# Cigarette Smoking and the Association with Glomerular Hyperfiltration and Proteinuria in Healthy Middle-Aged Men

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## Summary

**Background and objectives** Glomerular hyperfiltration and albuminuria accompanied by early-stage diabetic kidney disease predict future renal failure. Cigarette smoking has reported to be associated with elevated GFR in cross-sectional studies and with renal deterioration in longitudinal studies. The degree of glomerular hyperfiltration and proteinuria associated with smoking, which presumably is a phenomenon of early renal damage, has not been investigated in a satisfying manner so far.

**Design, setting, participants, & measurements** This study included 10,118 Japanese men aged 40 to 55 years without proteinuria or renal dysfunction at entry. Estimated GFR was calculated using the Modification of Diet in Renal Disease equation for Japanese. Glomerular hyperfiltration was defined as estimated GFR $\geq$117.0 ml/min per 1.73 $m^2$, which was the upper 2.5th percentile value of estimated GFR in the total population. Proteinuria was detected using standard dipstick.

**Results** During the 6-year observation period, there were 449 incident cases of glomerular hyperfiltration and 1653 cases of proteinuria. Current smokers had a 1.32-time higher risk for the development of glomerular hyperfiltration and a 1.51-time higher risk for proteinuria than nonsmokers after adjustment for baseline age, body mass index, systolic and diastolic BP, antihypertensive medication, diabetes, alcohol consumption, regular leisure-time physical activity, and estimated GFR. Both daily and cumulative cigarette consumption were associated with an increased risk for glomerular hyperfiltration and proteinuria in a dose-response manner.

**Conclusions** In middle-aged Japanese men, smoking was associated with an increased risk of glomerular hyperfiltration and dipstick proteinuria. Of importance, past smokers did not exhibit any increased risk for these conditions.

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## Introduction

Diabetes and obesity are leading causes of cardiovascular disease. These diseases are also associated with the risk of ESRD (1,2). The earliest manifestations of diabetic nephropathy and obesity-related glomerulopathy are glomerular hyperfiltration and albuminuria (3–5).

Cigarette smoking is an established risk factor for cardiovascular disease. Although smoking is related to ESRD in the long term (6), the effect of cigarette smoking on renal function in early-stage kidney disease is unclear. Smoking-related renal injury shares physiologic mechanisms with diabetic nephropathy and obesity-related glomerulopathy, such as insulin resistance and increased sympathetic nervous activity (7). Idiopathic nodular glomerulopathy, which is a histologic pattern accompanied by chronic smoking, reveals histologic findings such as glomerular basement membrane thickening and nodular mesangial sclerosis without immune-type deposit (8,9). These features are typical histologic findings of diabetic nephropathy and obesity-related glomerulopathy. As smoking-related renal injury has marked similarity, it might take a clinical course similar to those of diabetic nephropathy and obesity-related glomerulopathy.

Most previous cross-sectional studies have reported that cigarette smokers had an elevated GFR compared with nonsmokers (10–13). Conversely, in previous longitudinal studies, cigarette smoking was associated with an increased risk of reduced GFR (14–17) or ESRD (6). Because these longitudinal studies (*1*) included a lot of elderly subjects, (*2*), the follow-up examinations were conducted 16 to 23 years after the baseline, or (*3*) the definition of chronic kidney disease was defined as ESRD or death related to chronic kidney disease, the effect of cigarette smoking

  

on renal function in early-stage kidney disease was not assessed.

On the basis of both histologic findings of smoking-related renal injury and conflicting results of cross-sectional and longitudinal studies, we hypothesized that cigarette smoking is associated with the risk of glomerular hyperfiltration and proteinuria in early-stage kidney disease. To test our hypothesis, we examined the association between cigarette smoking and two outcomes, glomerular hyperfiltration and proteinuria, in a 6-year prospective observational study among apparently healthy middle-aged Japanese men.

