Systematic Reviews and Meta- and Pooled Analyses

Prediction of Cardiovascular Disease Mortality by Proteinuria and Reduced Kidney Function: Pooled Analysis of 39,000 Individuals From 7 Cohort Studies in Japan

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There are limited studies addressing whether proteinuria and estimated glomerular filtration rate (eGFR) are independently associated with cardiovascular disease in Asia. Using data from 7 prospective cohorts recruited between 1980 and 1994 in Japan, we assessed the influence of proteinuria (≥1+ on dipstick) and reduced eGFR on the risk of cardiovascular disease mortality in 39,405 participants (40–89 years) without kidney failure. During a 10.1-year follow-up, 1,927 subjects died from cardiovascular disease. Proteinuria was associated with a 1.75-fold (95% confidence interval (CI): 1.44, 2.11) increased risk of cardiovascular disease mortality after adjustment for potential confounding factors. Additionally, the multivariate-adjusted hazard ratio of cardiovascular disease mortality increased linearly with lower eGFR levels (P trend < 0.001): Subjects with eGFR of <45 mL/minute/1.73 m² had a 2.22-fold (95% CI: 1.60, 3.07) greater risk of cardiovascular disease mortality than those with eGFR of ≥90 mL/minute/1.73 m². Subjects with both proteinuria and eGFR of <45 mL/minute/1.73 m² had a 4.05-fold (95% CI: 2.55, 6.43) higher risk of cardiovascular disease mortality compared with those with neither of these risk factors. There was no evidence of interaction in the relationship between proteinuria and lower eGFR (P interaction = 0.77). The present results suggest that proteinuria and lower eGFR are independent risk factors for cardiovascular disease mortality in the Japanese population.

coronary artery disease; meta-analysis; proteinuria; renal insufficiency

Abbreviations: CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; EPOCH-JAPAN, Evidence for Cardiovascular Prevention from Observational Cohorts in Japan; ICD-9, International Classification of Diseases, Ninth Revision; ICD-10, International Classification of Diseases, Tenth Revision; IDMS-MDRD, isotope dilution mass spectrometry–traceable 4-variable Modification of Diet in Renal Disease; JSN-CKDI, Japan Society of Nephrology Chronic Kidney Disease Initiative; KDIGO, Kidney Disease: Improving Global Outcomes.

Kidney disease is increasingly being recognized as a leading public health issue. Chronic kidney disease, usually defined by the presence of proteinuria and/or reduced estimated glomerular filtration rate (eGFR), affects 10%–15% of the adult population in developed Western countries (1, 2). On the other hand, chronic kidney disease is expected to be more prevalent in Asian countries (3, 4). We previously reported that the prevalence of chronic kidney disease increased significantly over the last 3 decades in a general

Japanese population, indicating that the burden of chronic kidney disease is gradually increasing in Japan (5).

Growing evidence suggests that proteinuria and reduced eGFR are associated with an increased risk of not only progressive kidney failure but also cardiovascular disease (6, 7). A recent meta-analysis using data from community-based cohort studies has suggested that both proteinuria and reduced eGFR were independently associated with cardiovascular disease or death (8). On the basis of this finding,
the Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference has recommended the following: 1) the assessment of both proteinuria and eGFR in general practice and 2) the classification of chronic kidney disease stages by using both kidney parameters, that is, proteinuria and reduced eGFR (9). With regard to Asian populations, a prospective cohort study in Taiwan has demonstrated that the risk for all-cause mortality increased with the amount of proteinuria at any given eGFR level (10). However, few studies have addressed whether the influence of these 2 parameters on the risk of cardiovascular outcomes is mutually independent or synergistic in Asian populations.

In the present study, we discuss the findings of pooled analysis from the Evidence for Cardiovascular Prevention from Observational Cohorts in Japan (EPOCH-JAPAN), which is an overview of individual participants’ data from 13 longitudinal observational studies in Japan. The purpose of this study was to investigate the independent and combined influences of proteinuria and reduced eGFR on cardiovascular disease mortality in the Japanese population.

