that employees with shorter sleep duration were at higher risk of developing proteinuria (P_{trend} = 0.003; Fig 1). Compared with 6,535 employees with negative baseline urinary protein results, 299 employees with trace baseline urinary protein were at significantly higher risk of developing proteinuria (mainly 1+: 499 [90.7%] of 550 employees who developed proteinuria; Table 3).

To identify predictors of proteinuria, the incidence rate ratio (IRR) for each covariate was calculated (Table 4). In univariate models, significant predictors of the development of proteinuria were younger age, female sex, health care workers in university hospitals, lower MAP, heavier smoking, shorter sleep duration, trace urinary protein, hematuria of 2+ or higher, higher eGFR, higher hemoglobin A_{1c} level, lower uric acid level, and current treatment for heart disease. Even after adjustment for clinically relevant factors, shorter sleep duration of 5 or fewer hours was associated significantly with the development of proteinuria (compared with sleep duration ≥7 hours; IRRs of 1.28 [95% confidence interval (CI), 1.00-1.62] and 1.72 [95% CI, 1.16-2.53] for 5 and ≤4 hours, respectively). Also associated with proteinuria were younger age (compared with age 40-49 years, IRRs of 2.20 [95% CI, 1.61-3.00] and 1.48 [95% CI, 1.12-1.96] for ages 20-29 and 30-39 years, respectively), heavier smoking (compared with nonsmokers, IRR for current smokers with ≥21 cigarettes/d of 2.03 [95% CI, 1.16-3.56]), trace urinary protein (compared with negative result, IRR of 2.14 [95% CI, 1.56-2.92]), eGFR ≥120 mL/min/1.73 m^2 (vs 90-104 mL/min/1.73 m^2, IRR of 1.51 [95% CI, 1.05-2.16]), higher hemoglobin A_{1c} level (IRR of 1.30 [95% CI, 1.06-1.60] per 1% increase), and current treatment for heart disease (IRR of 6.06 [95% CI, 2.48-14.8]). No significant effect modification between sleep duration and other covariates was observed in multivariate models.

As a sensitivity analysis, an association between sleep duration and the development of proteinuria was assessed in employees who did not work the night shift, which might have an influence on sleep duration. Compared with employees with at least one night shift per month, employees not working the night shift had significantly longer sleep durations (6.1 ± 0.9 vs 5.8 ± 0.8 hours; $P < 0.001$), although the difference in mean baseline sleep duration was only 17 minutes (Table 1). Clerical workers, engineers, and technical assistants more likely were included in employees not working the night shift (1,848 [96.8%] of 1,909 clerical workers and 441 [93.2%] of 473 engineers and technical assistants), whereas substantial proportions of academic researchers and health care workers in university hospitals worked night shifts (1,379 [52.2%] of 2,641 academic researchers and 1,289 [74.3%] of 1,736 health care workers), indicating that whether employees worked the night shift was dependent chiefly on their occupa-

Table 3. Urinary Protein at the Baseline Visit and End of the Observational Period

Baseline Urinary Protein	No Proteinuria at End Point (n = 6,284; 92%)		Proteinuria at End Point (n = 550; 8%)			
	Negative	Trace	1+	2+	3+	Total
Negative	5,397 (82.6)	634 (9.7)	457 (7.0)	45 (0.7)	2 (0.0)	6,535 (100.0)
Trace	196 (65.6)	57 (19.1)	42 (14.0)	4 (1.3)	0 (0.0)	299 (100.0)
Total	5,593 (81.8)	691 (10.1)	499 (7.3)	49 (0.7)	2 (0.0)	6,834 (100.0)

Note: Proteinuria at end point is urinary protein by dipstick test at the time of the development of proteinuria for employees with the outcome and at the end of the observational period for employees without the outcome. Values given as number (percentage).