## Materials and Methods

### Site and Setting

The Kansai Healthcare Study is an ongoing cohort investigation designed to clarify the risk factors for cardiometabolic diseases. The details of the study have been described previously (18,19). Between April 2000 and March 2001, 12,647 male employees of a company in the area of Kansai, Japan, aged 40 to 55 years at entry and considered to be involved in sedentary jobs, were enrolled in this study. All employees in this company aged ≥40 years underwent annual medical checkups. The protocol for this research was reviewed and approved by the Human Subjects Review Committee, Osaka City University.

Eligible participants for the current study were defined as having normal renal function and being negative for proteinuria at entry. We excluded 1390 men whose baseline estimated GFR was less than 60 ml/min per 1.73 $m^2$ ($n = 341$) or 117.0 ml/min per 1.73 $m^2$ or higher ($n = 296$), and/or who had a positive result for dipstick proteinuria ($n = 834$). A total of 629 men were excluded because of missing variables. Because we defined past smokers as exsmokers who quit smoking 1 year or more before the study entry, 72 men who quit smoking less than 1 year beforehand were excluded. We excluded an additional 438 men who did not undergo annual checkups. Thus, the analytic cohort for the prospective analysis consisted of 10,118 men.

### Data Collection and Measurements

The clinical examination consisted of medical history; physical examination; anthropometric measurements; self-reported questionnaires on lifestyle characteristics such as smoking habit, frequency of alcohol drinking, and regular leisure-time physical activities; blood sampling for the measurements of serum creatinine and fasting plasma glucose; and dipstick urinalysis. Trained nurses carried out all measurements. Blood samples were drawn after an overnight 12-hour fast. Serum creatinine was mainly measured by an enzymatic method using a Hitachi 7350 automatic chemistry analyzer (Hitachi Ltd., Tokyo, Japan). Serum creatinine levels were also measured by the Jaffe method in 1855 participants at the baseline examination. We recalibrated the values of the Jaffe method to the values of enzymatic method: serum creatinine (mg/dl, enzymatic method) = 1.02 × serum creatinine (mg/dl, Jaffe method) − 0.25 ($r = 0.9996$). Then we calculated estimated GFR using the Modification of Diet in Renal Disease (MDRD) equation for Japanese (20), which was validated by standard inulin clearance techniques, as follows: estimated GFR = $194 \times \text{age}^{-0.287} \times \text{serum creatinine}^{-1.094}$ (mg/dl, the enzymatic method). Urine samples were collected as clean-catch, mid-stream, and random urine specimens. The results of dipstick urinalysis were interpreted as negative, ±, 1+, 2+, 3+, or 4+. Results of ± or less in dipstick urinalysis were regarded as normal. After about 5 minutes of rest in a quiet room, BP was measured in a sitting position at the right arm with a standard automated sphygmomanometer (BP-203RV; Omron Colin, Tokyo, Japan, and Udex-super; ELK Corp., Osaka, Japan). We classified participants as having normal, impaired fasting glucose, or diabetes, according to American Diabetes Association criteria (21). Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared ($kg/m^2$). The definition of obesity was a BMI of 25 or more. This value is recommended in Japan and the Asia-Oceania region (22). Participants were classified as engaging in leisure-time physical activity at least once weekly or less than once weekly. Questions about alcohol intake included the weekly frequency of alcohol consumption and the usual amount of alcohol consumed on a daily basis. Alcohol intake was converted to total alcohol consumption (in grams of ethanol per day).

### Measurement of Cigarette Smoking

The questionnaire about the smoking habit consisted of smoking status, average number of cigarettes smoked per day and duration of cigarette smoking for current smokers, and years since quitting for past smokers. Then participants were divided into three groups: nonsmokers, past smokers, and current smokers. Past smokers were defined as those who had stopped smoking at least 1 year before the study entry. Current smokers were subdivided into two groups based on the number of cigarettes smoked per day: 1 to 20, and ≥21 cigarettes per day. The number of pack-years of exposure (that is, the number of packs of cigarettes smoked per day multiplied by the number of years smoked) was also calculated to evaluate the long-term effect of cigarette smoking.

### Outcomes

Study outcome was the incidence of glomerular hyperfiltration. Glomerular hyperfiltration was diagnosed if estimated GFR was 117.0 ml/min per 1.73 $m^2$ or higher. This threshold was defined by the upper 2.5th percentile value of estimate GFR in the baseline population. Proteinuria was defined as 1+ or higher (30 mg/dl or higher) for dipstick examination at follow-up (23).