MATERIALS AND METHODS

Study design and participants

The rationale, study design, and methods of the EPOCH-JAPAN Study have been described elsewhere (11, 12). In brief, cohort studies were eligible for inclusion in this analysis if they met the following criteria: 1) collected health examination measures, 2) had almost 10 years of follow-up, and 3) included >1,000 participants. Both nationwide and regional cohort studies were included. Individual records of 188,141 participants in 13 cohort studies were included in the present analysis. Quality control of the collected cohort data was performed at the EPOCH-JAPAN Study Coordinating Center. Permission to submit data from each cohort to the EPOCH-JAPAN Study Coordinating Center was obtained from the relevant institutional review boards for ethical issues.

Of the 13 cohorts, 3 were excluded from the present analysis because of the absence of cause-of-death information, and 3 were excluded because of the lack of proteinuria or serum creatinine data. From a total of 44,588 participants in the remaining 7 cohorts (13–19), we excluded participants who were <40 years of age (n = 5,099) or ≥90 years of age (n = 59), as well as those with an eGFR of <15 mL/minute/1.73 m² (n = 25). A final total of 39,405 participants were included in the analysis, with 92.5% of the participants from 6 community-based cohorts and 7.5% from 1 work site–based cohort.

Risk factors

Proteinuria was tested by the dipstick method and defined as a result of 1+ or over. Because serum creatinine was measured by the Jaffé method in each cohort, the serum creatinine value was corrected by the subtraction of 18.3 μmol/L in order to convert the finding to a value measured by the enzymatic method (20). The value of eGFR was calculated by using the Japanese coefficient–modified Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (21). Other formulas of eGFR, that is, the Japan Society of Nephrology Chronic Kidney Disease Initiative (JSN-CKDI) equation (22) and the modified isotope dilution mass spectrometry–traceable 4-variable Modification of Diet in Renal Disease (IDMS-MDRD) Study equation with a Japanese correction coefficient of 0.808 (13), were used for sensitivity analyses. In accordance with the recommendation from the KDIGO (9), eGFR levels were classified in the following ranges: ≥90, 60–89, 45–59, and <45 mL/minute/1.73 m². Blood pressure was measured by a standard sphygmomanometer in all cohorts. The mean value was used in several cohorts that measured 2 or more blood pressure values. Diabetes was defined as a fasting blood glucose level of ≥7.0 mmol/L, a casual blood glucose level of ≥11.1 mmol/L, or current use of insulin or oral medication for diabetes. Body mass index was calculated by using the following equation: weight (kg)/height (m)². Measurement of serum total cholesterol was standardized in 5 cohorts such that values would be traceable to the Centers for Disease Control and Prevention reference method. Information on current smoking and drinking status was obtained through standard questionnaires and classified as current habitual use or lack thereof.

End points

For each deceased subject, a primary underlying cause of death was coded according to the International Classification of Diseases National Vital Statistics System based on criteria proposed by the World Health Organization. Causes of cardiovascular disease mortality were sought in great detail with the sources available in each cohort study, and the findings were classified as follows: coronary heart disease, stroke, and other cardiovascular diseases. In many studies, death certificates were reviewed and/or the National Vital Statistics System was utilized after obtaining permission from the Ministry of Internal Affairs and Communications of Japan. Other sources utilized in some studies included autopsy, medical records, health examination, and questionnaire. Causes of cardiovascular disease mortality were coded by either the International Classification of Diseases, Ninth Revision (ICD-9) or Tenth Revision (ICD-10), classification. Classification codes used in the study were as follows: death from cardiovascular disease (ICD-9 codes 390–459, ICD-10 codes I00–I99), coronary heart disease (ICD-9 codes 410–414, ICD-10 codes I20–I25), and stroke (ICD-9 codes 430–438, ICD-10 codes I60–I69).

Statistical analysis

The hazard ratio and its 95% confidence interval for the outcome were estimated with the Cox proportional hazards regression model stratified by cohort. The heterogeneity across cohorts was examined with the Cochran Q test and the I² statistic (23). The interaction effect of both proteinuria and reduced eGFR levels on the outcome was estimated by adding interaction terms between eGFR categories assigned serial numerical codes and the status of proteinuria to the relevant model. All statistical analyses were performed by
Table 1. Baseline Characteristics of EPOCH-JAPAN Participants in 7 Cohorts Recruited Between 1980 and 1994