Table 4. Predictors of Proteinuria in Included Employees

	Univariate Models		Multivariate Model	
	IRR (95% CI)	***P***	**IRR (95% CI)**	***P***
Demographic and physical data				
Age category				
20-29 y	2.13 (1.63-2.77)	<0.001	2.20 (1.61-3.00)	<0.001
30-39 y	1.36 (1.04-1.77)	0.02	1.48 (1.12-1.96)	0.006
40-49 y	1.00 (reference)		1.00 (reference)	
50-59 y	1.17 (0.81-1.67)	0.4	1.10 (0.76-1.60)	0.6
60-65 y	1.66 (0.76-3.59)	0.2	1.47 (0.66-3.28)	0.3
Sex				
Women	1.00 (reference)		1.00 (reference)	
Men	0.76 (0.64-0.89)	0.001	0.79 (0.60-1.04)	0.1
Occupation				
Clerical workers	1.00 (reference)		1.00 (reference)	
Academic researchers	0.96 (0.77-1.18)	0.7	1.23 (0.96-1.58)	0.1
Engineers and technical assistants	0.94 (0.65-1.36)	0.7	1.03 (0.71-1.49)	0.9
Health care workers	1.32 (1.06-1.65)	0.01	1.10 (0.87-1.38)	0.4
Other employees	1.22 (0.54-2.76)	0.6	1.31 (0.56-3.06)	0.5
BMI (/1 kg/m^2)	1.01 (0.98-1.03)	0.6	1.03 (1.00-1.06)	0.07
MAP (/10 mm Hg)	0.92 (0.86-0.99)	0.02	1.00 (0.92-1.09)	0.9
Lifestyle data				
Smoking status				
Nonsmokers	1.00 (reference)		1.00 (reference)	
Past smokers	0.93 (0.69-1.26)	0.7	1.10 (0.80-1.51)	0.6
Current smokers				
1-10 cigarettes/d	1.24 (0.83-1.84)	0.3	1.30 (0.87-1.94)	0.2
11-20 cigarettes/d	1.04 (0.72-1.49)	0.8	1.17 (0.80-1.70)	0.4
≥21 cigarettes/d	1.71 (1.00-2.91)	0.05	2.03 (1.16-3.56)	0.01
Alcohol consumption				
Rarely	1.00 (reference)		1.00 (reference)	
1-3 d/wk	0.89 (0.73-1.09)	0.3	0.95 (0.77-1.16)	0.6
4-6 d/wk	0.76 (0.55-1.07)	0.1	0.90 (0.64-1.26)	0.5
7 d/wk	0.79 (0.60-1.04)	0.1	1.01 (0.74-1.37)	0.9
Sleep duration				
≥7 h	1.00 (reference)		1.00 (reference)	
6 h	1.07 (0.86-1.32)	0.5	1.07 (0.87-1.33)	0.5
5 h	1.28 (1.01-1.62)	0.04	1.28 (1.00-1.62)	0.05
≤4 h	1.72 (1.17-2.51)	0.005	1.72 (1.16-2.53)	0.007
Excessive daytime somnolence	0.73 (0.44-1.22)	0.2	0.67 (0.40-1.13)	0.1
Laboratory data				
Urinary protein by dipstick test				
Negative	1.00 (reference)		1.00 (reference)	
Trace	2.59 (1.92-3.51)	<0.001	2.14 (1.56-2.92)	<0.001
Hematuria by dipstick test				
Negative	1.00 (reference)		1.00 (reference)	
Trace	1.46 (0.82-2.59)	0.2	1.26 (0.71-2.26)	0.4
1+	1.07 (0.81-1.41)	0.6	1.08 (0.81-1.43)	0.6
≥2+	1.57 (1.08-2.28)	0.02	1.25 (0.85-1.84)	0.3
eGFR				
120 mL/min/1.73 m^2	1.74 (1.22-2.47)	0.002	1.51 (1.05-2.16)	0.03
105-119 mL/min/1.73 m^2	1.33 (1.03-1.73)	0.03	1.20 (0.92-1.56)	0.2
90-104 mL/min/1.73 m^2	1.00 (reference)		1.00 (reference)	
75-89 mL/min/1.73 m^2	0.86 (0.70-1.06)	0.2	1.00 (0.80-1.24)	0.9
60-74 mL/min/1.73 m^2	0.79 (0.60-1.04)	0.09	1.03 (0.75-1.41)	0.9
Hemoglobin A_{1c} (/1%)	1.23 (1.04-1.46)	0.02	1.30 (1.06-1.60)	0.01
Total cholesterol (/10 mg/dL)	0.99 (0.96-1.01)	0.3	1.00 (0.97-1.03)	0.9
Triglycerides (/1 log mg/dL)	0.96 (0.68-1.36)	0.8	1.47 (0.95-2.29)	0.09
Uric acid (/1 mg/dL)	0.92 (0.86-0.98)	0.006	0.93 (0.85-1.02)	0.1
Treatments for comorbid conditions				
Hypertension	0.95 (0.54-1.68)	0.9	1.17 (0.62-2.20)	0.6
Diabetes	2.18 (0.97-4.86)	0.06	1.39 (0.52-3.71)	0.5
Dyslipidemia	0.65 (0.27-1.56)	0.3	0.60 (0.23-1.55)	0.3
Hyperuricemia	0.58 (0.14-2.32)	0.4	0.74 (0.18-3.04)	0.7
Heart diseases	5.59 (2.32-13.5)	<0.001	6.06 (2.48-14.8)	<0.001