### Statistical Analyses

Differences in baseline characteristics between participants who developed glomerular hyperfiltration and those who did not or who developed proteinuria and those who did not were evaluated by the unpaired $t$ test, Mann–Whitney test, or chi-squared test (Table 1). Differences in baseline characteristics according to smoking habits were compared with one-way ANOVA, Kruskal–Wallis test, or chi-squared test. Multiple pairwise comparison was made with Bonferroni correction (Table 2). We used Cox proportional hazard models to investigate separately the associ-

**Table 1. Characteristics of study participants at baseline according to whether glomerular hyperfiltration or proteinuria developed during the 6-year follow-up period**

| | Glomerular Hyperfiltration Status during the Follow-up Period | | | Proteinuria Status during the Follow-up Period | | |
|---|---|---|---|---|---|---|
| | No Glomerular Hyperfiltration | Glomerular Hyperfiltration | $P$[a] | No Proteinuria | Proteinuria | $P$[a] |
| Number | 9669 | 449 | | 8465 | 1653 | |
| Age (years)[b] | 48.0 ± 4.2 | 47.9 ± 3.9 | 0.75 | 48.0 ± 4.2 | 47.8 ± 4.2 | 0.06 |
| Body mass index (kg/m$^2$)[b,c] | 23.4 ± 2.9 | 23.1 ± 3.1 | 0.04 | 23.3 ± 2.8 | 23.8 ± 3.3 | <0.01 |
| Obesity (body mass index ≥25) (%) | 26.8 | 26.1 | 0.71 | 25.7 | 35.2 | <0.01 |
| Systolic blood pressure (mmHg)[b] | 129.0 ± 18.4 | 129.9 ± 18.7 | 0.31 | 128.3 ± 17.9 | 133.0 ± 20.3 | <0.01 |
| Diastolic blood pressure (mmHg)[b] | 80.5 ± 12.1 | 81.3 ± 12.1 | 0.15 | 80.0 ± 11.7 | 83.0 ± 13.3 | <0.01 |
| Antihypertensive medication (%) | 6.5 | 6.0 | 0.67 | 5.6 | 11.1 | <0.01 |
| Hypertension (%)[d] | 33.7 | 33.6 | 0.96 | 31.8 | 43.4 | <0.01 |
| Fasting plasma glucose (mmol/L)[b] | 5.6 ± 1.1 | 6.0 ± 2.0 | <0.01 | 5.6 ± 1.1 | 5.8 ± 1.4 | <0.01 |
| Diabetes (%) | 6.5 | 15.4 | <0.01 | 6.0 | 11.1 | <0.01 |
| Serum creatinine ($\mu$mol/L)[b,e] | 70.6 ± 8.9 (0.80 ± 0.10) | 58.6 ± 7.3 (0.66 ± 0.08) | <0.01 | 70.3 ± 9.1 (0.8 ± 0.1) | 69.2 ± 9.5 (0.8 ± 0.1) | <0.01 |
| Estimated GFR (ml/min per 1.73 m$^2$)[b] | 83.3 ± 11.9 | 101.8 ± 11.9 | <0.01 | 83.8 ± 12.3 | 85.6 ± 13.1 | <0.01 |
| Current smoker (%) | 56.1 | 74.4 | <0.01 | 55.4 | 64.7 | <0.01 |
| Number of cigarettes smoked per day[f] | 20 (0 to 30) | 20 (20 to 30) | <0.01 | 20 (0 to 30) | 20 (10 to 30) | <0.01 |
| Cumulative amount of smoking (pack-years)[f] | 25.0 (0 to 35.0) | 30.0 (20.0 to 40.0) | <0.01 | 25.0 (0 to 35.0) | 28.0 (12.3 to 39.0) | <0.01 |
| Regular leisure-time physical activity (%) | 18.4 | 12.5 | 0.02 | 18.5 | 16.1 | 0.02 |
| Alcohol consumption (g ethanol/day)[f] | 23.0 (3.3 to 46.0) | 29.6 (8.2 to 46.0) | <0.01 | 23.0 (3.3 to 46.0) | 23.0 (3.3 to 46.0) | 0.05 |