<table>
<thead>
<tr>
<th>Cohort, Year (Reference No.)</th>
<th>No. of Participants</th>
<th>Mean Age (SD), Years</th>
<th>Men, %</th>
<th>Baseline Survey Year</th>
<th>Mean Follow-up Period (SD), Years</th>
<th>Mean eGFR (SD), mg/dL/1.73 m²</th>
<th>Proteinuria*, %</th>
<th>Mean SBP (SD), mm Hg</th>
<th>Mean DBP (SD), mm Hg</th>
<th>Diabetes, %</th>
<th>Mean BMI (SD)b</th>
<th>Mean Total Cholesterol (SD), mmol/L</th>
<th>Current Smoking, %</th>
<th>Current Drinking, %</th>
<th>No. of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osaki, 1994 (13)</td>
<td>15,989</td>
<td>62 (9)</td>
<td>42.5</td>
<td>1994</td>
<td>6.0 (1.4)</td>
<td>92.1 (14.0)</td>
<td>1.7</td>
<td>131 (18)</td>
<td>79 (11)</td>
<td>4.6</td>
<td>23.9 (3.1)</td>
<td>5.3 (0.9)</td>
<td>21.8</td>
<td>41.7</td>
<td>251</td>
</tr>
<tr>
<td>Ohasama®, 1987 (14)</td>
<td>189</td>
<td>64 (9)</td>
<td>51.3</td>
<td>1987</td>
<td>7.0 (2.1)</td>
<td>76.6 (11.0)</td>
<td>12.2</td>
<td>137 (18)</td>
<td>78 (11)</td>
<td>1.1</td>
<td>23.6 (3.2)</td>
<td>5.0 (0.9)</td>
<td>19.6</td>
<td>24.3</td>
<td>10</td>
</tr>
<tr>
<td>YKK workers, 1990 (15)</td>
<td>2,966</td>
<td>47 (5)</td>
<td>65.4</td>
<td>1990</td>
<td>10.9 (2.4)</td>
<td>90.0 (8.8)</td>
<td>4.1</td>
<td>119 (16)</td>
<td>74 (12)</td>
<td>2.7</td>
<td>22.5 (2.6)</td>
<td>5.3 (0.9)</td>
<td>37.5</td>
<td>59.6</td>
<td>13</td>
</tr>
<tr>
<td>RERF cohort, 1986 (16)</td>
<td>4,553</td>
<td>62 (12)</td>
<td>32.7</td>
<td>1986</td>
<td>14.3 (4.7)</td>
<td>68.7 (11.1)</td>
<td>4.4</td>
<td>135 (23)</td>
<td>82 (12)</td>
<td>13.6</td>
<td>22.7 (3.5)</td>
<td>5.4 (1.0)</td>
<td>22.3</td>
<td>41.8</td>
<td>574</td>
</tr>
<tr>
<td>Hisayama, 1988 (17)</td>
<td>2,711</td>
<td>59 (12)</td>
<td>42.7</td>
<td>1988</td>
<td>11.0 (2.6)</td>
<td>73.8 (11.6)</td>
<td>5.7</td>
<td>134 (21)</td>
<td>78 (11)</td>
<td>9.1</td>
<td>22.8 (3.2)</td>
<td>5.3 (1.1)</td>
<td>25.2</td>
<td>30.8</td>
<td>158</td>
</tr>
<tr>
<td>NIPPON DATA 80, 1980 (18)</td>
<td>7,065</td>
<td>56 (11)</td>
<td>44.0</td>
<td>1980</td>
<td>16.7 (4.5)</td>
<td>78.8 (12.3)</td>
<td>2.8</td>
<td>140 (22)</td>
<td>83 (12)</td>
<td>4.6</td>
<td>22.8 (3.2)</td>
<td>5.0 (0.9)</td>
<td>31.6</td>
<td>41.8</td>
<td>719</td>
</tr>
<tr>
<td>NIPPON DATA 90, 1990 (19)</td>
<td>5,932</td>
<td>57 (11)</td>
<td>42.9</td>
<td>1990</td>
<td>9.5 (1.7)</td>
<td>86.2 (12.6)</td>
<td>3.0</td>
<td>139 (20)</td>
<td>83 (12)</td>
<td>4.8</td>
<td>23.1 (3.2)</td>
<td>5.4 (0.9)</td>
<td>27.5</td>
<td>28.3</td>
<td>202</td>
</tr>
<tr>
<td>Total</td>
<td>39,405</td>
<td>59 (11)</td>
<td>43.5</td>
<td></td>
<td>10.1 (5.0)</td>
<td>84.6 (15.2)</td>
<td>2.9</td>
<td>134 (20)</td>
<td>80 (12)</td>
<td>5.8</td>
<td>23.3 (3.2)</td>
<td>5.3 (1.0)</td>
<td>25.9</td>
<td>40.2</td>
<td>1,927</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; EPOCH-JAPAN, Evidence for Cardiovascular Prevention from Observational Cohorts in Japan; NIPPON DATA 80 or 90, the cohort study of the National Survey on Circulatory Disorders in 1980 or 1990 in Japan; RERF, Radiation Effects Research Foundation; SBP, systolic blood pressure; SD, standard deviation; YKK, Yoshida Kogyo K.K.