Note: N = 6,834.

Abbreviations: BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; IRR, incidence rate ratio; MAP, mean arterial pressure.

tions ($P < 0.001$). Additionally, statistically significant differences were observed between night- and day-shift employees in age, sex, BMI, smoking status, alcohol consumption, urinary protein, hematuria, eGFR, hemoglobin A_{1c} level, total cholesterol level, triglyceride level, uric acid level, and prevalence of hypertension. For 4,061 employees who did not work the night shift, shorter sleep duration was associated with older age ($P_{trend} = 0.008$), female sex ($P_{trend} = 0.01$), higher proportions of engineers and technical assistants ($P_{trend} < 0.001$), health care workers in university hospitals ($P_{trend} < 0.001$) and other occupations ($P_{trend} = 0.003$), higher prevalence of excessive daytime somnolence ($P_{trend} < 0.001$), lower eGFR ($P_{trend} = 0.002$), higher hemoglobin A_{1c} level ($P_{trend} = 0.001$), lower triglyceride level ($P_{trend} = 0.04$), and higher prevalence of dyslipidemia ($P_{trend} = 0.01$; Table 5). A multivariate Poisson regression model identified shorter sleep duration as a significant predictor of the development of proteinuria (vs 7 hours; IRRs of 1.86 [95% CI, 1.07-3.24] and 1.47 [95% CI, 1.06-2.04] for ≤4 and 5 hours, respectively), along with younger age, heavier smoking, trace urinary protein, higher eGFR, higher hemoglobin A_{1c} level, and current treatment for heart disease (Table 6), confirming the previous results.

DISCUSSION

In this study, we identified short sleep duration as a modifiable lifestyle predictor of proteinuria, one of the vital risk factors for end-stage renal disease and CVD. In the cohort examined, employees with 5 or fewer hours of sleep duration were at significantly higher risk of developing proteinuria, even after adjusting for clinically relevant factors. These results provide novel insight into an association between sleep duration and proteinuria, which few studies have reported before. Key advantages of the present study were inclusion of a large number of younger employees (1,997 [29.2%] and 4,786 [70.0%] employees aged <30 and 40 years), age groups that rarely have been included in previous studies; ascertainment of mean sleep duration during the entire observational period; and sensitivity analysis performed after excluding employees who worked night shifts, a trait that might affect sleep duration.

Our study shows that sleep duration is associated with the development of proteinuria in a stepwise manner (Tables 4 and 6), whereas a large number of studies have shown an association between sleep duration and all-cause mortality[10,15,23,24] and cardiovascular events[12] and mortality[13] in a U-like fashion, chiefly with 7 hours of sleep duration at lowest risk. Compared with the previous studies, in this cohort, shorter mean sleep duration (6.0 ± 0.9 hours) with a small number of employees having 8 or fewer hours of sleep (n = 115 [1.7%]) hindered a statistically meaningful analysis to assess an association between longer sleep duration and development of proteinuria. Due to the large number of participants in the present study who had shorter sleep durations, many of these individuals might be at higher risk of future poor health. Because employment status and occupations greatly contribute to shorter sleep duration (Tables 2 and 5),[25,26] the present study suggests that sleep duration is one of the key factors to consider in improving occupational health.