[a] Differences between the groups were evaluated by unpaired t-test, Mann–Whitney test, or chi-squared test.
[b] Values are expressed as mean ± SD.
[c] Calculated as weight in kilograms divided by height in meters squared.
[d] Hypertension was defined as systolic blood pressure 140 mmHg or greater, diastolic blood pressure 90 mmHg or greater, or if the participant was receiving antihypertensive medications.
[e] Values in parentheses are expressed as milligrams per deciliter.
[f] Values are median, with interquartile range in parentheses.

**Table 2. Characteristics of study participants at baseline according to smoking habits**

| | Smoking Habits | | |
|---|---|---|---|
| | Nonsmokers | Past Smokers | Current Smokers |
| Number | 2227 | 2135 | 5756 |
| Age (years)[a] | 47.7 ± 4.3 | 48.4 ± 4.2[b] | 47.9 ± 4.2[bc] |
| Body mass index (kg/m$^2$)[a,d] | 23.7 ± 2.9 | 23.8 ± 2.8 | 23.2 ± 2.9[bc] |
| Obesity (body mass index ≥25) (%) | 30.1 | 30.0 | 24.4[bc] |
| Systolic blood pressure (mmHg)[a] | 130.8 ± 17.3 | 132.1 ± 18.0 | 127.3 ± 18.7[bc] |
| Diastolic blood pressure (mmHg)[a] | 82.1 ± 11.5 | 82.7 ± 12.0 | 79.1 ± 12.1[bc] |
| Antihypertensive medication (%) | 7.1 | 9.2[b] | 5.3[bc] |
| Hypertension (%)[e] | 37.1 | 41.1[b] | 29.7[bc] |
| Fasting plasma glucose (mmol/L)[a] | 5.7 ± 1.1 | 5.7 ± 1.1 | 5.6 ± 1.1[bc] |
| Diabetes (%) | 6.4 | 7.7 | 6.7 |
| Serum creatinine ($\mu$mol/L)[a] | 71.8 ± 9.2 | 71.9 ± 9.0 | 68.8 ± 9.1[bc] |
| Estimated GFR (ml/min per 1.73 m$^2$)[a] | 82.1 ± 12.0 | 81.5 ± 11.7 | 85.9 ± 12.6[bc] |
| Number of cigarettes smoked per day[f] | 0 | N/A | 20.0 (20.0 to 30.0)[b] |
| Cumulative amount of smoking (pack-years)[f] | 0 | N/A | 30.0 (24.0 to 42.0)[b] |
| Regular leisure-time physical activity (%) | 22.2 | 23.4 | 14.5[bc] |
| Alcohol consumption (g ethanol/day)[f] | 16.4 (1.6 to 32.9) | 23.0 (8.2 to 46.0) | 23.0 (6.6 to 46.0)[b] |

Differences between the groups were evaluated by one-way ANOVA, Kruskal–Wallis test, or chi-squared test with Bonferroni multiple comparison correction.
[a] Values are expressed as mean ± SD.
[b] $P < 0.02$ *versus* nonsmoker.
[c] $P < 0.02$ *versus* past smoker.
[d] Calculated as weight in kilograms divided by height in meters squared.
[e] Hypertension was defined as systolic blood pressure 140 mmHg or greater, diastolic blood pressure 90 mmHg or greater, or if the participant was receiving antihypertensive medications.
[f] Values are median, with interquartile range in parentheses. N/A, not available.

ations between cigarette smoking and the incidence of two outcomes: glomerular hyperfiltration and proteinuria. Follow-up of each participant was continued until diagnosis of the outcome occurrence or until March 31, 2007, whichever came first. In all multivariate models, nonlinear effects of continuous independent variables were evaluated by plotting the regression coefficients against the variables (24). The linear trends in risks were evaluated by entering indicators for each categorical level of exposure, using the median value for each category. Proportional hazards assumption was confirmed by log minus log plot. The presence of effect-modifications was tested by insertion of a first-order interaction term into appropriate models. Multicollinearity was assessed by using the variance inflation factor (25). We calculated the 95% confidence intervals for each hazard ratio. *P*-values were two-tailed and were considered statistically significant if the values were less than 0.05. Statistical analyses were performed using PASW Statistics 17.0 (SPSS Inc., Chicago, IL).