* Proteinuria was defined as ≥1+ on dipstick.

b Body mass index: weight (kg)/height (m)^2.

c In the Ohasama cohort, those without serum creatinine data (n=2,965) or proteinuria data (n=60) were excluded from a total of 3,174 participants, and the remaining 189 participants were included in the analysis.
Participants Recruited Between 1980 and 1994 With an Average 10.1-Year Follow-up

RESULTS

The characteristics of the study participants in 7 cohorts are shown in Table 1. Overall, the mean age was 59 years, and the proportion of men was 43.5%. The subjects were followed for an average of 10.1 years. The mean eGFR value was 84.6 mL/minute/1.73 m², and the frequency of proteinuria was 2.9%. During the follow-up period, a total of 1,927 experienced cardiovascular disease mortality, of which 397 subjects died from coronary heart disease and 846 from stroke.

Table 2 shows the pooled estimate of adjusted hazard ratios for cardiovascular disease mortality according to the status of proteinuria. Subjects with proteinuria had a 1.75-fold (95% CI: 1.44, 2.11) higher risk of cardiovascular disease mortality than those with negative proteinuria after adjustment for age, sex, systolic blood pressure, diabetes, total cholesterol, body mass index, history of cardiovascular disease, current smoking, and current drinking. This relationship was not altered substantially after adjustment for the aforementioned confounding factors and eGFR levels. Comparable results were found for mortalities from coronary heart disease and stroke. Additionally, when we divided proteinuria levels into 3 categories of negative, trace, and ≥1+ proteinuria, subjects with trace proteinuria and ≥1+ proteinuria had a 1.44-fold (95% CI: 1.17, 1.77) and 1.80-fold (95% CI: 1.48, 2.17) higher risk of cardiovascular disease mortality than those with negative proteinuria after adjustment for the aforementioned risk factors, respectively (Appendix Table 1).

Next, we estimated the relationship between eGFR levels and the risk of cardiovascular disease outcomes (Table 3). The risk of mortality from cardiovascular disease and stroke increased progressively with declining eGFR levels after adjustment for the aforementioned confounding factors. Likewise, an increasing trend was observed in the risk of mortality from coronary heart disease. Subjects with an eGFR of <45 mL/minute/1.73 m² had a 2.22-fold (95% CI: 1.60, 3.07) greater risk of cardiovascular disease mortality than those with an eGFR of ≥90 mL/minute/1.73 m². The relationships showed little change after adjustment for the aforementioned confounding factors and proteinuria levels. Furthermore, similar associations of proteinuria or reduced eGFR with the risk of cardiovascular disease mortality were observed in middle-aged (<60 years of age) and elderly (≥60 years of age) populations. Additionally, we compared the influence of proteinuria and eGFR of <60 (vs. ≥60) mL/minute/1.73 m² on the risk of cardiovascular disease mortality among study cohorts (Figure 1). We found no evidence of heterogeneity in the effects across study cohorts (Q = 4.3, I² = 0 %, P = 0.64 for proteinuria; and Q = 2.3, I² = 0 %, P = 0.89 for eGFR of <60 mL/minute/1.73 m²).