The underlying mechanism of an association between short sleep duration and proteinuria remains to be investigated. One plausible factor is systemic inflammation,[27] which potentially leads to glomerular endothelial dysfunction and subsequent albuminuria.[28] Pertinent to this, a randomized controlled trial showed that serum C-reactive protein level significantly increased in healthy volunteers with sleep restriction (4.2 hours) for 10 days compared with those with 8 hours of sleep duration.[27] Sleep deprivation also induces an increase in peripheral white blood cell count[29] and serum interleukin 6 level.[30,31] These studies suggest that inflammation induced by short sleep duration may have contributed in part to proteinuria in the present study.

Excessive daytime somnolence, a cardinal symptom of sleep apnea,[32] was not identified as a predictor of proteinuria in the present study. Excessive daytime somnolence was associated with CVD in white and black Americans (National Health and Nutrition Examination Survey [NHANES] I epidemiologic follow-up study).[33] Because this previous study included a large number of obese participants (27.2% of participants with BMI ≥27.8 kg/m^2 in men and ≥27.3 kg/m^2 in women), who were highly vulnerable to sleep apnea, excessive daytime somnolence might partly reflect the concomitant sleep apnea. Several cross-sectional studies including many obese participants (mean BMI >30 kg/m^2) have shown that sleep apnea is associated with albuminuria.[34,35] On the contrary, the present study included a substantially smaller number of obese participants compared with previous studies, namely 1,058 (15.5%), 363 (5.3%), and 127 (1.9%) employees with BMI ≥25.0, ≥27.5, and ≥30.0 kg/m^2, respectively. An insignificant difference in BMI between 248 (3.6%) and 6,586 (96.4%) employees with and without excessive daytime somnolence (22.0 ± 3.2 and 21.8 ± 3.2 kg/m^2; $P = 0.2$) suggests that excessive daytime somnolence in the present study was unlikely to be due to sleep apnea. Rather, a significantly higher prevalence of excessive daytime somnolence in employees with shorter sleep durations (11.3%, 4.9%, 3.2%, and 2.2% in employees with ≤4, 5, 6, and ≥7 hours of sleep duration,

Table 5. Clinical Characteristics of Included Employees Who Did Not Work the Night Shift