## Results

### Baseline Characteristics

The mean age of the total population ($n$ = 12,647) was 48.1 ± 4.2 years at entry. Baseline estimated GFR had an almost normal distribution, and the mean value was 84.3 ± 15.4 ml/min per 1.73 m$^2$. Among the group, 341 men (2.7% of the total population) had a baseline estimated GFR less than 60 ml/min per 1.73 m$^2$, and 296 men revealed glomerular hyperfiltration defined by estimated GFR ≥117.0 ml/min per 1.73 m$^2$.

The characteristics of the analytic cohort ($n$ = 10,118) are shown in Tables 1 and 2. The proportion of current smokers was higher among participants who developed glomerular hyperfiltration than those who did not. In participants with subsequent glomerular hyperfiltration, diabetes was more common, and exercise habit was less common than in those without glomerular hyperfiltration throughout the study. Participants who developed glomerular hyperfiltration had a lower level of serum creatinine than those who did not. These baseline characteristics between participants with and without subsequent proteinuria tended to be similar to those between participants with and without subsequent glomerular hyperfiltration. Furthermore, participants with subsequent proteinuria had a higher BMI and higher systolic and diastolic BP than those without subsequent proteinuria.

### Prospective Analysis

For the total follow up of 51,373 person-years, there were 449 incident cases of glomerular hyperfiltration. Incidence rate and crude and multivariable-adjusted hazard ratios are shown in Table 3. Current smokers revealed an incidence rate twice as high as nonsmokers. With increased daily and cumulative cigarette consumption, the incidence rate of glomerular hyperfiltration was elevated.

Current smoking and more cigarettes smoked daily were both associated with an increased risk of the incidence of glomerular hyperfiltration. After adjustment for age, BMI, systolic and diastolic BP, antihypertensive medication, diabetes status, alcohol consumption, and regular

**Table 3. Incidence rates and hazard ratios for the incidence of glomerular hyperfiltration during the 6-year follow-up period**

| | Incidence Rate[b] | Hazard Ratio[a] | | |
|---|---|---|---|---|
| | | Crude Model | Multiple-Adjusted Models[c] | Further Multiple-Adjusted Models[d] |
| Smoking status | | | | |
| nonsmokers | 5.8 (66/11402) | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| past smokers | 4.5 (49/10895) | 0.78 (0.54 to 1.12) | 0.73 (0.50 to 1.06) | 0.83 (0.57 to 1.20) |
| current smokers | 11.5 (334/29076) | 1.98 (1.52 to 2.58) | 1.82 (1.39 to 2.38) | 1.32 (1.01 to 1.73) |
| Daily cigarette consumption | | | | |
| nonsmokers | 5.8 (66/11402) | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| 1 to 20 cigarettes/day | 10.5 (175/16696) | 1.81 (1.36 to 2.40) | 1.72 (1.29 to 2.29) | 1.33 (1.00 to 1.77) |
| 21 cigarettes/day | 12.8 (159/12380) | 2.21 (1.66 to 2.95) | 1.99 (1.48 to 2.68) | 1.36 (1.01 to 1.83) |
| *P* for trend | | <0.001 | <0.001 | 0.04 |
| Cumulative cigarette consumption | | | | |
| nonsmokers | 5.8 (66/11402) | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| 0.1 to 20 pack-years | 8.3 (45/5434) | 1.43 (0.98 to 2.08) | 1.40 (0.96 to 2.06) | 1.07 (0.73 to 1.57) |
| 20.1 to 40 pack-years | 11.8 (190/16124) | 2.03 (1.54 to 2.69) | 1.90 (1.43 to 2.52) | 1.40 (1.05 to 1.87) |
| ≥40.1 pack-years | 13.2 (99/7518) | 2.26 (1.66 to 3.09) | 2.03 (1.47 to 2.81) | 1.42 (1.03 to 1.96) |
| *P* for trend | | <0.001 | <0.001 | 0.01 |