Finally, we investigated the combined influences of proteinuria and reduced eGFR levels on the risk of cardiovascular disease mortality (Figure 2). The influence of proteinuria and that of lower eGFR on the risk of cardiovascular disease mortality were independent of each other (Pinteraction = 0.77). Compared with those subjects lacking proteinuria who had an eGFR level of ≥90 mL/minute/1.73 m², those with both proteinuria and an eGFR of <45 mL/minute/1.73 m² were at 4.05-fold (95% CI: 2.55, 6.43) higher risk of cardiovascular disease mortality. The sensitivity analysis, in which proteinuria levels were divided into 3 categories of negative, trace,
### Table 3. Adjusted Mortality Rates and Hazard Ratios of Cardiovascular Disease According to eGFR Levels From EPOCH-JAPAN Participants Recruited Between 1980 and 1994 With an Average 10.1-Year Follow-up

<table>
<thead>
<tr>
<th>eGFR, mg/dL/1.73 m²</th>
<th>No. of Participants</th>
<th>No. of Deaths</th>
<th>Person-Years</th>
<th>Mortality Rate/1,000 Person-Years&lt;sup&gt;a&lt;/sup&gt;</th>
<th>95% CI&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Age and Sex Adjusted</th>
<th>Multivariate Adjusted (Model A)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Multivariate Adjusted (Model B)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HR 95% CI P&lt;sub&gt;trend&lt;/sub&gt;</td>
<td>HR 95% CI P&lt;sub&gt;trend&lt;/sub&gt;</td>
<td>HR 95% CI P&lt;sub&gt;trend&lt;/sub&gt;</td>
</tr>
<tr>
<td>≥90</td>
<td>14,720</td>
<td>135</td>
<td>123,511</td>
<td>1.8</td>
<td>0.5, 3.2</td>
<td>1 Referent &lt;0.001</td>
<td>1 Referent &lt;0.001</td>
<td>1 Referent &lt;0.001</td>
</tr>
<tr>
<td>60–89</td>
<td>22,736</td>
<td>1,286</td>
<td>256,444</td>
<td>4.7</td>
<td>4.4, 5.0</td>
<td>1.20 0.98, 1.46</td>
<td>1.19 0.96, 1.48 &lt;0.001</td>
<td>1.96 0.96, 1.48</td>
</tr>
<tr>
<td>45–59</td>
<td>1,593</td>
<td>403</td>
<td>16,267</td>
<td>8.8&lt;sup&gt;***&lt;/sup&gt;</td>
<td>6.9, 10.7</td>
<td>1.78&lt;sup&gt;***&lt;/sup&gt; 1.40, 2.26</td>
<td>1.58&lt;sup&gt;***&lt;/sup&gt; 1.21, 2.05</td>
<td>1.56&lt;sup&gt;**&lt;/sup&gt; 1.20, 2.02</td>
</tr>
<tr>
<td>&lt;45</td>
<td>356</td>
<td>103</td>
<td>2,676</td>
<td>16.9&lt;sup&gt;***&lt;/sup&gt;</td>
<td>11.2, 22.6</td>
<td>2.45&lt;sup&gt;***&lt;/sup&gt; 1.82, 3.28</td>
<td>2.22&lt;sup&gt;***&lt;/sup&gt; 1.60, 3.07</td>
<td>2.06&lt;sup&gt;***&lt;/sup&gt; 1.48, 2.85</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cardiovascular Disease</td>
<td>Coronary Heart Disease</td>
<td>Stroke</td>
</tr>
<tr>
<td>≥90</td>
<td>14,720</td>
<td>46</td>
<td>123,511</td>
<td>0.7</td>
<td>0.4, 0.9</td>
<td>1 Referent &lt;0.001</td>
<td>1 Referent &lt;0.001</td>
<td>1 Referent 0.08</td>
</tr>
<tr>
<td>60–89</td>
<td>22,736</td>
<td>256</td>
<td>256,444</td>
<td>1.0</td>
<td>0.8, 1.1</td>
<td>0.79 0.55, 1.14</td>
<td>0.75 0.51, 1.10 0.04</td>
<td>0.75 0.51, 1.10</td>
</tr>
<tr>
<td>45–59</td>
<td>1,593</td>
<td>70</td>
<td>16,267</td>
<td>1.6</td>
<td>1.0, 2.3</td>
<td>1.20 0.74, 1.94</td>
<td>0.96 0.57, 1.62</td>
<td>0.95 0.57, 1.60</td>
</tr>
<tr>
<td>&lt;45</td>
<td>356</td>
<td>25</td>
<td>2,676</td>
<td>4.8&lt;sup&gt;*&lt;/sup&gt;</td>
<td>1.6, 8.0</td>
<td>2.11&lt;sup&gt;*&lt;/sup&gt; 1.18, 3.76</td>
<td>1.71 0.90, 3.23</td>
<td>1.55 0.82, 2.93</td>
</tr>
</tbody>
</table>