	Baseline Sleep Duration				
	≤4 h	5 h	6 h	≥7 h	P_{trend}
No. of employees	130	749	1,864	1,318	
Mean sleep duration during observational period (h)	4.6 ± 0.7	5.3 ± 0.6	6.0 ± 0.6	6.8 ± 0.6	
Demographic and physical data					
Age (y)	37 (30-46)	36 (30-46)	35 (29-45)	34 (29-43)	0.008
Age category					
20-29 y	32 (24.6)	181 (24.2)	496 (26.6)	344 (26.1)	
30-39 y	44 (33.8)	273 (36.4)	683 (36.6)	539 (40.9)	
40-49 y	34 (26.2)	171 (22.8)	397 (21.3)	230 (17.5)	
50-59 y	17 (13.1)	110 (14.7)	250 (13.4)	169 (12.8)	
60-65 y	3 (2.3)	14 (1.9)	38 (2.0)	36 (2.7)	
Men	48 (36.9)	309 (41.3)	769 (41.3)	597 (45.3)	0.01
Occupation					
Clerical workers	56 (43.1)	345 (46.1)	891 (47.8)	556 (42.2)	0.1[a]
Academic researchers	23 (17.7)	167 (22.3)	546 (29.3)	526 (39.9)	<0.001[a]
Engineers and technical assistants	21 (16.2)	101 (13.5)	204 (10.9)	115 (8.7)	<0.001[a]
Health care workers	25 (19.2)	113 (15.1)	207 (11.1)	102 (7.7)	<0.001[a]
Other employees	5 (3.8)	23 (3.1)	16 (0.9)	19 (1.4)	0.003[a]
BMI (kg/m^2)	21.6 ± 3.6	21.9 ± 3.5	21.5 ± 3.2	21.4 ± 3.1	0.07
MAP (mm Hg)	87 ± 14	86 ± 13	85 ± 12	85 ± 13	0.06
Lifestyle data					
Smoking status					
Nonsmokers	107 (82.3)	624 (83.3)	1516 (81.3)	1067 (81.0)	0.2[b]
Past smokers	10 (7.7)	48 (6.4)	157 (8.4)	112 (8.5)	
Current smokers					
1-10 cigarettes/d	6 (4.6)	22 (2.9)	58 (3.1)	53 (4.0)	
11-20 cigarettes/d	4 (3.1)	43 (5.7)	100 (5.4)	67 (5.1)	
≥21 cigarettes/d	3 (2.3)	12 (1.6)	33 (1.8)	19 (1.4)	
Alcohol consumption					
Rarely	77 (59.2)	423 (56.5)	1,029 (55.2)	705 (53.5)	0.1[c]
1-3 d/wk	33 (25.4)	198 (26.4)	491 (26.3)	335 (25.4)	
4-6 d/wk	10 (7.7)	50 (6.7)	139 (7.5)	105 (8.0)	
7 d/wk	10 (7.7)	78 (10.4)	205 (11.0)	173 (13.1)	
Excessive daytime somnolence	17 (13.1)	41 (5.5)	61 (3.3)	32 (2.4)	<0.001
Laboratory data					
Urinary protein by dipstick test					
Negative	118 (90.8)	725 (96.8)	1,807 (96.9)	1,273 (96.6)	0.1
Trace	12 (9.2)	24 (3.2)	57 (3.1)	45 (3.4)	
Hematuria by dipstick test					
Negative	103 (79.2)	629 (84.0)	1,544 (82.8)	1,089 (82.6)	
Trace	6 (4.6)	16 (2.1)	38 (2.0)	24 (1.8)	0.5[d]
1+	14 (10.8)	80 (10.7)	208 (11.2)	148 (11.2)	
≥2+	7 (5.4)	24 (3.2)	74 (4.0)	57 (4.3)	
eGFR	88 ± 14	88 ± 14	90 ± 15	91 ± 17	0.002
≥120 mL/min/1.73 m^2	3 (2.3)	23 (3.1)	75 (4.0)	78 (5.9)	
105-119 mL/min/1.73 m^2	11 (8.5)	68 (9.1)	225 (12.1)	156 (11.8)	
90-104 mL/min/1.73 m^2	42 (32.3)	218 (29.1)	569 (30.5)	389 (29.5)	
75-89 mL/min/1.73 m^2	50 (38.5)	309 (41.3)	698 (37.4)	490 (37.2)	
60-74 mL/min/1.73 m^2	24 (18.5)	131 (17.5)	297 (15.9)	205 (15.6)	
Hemoglobin A_{1c} (%)	5.0 ± 0.4	5.0 ± 0.4	4.9 ± 0.4	4.9 ± 0.4	0.001
Total cholesterol (mg/dL)	193 ± 35	193 ± 34	193 ± 32	193 ± 34	0.9
Triglycerides (mg/dL)	61 (43-93)	62 (44-90)	60 (44-90)	64 (46-93)	0.04
Uric acid (mg/dL)	4.9 ± 1.4	4.9 ± 1.4	4.9 ± 1.3	5.0 ± 1.4	0.08

(Continued)

Table 5 (Cont'd). Clinical Characteristics of Included Employees Who Did Not Work the Night Shift

	Baseline Sleep Duration				
	≤4 h	5 h	6 h	≥7 h	P_{trend}
Treatments for comorbid conditions					
Hypertension	3 (2.3)	22 (2.9)	42 (2.3)	33 (2.5)	0.7
Diabetes	0 (0.0)	7 (0.9)	10 (0.5)	8 (0.6)	0.8
Dyslipidemia	2 (1.5)	19 (2.5)	23 (1.2)	12 (0.9)	0.01
Hyperuricemia	1 (0.8)	6 (0.8)	13 (0.7)	7 (0.5)	0.5
Heart diseases	0 (0.0)	2 (0.3)	3 (0.2)	5 (0.4)	0.4
Outcome and follow-up data					
Observational period (y)	2.2 (1.1-4.0)	2.5 (1.5-3.9)	2.3 (1.3-3.9)	2.4 (1.5-3.9)	0.7
No. of examinations					0.3
1	43 (33.1)	212 (28.3)	607 (32.6)	419 (31.8)	
2	39 (30.0)	181 (24.2)	462 (24.8)	328 (24.9)	
3	16 (12.3)	135 (18.0)	321 (17.2)	221 (16.8)	
4	32 (24.6)	220 (29.4)	473 (25.4)	344 (26.1)	
5	0 (0.0)	1 (0.1)	1 (0.1)	6 (0.5)	
Development of proteinuria	16 (12.3)	68 (9.1)	125 (6.7)	89 (6.8)	0.01

Note: N = 4,061. Continuous variables are shown as mean ± standard deviation or median (25th-75th percentile); categorical variables given as number (percentage).