[a] 95% confidence intervals in parentheses.
[b] Incidence rates are expressed as incidence per 1000 person-years, with number of cases per person-years in parentheses.
[c] Adjusted for age, body mass index, systolic blood pressure, diastolic blood pressure, antihypertensive medication (yes/no), diabetes status (normal, impaired fasting glucose, and diabetes), alcohol consumption, and regular leisure-time physical activity (yes/no).
[d] Further adjusted for baseline estimated glomerular filtration rate in addition to the variables in the multiple-adjusted models.

leisure-time physical activity, current smokers had a 1.82 times higher hazard ratio than nonsmokers. The number of cigarettes smoked daily was positively and significantly associated with an increased risk of future incidence of glomerular hyperfiltration in a dose-response manner. Participants smoking ≥21 per day had a 1.99 times higher hazard ratio than nonsmokers (multiple-adjusted model of Table 3). The number of pack-years of exposure was calculated to evaluate the cumulative dose-effect of cigarette smoking. The number of pack-years was also positively and significantly associated with an increased risk of future incidence of glomerular hyperfiltration in a dose-response manner. Participants with a pack-year value ≥40.1 had a 2.03 times higher hazard ratio than nonsmokers. After further adjustment for baseline estimated GFR, these relationships remained statistically significant. In all models, past smokers did not show an elevated risk of glomerular hyperfiltration. Even if we included 72 past smokers who quit smoking less than 1 year at study entry, the results did not change (data not shown). Further adjustment for updated BMI as a time-dependent covariate did not change all results in Tables 3 and 4 (data not shown). On the other hand, in participants who had proteinuria at baseline, we could not find a significant relationship between smoking and glomerular hyperfiltration (data not shown).

Hazard ratios of each independent variable for the development of glomerular hyperfiltration are shown in Table 4. Baseline estimated GFR was a strong risk factor of future glomerular hyperfiltration. With every 10-ml/min per 1.73 $m^2$ increase in baseline estimated GFR, the hazard ratio for the incidence of glomerular hyperfiltration during follow-up was elevated nearly threefold.

During the 6-year follow-up period (49,657 person-years), we observed 1653 incident cases of dipstick proteinuria. Current smoking and greater daily or cumulative cigarette consumption were associated with an elevated risk for the development of proteinuria after adjustment for potential confounders (Table 4).

We examined the effect modifications in all models of Tables 3 and 4 between smoking status, daily cigarette consumption, or cumulative cigarette consumption and the other variables. None of these interactions was significant. All independent variables in the multivariable models met proportional hazards assumption. Evidence of multicollinearity was absent because the variance inflation factor for each independent variable in the multivariable models was less than 3.

## Discussion

These data demonstrated that cigarette smoking was associated with an increased incidence of glomerular hyperfiltration and proteinuria. Both daily and cumulative cigarette exposures were dose-dependently associated with elevated risk for these conditions. Past smokers did not have any elevated risk for the incidence of glomerular hyperfiltration and proteinuria.

With one exception (26), almost all community-based cross-sectional studies from France, Japan, Korea, and the Netherlands have reported that current smokers had a higher GFR than nonsmokers or that current smoking was associated with a higher prevalence of elevated GFR (11–14). Some of these studies reported that the number of cigarettes smoked daily was positively related to the prevalence of glomerular hyperfiltration in a dose-response manner (12,14). On the other hand, no longitudinal studies

**Table 4. Hazard ratios for the incidence of glomerular hyperfiltration and dipstick proteinuria during the 6-year follow-up period**