### Abbreviations:
- CI, confidence interval; eGFR, estimated glomerular filtration rate; EPOCH-JAPAN, Evidence for Cardiovascular Prevention from Observational Cohorts in Japan; HR, hazard ratio.
- ≥90: ≥90 years; 60–89: 60–89 years; 45–59: 45–59 years; <45: <45 years.
- *P < 0.05; **P < 0.01; ***P < 0.001.
- Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; EPOCH-JAPAN, Evidence for Cardiovascular Prevention from Observational Cohorts in Japan; HR, hazard ratio.
- Mortality rates and their 95% confidence intervals were adjusted for age and sex by using the direct standardized method.
- Model A was adjusted for age, sex, systolic blood pressure, diabetes, total cholesterol, body mass index, history of cardiovascular disease, current smoking, and current drinking.
- Model B was adjusted for the potential confounding factors included in Model A and albuminuria levels.
The sensitivity analyses using other formulas of eGFR, namely, the JSN-CKDI equation (22) and the Japanese coefficient modified IDMS-MDRD Study equation (20), did not reveal any material differences in the respective influences of proteinuria and eGFR levels on cardiovascular disease mortality (Table 4).

**DISCUSSION**

On the basis of a pooled analysis of individual data from 39,405 Japanese participants, we confirmed a clear association of proteinuria or reduced eGFR with the risk of cardiovascular disease death. Additionally, we demonstrated that both proteinuria and reduced eGFR were associated significantly and independently with the risk of cardiovascular disease mortality. There was no evidence of any interaction between these risk factors, and those subjects with both proteinuria and reduced eGFR were at the highest risk of cardiovascular disease. Therefore, these findings highlight the potential clinical value of the measurement of both proteinuria and eGFR levels for cardiovascular risk assessment in the Japanese population.

The effects of the combined assessment of proteinuria and eGFR on cardiovascular risk have been addressed in several community-based cohort studies (24–26). Additionally, the...
Recent results support the view that assessment of both proteinuria and eGFR level is needed in order to independently associate with other potential cardiovascular risk factors (8). A meta-analysis of 7 Japanese cohort studies. These results demonstrated that an albumin/creatinine ratio of >1.1 mg/mmol and an eGFR of <60 mL/minute/1.73 m² were independently associated with cardiovascular disease mortality and traditional cardiovascular risk factors (8). Comparable findings were also observed in the meta-analysis of 10 high-risk population cohorts (27).

Chronic Kidney Disease Prognosis Consortium has presented results from a collaborative meta-analysis of 21 general population cohorts (8), which included more than 1.2 million participants from 14 countries in North America, Europe, Asia, and Oceania. The meta-analysis demonstrated that an albumin/creatinine ratio of >1.1 mg/mmol and an eGFR of <60 mL/minute/1.73 m² were independently associated with cardiovascular disease mortality and traditional cardiovascular risk factors (8). Comparable findings were also observed in the meta-analysis of 10 high-risk population cohorts (27).

In the present study, the absence of data on the albumin/creatinine ratio rendered it impossible to assess the influence of low albuminuria levels. However, on the basis of the most recent findings, the KDIKO Controversies Conference proposed a new chronic kidney disease stage classification, in which chronic kidney disease stages were divided by both eGFR levels, regardless of the albuminuria level. However, on the basis of the most recent findings, the KDIKO Controversies Conference proposed a new chronic kidney disease stage classification, in which chronic kidney disease stages were divided by both albuminuria and eGFR levels. Likewise, the present study clearly showed that proteinuria and reduced eGFR were associated with the risk of cardiovascular disease mortality in a manner independent of each other and were also independently associated with other potential cardiovascular risk factors in a meta-analysis of 7 Japanese cohort studies. These results support the view that assessment of both proteinuria (or albuminuria) and eGFR level is needed in order to improve the identification of individuals at high risk of cardiovascular complications and to establish appropriate preventative measures for the Japanese population.