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; MAP, mean arterial pressure.

[a]Each occupation versus others (eg, clerical workers vs nonclerical workers).

[b]Nonsmokers versus others.

[c]Drinking rarely versus others.

[d]Negative or trace for hematuria by dipstick test versus 1+ or more.

respectively; $P_{trend} < 0.001$; Table 2) implies that excessive daytime somnolence merely reflected a shortage of sleep. Lower, although insignificant, IRRs of excessive daytime somnolence (0.67 [95% CI, 0.40-1.13; $P = 0.1$] in all included employees [Table 4] and 0.86 [95% CI, 0.47-1.60; $P = 0.6$] in employees who did not work the night shift [Table 6]) possibly might be due to employees with shorter sleep durations who took unmeasured daytime sleep as a nap.

In addition to shorter sleep duration, younger age was identified by this study as a significant predictor of proteinuria; furthermore, our analysis found a J-shaped association between age and development of proteinuria, although a small number of employees 50 years or older failed in a statistically significant association between older age and development of proteinuria (Tables 4 and 6). Most previous studies, including the PREVEND (Prevention of Renal and Vascular End-Stage Disease)[36] and KMIC (Korea Medical Insurance Corp) studies,[37] assessed predictors of proteinuria mainly in middle-aged or older persons. Little information was available about predictors of proteinuria in persons 40 years or younger, which was the main group enrolled in the present study (70.0%). Because the IRR for those aged 20-29 years decreased from 2.20 [95% CI, 1.61-3.00] to 1.69 [95% CI, 1.13-2.53] after excluding employees who worked the night shift in the present study and since several previous studies showed that rotating shift was a risk factor for CVD,[38-40] the occupational environment might contribute in part to the development of proteinuria in younger employees. Further study is essential to show an association between younger age and development of proteinuria.

The present study had several limitations. First, the present study was based on employees in a national university, including many academic researchers and health care workers in the university hospital, who are not representative of the general population. External validity should be verified in different cohorts. Second, inadequate follow-up of employees might lead to biased results. Considering the relative youth of the employees in the present study, loss to follow-up was ascribed not to retirement or leave due to severe illness, but probably a job change, which would be expected to be related to characteristics of their workplaces. Because sleep duration also was linked to occupation (Table 2),[25,26] results of the present study should be validated in cohorts comprising different occupations. Third, self-reported sleep duration might be biased, although several studies have shown that self-reported sleep duration is correlated moderately with those measured by polysomnography[41] and actigraphy.[42] Fourth, the outcome measure in the present study was time to first proteinuria (≥1+) after the baseline examination, not persistent proteinuria. This was because of a short observational period, namely, a median of 2.5 (25th-75th percentile, 1.4-3.9) years. Further observation would be essential to ascertain an association between sleep duration and persistent proteinuria. Fifth, inflammation might be a key factor in the link between

Table 6. Predictors of Proteinuria in Included Employees Who Did Not Work the Night Shift