| | Hazard Ratio for the Incidence of Glomerular Hyperfiltration[a] | | Hazard Ratio for the Incidence of Dipstick Proteinuria[a] | |
|---|---|---|---|---|
| | Multiple-Adjusted Model[b] | Further Multiple-Adjusted Model[c] | Multiple-Adjusted Model[b] | Further Multiple-Adjusted Model[c] |
| Cumulative cigarette consumption | | | | |
| nonsmokers | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| 0.1 to 20 pack-years | 1.40 (0.96 to 2.06) | 1.07 (0.73 to 1.57) | 1.39 (1.15 to 1.68) | 1.37 (1.13 to 1.65) |
| 20.1 to 40 pack-years | 1.90 (1.43 to 2.52) | 1.40 (1.05 to 1.87) | 1.49 (1.29 to 1.72) | 1.46 (1.26 to 1.69) |
| ≥40.1 pack-years | 2.03 (1.47 to 2.81) | 1.42 (1.03 to 1.96) | 1.78 (1.51 to 2.11) | 1.74 (1.47 to 2.05) |
| *P* for trend | <0.001 | 0.01 | <0.001 | <0.001 |
| Age (per 5 years) | 0.96 (0.84 to 1.09) | 1.13 (1.00 to 1.29) | 0.93 (0.87 to 1.00) | 0.94 (0.88 to 1.01) |
| Body mass index (per 1 kg/m$^2$)[d] | 0.95 (0.92 to 0.98) | 0.99 (0.95 to 1.02) | 1.02 (1.00 to 1.04) | 1.02 (1.00 to 1.04) |
| Systolic blood pressure (per 10 mmHg) | 0.99 (0.92 to 1.07) | 0.96 (0.89 to 1.03) | 1.06 (1.02 to 1.11) | 1.06 (1.02 to 1.11) |
| Diastolic blood pressure (per 10 mmHg) | 1.12 (1.00 to 1.26) | 1.17 (1.04 to 1.31) | 1.10 (1.03 to 1.17) | 1.10 (1.03 to 1.17) |
| Antihypertensive medication | 0.88 (0.57 to 1.37) | 0.93 (0.60 to 1.45) | 1.81 (1.51 to 2.16) | 1.82 (1.52 to 2.18) |
| Diabetes status | | | | |
| normal | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| impaired fasting glucose | 1.54 (1.13 to 2.11) | 1.38 (1.01 to 1.88) | 1.12 (0.94 to 1.34) | 1.11 (0.93 to 1.32) |
| diabetes | 2.88 (2.17 to 3.82) | 1.72 (1.30 to 2.29) | 1.55 (1.30 to 1.86) | 1.50 (1.25 to 1.79) |
| Alcohol consumption (per 10 g ethanol/day) | 1.07 (1.03 to 1.12) | 1.03 (0.99 to 1.08) | 1.02 (0.99 to 1.04) | 1.01 (0.99 to 1.04) |
| Regular leisure-time physical activity | 0.72 (0.53 to 0.97) | 0.99 (0.73 to 1.34) | 0.96 (0.83 to 1.11) | 0.97 (0.84 to 1.12) |
| Estimated GFR (per 10 ml/min per 1.73 m$^2$) | —[e] | 2.72 (2.51 to 2.95) | —[e] | 1.07 (1.02 to 1.11) |

[a] 95% confidence intervals in parentheses.
[b] Listed variables except for estimated glomerular filtration rate were included in this model.
[c] Further adjusted for estimated glomerular filtration rate in addition to the variables in the multiple-adjusted model.
[d] Calculated as weight in kilograms divided by height in meters squared.
[e] —, not available.

have examined the relationship between cigarette smoking and glomerular hyperfiltration. Fox *et al.* (15) in the Framingham Offspring Study and Stengel *et al.* (16) in the second National Health and Nutrition Examination Survey reported that cigarette smoking was associated with the risk of future incidence of chronic kidney disease. Because in the former study the follow-up examinations were conducted 16 to 23 years after baseline and in the latter study chronic kidney disease was defined as treated ESRD or death related to chronic kidney disease, these studies had shortcomings in examining the association between cigarette smoking and the risk of early-stage kidney disease. In two population-based cohorts, Shankar *et al.* (14) in Wisconsin and Yamagata *et al.* (17) in Ibaraki, Japan, reported that cigarette smoking increased the risk of chronic kidney disease. Because these studies included many elderly as well as middle-aged subjects, the authors did not examine the effect of cigarette smoking on the age-specific incidence of chronic kidney disease. Bleyer *et al.* reported in the Cardiovascular Health Study focusing on subjects older than 65 years that cigarette smoking was associated with an increase in serum creatinine (27). If smoking-induced glomerular hyperfiltration could be an early marker of kidney disease, epidemiologic studies focusing on older subjects would be inadequate to explore the association between cigarette smoking and the risk of glomerular hyperfiltration because some of the older subjects presumably have had a long exposure to smoking and it is possible that they would have already experienced this stage of glomerular hyperfiltration. In our study focusing on middle-aged subjects, cigarette smoking was associated with an increased risk of future glomerular hyperfiltration in a middle-term follow-up period. This discrepancy suggests that the effect of smoking on renal function might vary with age and time of follow-up.