The mechanism by which the relationship between proteinuria or glomerular filtration rate and cardiovascular and renal outcomes might be mediated is an area of great interest. In the present study, the effects of proteinuria and reduced eGFR on the risk of cardiovascular disease mortality were independent of each other. This suggests that proteinuria and reduced glomerular filtration rate are markers of different pathological processes. It has been acknowledged that proteinuria reflects systemic endothelial dysfunction (28, 29), whereas the reduced glomerular filtration rate is associated with the severity of systemic atherosclerosis (30, 31). The pathophysiology of influence of both risk factors requires further exploration.

The strengths of this study include the large sample size that allowed for precise estimations of the independent influences of proteinuria and the glomerular filtration rate level on the risk of cardiovascular disease mortality. The limitations of this study should also be noted. First, it has been recognized that the eGFR determined by using the modified CKD-EPI equation may not be sufficiently accurate (21) and might lead to some misclassifications. Such misclassifications would weaken the association found in this study, biasing the results toward the null hypothesis. Furthermore, the sensitivity analyses using other formulas of eGFR, namely, the JSN-CKDI equation (22) and the modified IDMS-MDRD Study equation (20), did not lead to any material differences in the findings. Second, measurements of serum creatinine and proteinuria were conducted locally rather than at a central laboratory and without calibration among laboratories, which may have produced substantial variability in the measured values, likely weakening the association found in the present study. Third, because the YKK workers cohort, one of our study cohorts, was a work site-based cohort, the estimates from this cohort might be biased by a healthy-worker effect to some extent. However, the findings did not change with exclusion of the YKK workers cohort. Fourth, we could not use finer categories of proteinuria (e.g., negative, trace, 1+, and ≥2+) and eGFR levels (e.g., ≥90, 60–89, 45–59, 30–44, and 15–29 mL/minute/1.73 m²) because the number of subjects with proteinuria of ≥2+ (273 subjects, 0.7%) and that with an eGFR of 15–29 mL/minute/1.73 m² (119 subjects, 0.3%) were too small to assess the findings reliably. Finally, in the present study, the absence of data on the albumin/creatinine ratio rendered it impossible to assess the influences of low levels of albuminuria.
of albuminuria on the risk of cardiovascular disease outcomes.

In conclusion, the present findings clarified that proteinuria and reduced eGFR were significantly and independently associated with cardiovascular disease outcomes. Measurement of both proteinuria and eGFR is likely to improve the protocol for cardiovascular risk assessment in the Japanese population.

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Conflict of interest: none declared.

REFERENCES


(Appendix follows)
### Appendix Table 1. Adjusted Mortality Rates and Hazard Ratios of Cardiovascular Disease According to Proteinuria Levels From EPOCH-JAPAN Participants Recruited Between 1980 and 1994 With an Average 10.1-Year Follow-up