	Univariate Models		Multivariate Model	
	IRR (95% CI)	***P***	**IRR (95% CI)**	***P***
Demographic and physical data				
Age				
20-29 y	1.63 (1.16-2.29)	0.004	1.69 (1.13-2.53)	0.01
30-39 y	1.21 (0.87-1.69)	0.3	1.28 (0.90-1.83)	0.2
40-49 y	1.00 (reference)			
50-59 y	1.06 (0.70-1.61)	0.7	0.93 (0.60-1.45)	0.8
60-65 y	1.41 (0.61-3.29)	0.4	1.26 (0.52-3.05)	0.6
Sex				
Women	1.00 (reference)			
Men	0.95 (0.75-1.19)	0.6	0.85 (0.59-1.24)	0.4
Occupation				
Clerical workers	1.00 (reference)			
Academic researchers	0.96 (0.74-1.25)	0.8	1.13 (0.83-1.55)	0.4
Engineers and technical assistants	1.03 (0.71-1.48)	0.9	1.10 (0.75-1.59)	0.6
Health care workers	0.80 (0.53-1.23)	0.3	0.76 (0.49-1.16)	0.2
Other employees	1.42 (0.63-3.22)	0.4	1.13 (0.47-2.74)	0.8
BMI (/1 kg/m^2)	1.01 (0.98-1.05)	0.5	1.00 (0.96-1.04)	0.9
MAP (/10 mm Hg)	0.99 (0.91-1.09)	0.9	1.02 (0.91-1.15)	0.7
Lifestyle data				
Smoking status				
Nonsmokers	1.00 (reference)			
Past smokers	1.01 (0.67-1.52)	0.9	1.13 (0.73-1.75)	0.6
Current smokers				
1-10 cigarettes/d	1.12 (0.61-2.06)	0.7	1.14 (0.62-2.12)	0.7
11-20 cigarettes/d	1.26 (0.79-2.01)	0.3	1.28 (0.78-2.10)	0.3
≥21 cigarettes/d	2.02 (1.07-3.79)	0.03	2.06 (1.04-4.07)	0.04
Alcohol consumption				
Rarely	1.00 (reference)			
1-3 d/wk	0.86 (0.65-1.13)	0.3	0.85 (0.64-1.13)	0.3
4-6 d/wk	0.86 (0.54-1.35)	0.5	0.91 (0.57-1.45)	0.7
7 d/wk	0.85 (0.59-1.22)	0.4	0.88 (0.59-1.33)	0.5
Sleep duration				
≥7 h	1.00 (reference)			
6 h	1.01 (0.77-1.32)	0.9	1.07 (0.81-1.41)	0.6
5 h	1.32 (0.96-1.81)	0.08	1.47 (1.06-2.04)	0.02
≤4 h	1.84 (1.08-3.13)	0.03	1.86 (1.07-3.24)	0.03
Excessive daytime somnolence	0.96 (0.53-1.76)	0.9	0.86 (0.47-1.60)	0.6
Laboratory data				
Urinary protein by dipstick test				
Negative	1.00 (reference)			
Trace	3.28 (2.16-4.97)	<0.001	2.78 (1.79-4.33)	<0.001
Hematuria by dipstick test				
Negative	1.00 (reference)			
Trace	1.84 (0.91-3.72)	0.09	1.46 (0.70-3.03)	0.3
1+	1.20 (0.85-1.69)	0.3	1.30 (0.91-1.85)	0.2
≥2+	1.62 (0.99-2.64)	0.06	1.49 (0.90-2.48)	0.1
eGFR				
≥120 mL/min/1.73 m^2	1.95 (1.24-3.06)	0.004	1.91 (1.20-3.06)	0.007
105-119 mL/min/1.73 m^2	1.23 (0.85-1.79)	0.3	1.14 (0.78-1.67)	0.5
90-104 mL/min/1.73 m^2	1.00 (reference)			
75-89 mL/min/1.73 m^2	0.90 (0.67-1.19)	0.4	0.92 (0.69-1.24)	0.6
60-74 mL/min/1.73 m^2	0.83 (0.57-1.19)	0.3	0.88 (0.58-1.34)	0.6
Hemoglobin A_{1c} (/1%)	1.28 (1.04-1.58)	0.02	1.29 (1.01-1.65)	0.04
Total cholesterol (/10 mg/dL)	0.99 (0.96-1.03)	0.7	1.00 (0.96-1.04)	0.9
Triglycerides (/1 Log_{10} [mg/dL])	1.27 (0.79-2.02)	0.3	1.47 (0.80-2.71)	0.2
Uric acid (/1 mg/dL)	1.02 (0.93-1.10)	0.7	1.05 (0.93-1.19)	0.4
Treatments for comorbid conditions				
Hypertension	1.03 (0.51-2.08)	0.9	0.98 (0.44-2.20)	0.9
Diabetes	2.78 (1.03-7.45)	0.04	1.73 (0.51-5.84)	0.4
Dyslipidemia	1.19 (0.49-2.87)	0.7	1.08 (0.39-3.00)	0.9
Hyperuricemia	1.06 (0.26-4.26)	0.9	1.11 (0.26-4.77)	0.9
Heart diseases	6.25 (2.33-16.8)	<0.001	7.07 (2.53-19.7)	<0.001

Note: N = 4,061.

Abbreviations: BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; IRR, incidence rate ratio; MAP, mean arterial pressure.