Another key finding in our study was the relationship between cigarette smoking and proteinuria. This relationship was concordant with previous studies (10,28). However, previous studies only examined the associations of current smokers *versus* past smokers or nonsmokers with the risk of proteinuria. No previous prospective studies examined the relationships between the number of cigarettes smoked daily or pack-years of exposure and the risk of proteinuria.

The mechanism of how cigarette smoking increases the risk for glomerular hyperfiltration is unclear. A potential explanation that connects smoking and glomerular hyperfiltration is insulin resistance. Smoking is known to induce insulin resistance and increases the risk of future type 2 diabetes (29). Higher insulin resistance was reported to be associated with an increased GFR measured by $^{99m}$Tc-diethylenetriamine-pentaacetic acid technique in subjects without diabetes and renal diseases (30). In addition, Polish young men with accumulated metabolic risk factors including insulin resistance exhibited higher prevalence of glomerular hyperfiltration than those without metabolic abnormalities (31). These findings suggest that insulin resistance is one mechanism that can explain the association between cigarette smoking and glomerular hyperfiltration. Interestingly, idiopathic nodular glomerulosclerosis, which is associated with long-term smoking, has various pathologic patterns resembling diabetic nephropathy and obesity-related glomerulopathy, such as nodular mesangial sclerosis, glomerular basement membrane thickening, and absence of immune-type deposit (8,9). Smoking-related kidney disease may take a course similar to diabetic nephropathy and obesity-related glomerulopathy. Furthermore, loss of muscle mass might affect our findings, but adjustment for updated BMI as a time-dependent covariate did not remove a significant relationship between cigarette smoking and the risk of glomerular hyperfiltration. Therefore, cigarette smoking may affect through mechanisms unrelated the loss of muscle mass.

Some limitations in our study should be noted. First, the population of the current study was limited to middle-aged Japanese men, so whether we can extend our results to women, older men, and other ethnic groups is unclear. Second, the results might be biased because of lack of direct measurement of GFR. Direct measurement of renal function is impractical, and this limitation is common in large cohort studies. Using the MDRD formula to estimate renal function should be permitted (32). In addition, our results about the association between cigarette smoking and glomerular hyperfiltration should not be due to the increment in creatinine excretion through renal tubules because smoking was reported not to alter the renal tubular handling of creatinine (33). The use of standard body surface area indexed GFR has been debated, especially for obese subjects (34,35). As we obtained similar results when we used back-corrected GFR or creatinine clearance computed by the Cockcroft–Gault equation, the use of MDRD-GFR did not cause a critical bias. Third, we could not mention the class effect of antihypertensive drugs on the development of glomerular hyperfiltration because we did not have any data for the class of antihypertensive agents. Fourth, we could not detect a significant relationship between smoking and glomerular hyperfiltration in participants with dipstick proteinuria at baseline. This could be due to the lack of sufficient statistical power in participants with proteinuria. Finally, because we saw no major differences of baseline characteristics between participants who did or did not undergo follow-up examination (data not shown), we do not believe that there is a high likelihood for bias in our results due to differential loss to follow-up.

In conclusion, cigarette smoking was positively associated with the incidence of glomerular hyperfiltration and proteinuria in middle-aged participants. This relationship was independent of diabetes and obesity. Smoking-induced glomerular hyperfiltration and proteinuria could be an early marker of kidney disease. Because cigarette smoking is a strong but modifiable risk factor for kidney damage, smoking cessation is recommended to restore renal function and prevent future renal dysfunction.

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**Disclosures**

None.

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