<table>
<thead>
<tr>
<th>Proteinuria</th>
<th>No. of Participants</th>
<th>No. of Deaths</th>
<th>Person-Years</th>
<th>Mortality Rate/1,000 Person-Years(^a)</th>
<th>95% CI(^a)</th>
<th>Age and Sex Adjusted</th>
<th>Multivariate Adjusted (Model A)(^b)</th>
<th>Multivariate Adjusted (Model B)(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HR 95% CI</td>
<td>(P_{\text{trend}})</td>
<td>HR 95% CI</td>
</tr>
<tr>
<td>Cardiovascular Disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>36,692</td>
<td>1,670</td>
<td>387,918</td>
<td>4.4</td>
<td>4.1, 4.6</td>
<td>1 Referent</td>
<td>1</td>
<td>Referent</td>
</tr>
<tr>
<td>Trace</td>
<td>1,564</td>
<td>106</td>
<td>8,597</td>
<td>6.6***</td>
<td>5.1, 8.1</td>
<td>1.54*** 1.26, 1.89</td>
<td>&lt;0.001</td>
<td>1.44***  1.17, 1.77</td>
</tr>
<tr>
<td>(\geq 1+)</td>
<td>1,149</td>
<td>151</td>
<td>2,383</td>
<td>10.8***</td>
<td>8.7, 12.9</td>
<td>2.08*** 1.76, 2.47</td>
<td>1.80*** 1.48, 2.17</td>
<td>1.71***  1.41, 2.08</td>
</tr>
<tr>
<td>Coronary Heart Disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>36,692</td>
<td>340</td>
<td>387,918</td>
<td>0.9</td>
<td>0.8, 1.1</td>
<td>1 Referent</td>
<td>1</td>
<td>Referent</td>
</tr>
<tr>
<td>Trace</td>
<td>1,564</td>
<td>19</td>
<td>8,597</td>
<td>1.2</td>
<td>0.6, 1.9</td>
<td>1.34 0.83, 2.16</td>
<td>&lt;0.001</td>
<td>1.19  0.73, 1.94</td>
</tr>
<tr>
<td>(\geq 1+)</td>
<td>1,149</td>
<td>38</td>
<td>2,383</td>
<td>2.7***</td>
<td>1.7, 3.7</td>
<td>2.56*** 1.82, 3.61</td>
<td>1.91** 1.30, 2.82</td>
<td>1.85**  1.25, 2.73</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>36,692</td>
<td>744</td>
<td>387,918</td>
<td>1.9</td>
<td>1.7, 2.1</td>
<td>1 Referent</td>
<td>1</td>
<td>Referent</td>
</tr>
<tr>
<td>Trace</td>
<td>1,564</td>
<td>48</td>
<td>8,597</td>
<td>2.9**</td>
<td>1.9, 3.9</td>
<td>1.55** 1.14, 2.09</td>
<td>&lt;0.001</td>
<td>1.45*  1.09, 2.01</td>
</tr>
<tr>
<td>(\geq 1+)</td>
<td>1,149</td>
<td>54</td>
<td>2,383</td>
<td>4.2***</td>
<td>2.9, 5.5</td>
<td>1.64*** 1.24, 2.18</td>
<td>1.55** 1.14, 2.11</td>
<td>1.49*  1.09, 2.03</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; EPOCH-JAPAN, Evidence for Cardiovascular Prevention from Observational Cohorts in Japan; HR, hazard ratio.

\(^a\) Mortality rates and their 95% confidence intervals were adjusted for age and sex by using the direct standardized method.

\(^b\) Model A was adjusted for age, sex, systolic blood pressure, diabetes, total cholesterol, body mass index, history of cardiovascular disease, current smoking, and current drinking.

\(^c\) Model B was adjusted for the potential confounding factors included in model A and estimated glomerular filtration rate levels.
## Appendix Table 2. The Combined Influence of Proteinuria and Reduced eGFR Levels on the Risk of Cardiovascular Disease Mortality From EPOCH-JAPAN Participants Recruited Between 1980 and 1994 With an Average 10.1-Year Follow-up

<table>
<thead>
<tr>
<th>Proteinuria</th>
<th>eGFR, mL/minute/1.73 m²</th>
<th>HR*</th>
<th>95% CI</th>
<th>HR*</th>
<th>95% CI</th>
<th>HR*</th>
<th>95% CI</th>
<th>HR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥90</td>
<td></td>
<td></td>
<td>60–89</td>
<td></td>
<td>45–59</td>
<td></td>
<td>&lt;45</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>1</td>
<td>Referent</td>
<td>1.22</td>
<td>0.98, 1.53</td>
<td>1.59**</td>
<td>1.20, 2.09</td>
<td>1.83***</td>
<td>1.25, 2.68</td>
<td></td>
</tr>
<tr>
<td>Trace</td>
<td>1.63</td>
<td>0.72, 3.71</td>
<td>1.58**</td>
<td>1.13, 2.21</td>
<td>2.46***</td>
<td>1.53, 3.95</td>
<td>3.66***</td>
<td>1.87, 7.16</td>
<td></td>
</tr>
<tr>
<td>≥1+</td>
<td>2.37*</td>
<td>1.04, 5.41</td>
<td>2.02***</td>
<td>1.45, 2.81</td>
<td>2.31***</td>
<td>1.45, 3.69</td>
<td>4.18***</td>
<td>2.62, 6.65</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; EPOCH-JAPAN, Evidence for Cardiovascular Prevention from Observational Cohorts in Japan; HR, hazard ratio.

* P < 0.05; ** P < 0.01; *** P < 0.001.

a Adjusted for age, sex, systolic blood pressure, diabetes, total cholesterol, body mass index, history of cardiovascular disease, current smoking status, and current drinking status.