Elevated Levels of hs-CRP Are Associated With High Prevalence of Depression in Japanese Patients With Type 2 Diabetes: The Diabetes Distress and Care Registry at Tenri (DDCRT 6)

OBJECTIVE
Because of the absence of data on the direct association between inflammation and depression in patients with diabetes, we examined the association between hs-CRP levels and the high prevalence of depression in adult patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS
Cross-sectional data were obtained from 3,573 patients with type 2 diabetes recruited from a Japanese diabetes registry. A multiple logistic regression analysis adjusted for potential confounders was used to assess independent associations between hs-CRP levels and major depression, as defined by the Patient Health Questionnaire-9.

RESULTS
Mean age, BMI, and HbA1c levels were 66.0 years, 24.6 kg/m², and 7.4% (57.8 mmol/mol), respectively, and 122 patients (3.4%) suffered from major depression. In the age- and sex-adjusted model, the odds ratio (OR) for major depression was 1.86 (95% CI 1.01–3.42; P = 0.045) in the highest CRP quintile compared with that in the 3rd CRP quintile; however, this association disappeared after adjustment for other possible confounders (OR 1.58 [95% CI 0.85–2.94]; P = 0.148). Among patients with a BMI of ≥25 kg/m², a significant association was observed between the highest hs-CRP quintile and major depression (multivariable-adjusted OR 2.69 [95% CI 1.09–7.08]; P = 0.032).

CONCLUSIONS
We observed a significant positive association between high hs-CRP levels and depression in patients with diabetes who had a high BMI.

In the last decade, several studies have been published that suggest a close association between diabetes and depression. Patients with diabetes have a high prevalence of depression (1), particularly that associated with poor treatment adherence and glycemic control (1,2), and a high prevalence of complications (3). In addition, depression is associated with mortality in these patients (4).
Because of this strong association, several recent studies have suggested the possibility of a common biological pathway such as inflammation as an underlying mechanism of the association between depression and diabetes (5). However, few studies have examined the clinical role of inflammation and depression as biological correlates in patients with diabetes. Moreover, some studies have failed to determine the association of depression with diabetes in very young patients (6). Many studies have suggested the role of increased immune system activity and inflammation in both diabetes and depression (7–9). Multiple mechanisms are involved in the association between diabetes and inflammation, including modulation of lipolysis, alteration of glucose uptake by adipose tissue, and an indirect mechanism involving an increase in free fatty acid levels blocking the insulin signaling pathway (10). Psychological stress can also cause inflammation via innervation of cytokine-producing cells and activation of the sympathetic nervous systems and adrenergic receptors on macrophages (11). Depression enhances the production of inflammatory cytokines (12–14). Overproduction of inflammatory cytokines may stimulate corticotropin-releasing hormone production, a mechanism that leads to hypothalamic-pituitary axis activity. Conversely, cytokines induce depressive-like behaviors; in studies where healthy participants were given endotoxin infusions to trigger cytokine release, the participants developed classical depressive symptoms (15). Based on this evidence, it could be hypothesized that inflammation is the common biological pathway underlying the association between diabetes and depression. Recently, Doyle et al. (16) examined the association between inflammation and elevated depressive symptoms, and they found that higher C-reactive protein (CRP) levels were observed in patients with diabetes with depression than in those without. However, in this study, the subjects are relatively obese, and thus this study did not answer the question of whether the association between CRP levels and depression in patients with diabetes could be applicable to the relatively lean population. In addition, the study included a small sample of patients with diabetes and depression (n = 14 for CRP analysis), so the robustness of the results needs to be tested in a larger study population.

In this study, we hypothesized that high CRP levels were associated with the high prevalence of depression in patients with diabetes and that this association may be modified by obesity or glycemic control. The large sample size of our study enabled us to examine the association between hs-CRP levels and the prevalence of depression in adult patients with type 2 diabetes stratified by obesity or glycemic control.

RESEARCH DESIGN AND METHODS

Assay of hs-CRP Levels

Technicians blinded to the patients’ clinical data collected random blood samples on the same day as registration before patients answered the self-administered survey using the Patient Health Questionnaire-9 (PHQ-9). Shortly thereafter, technicians performed measurement of hs-CRP levels with separated serum samples using a latex immunassay method with the commercial kits LT CRP-HS II (Wako Pure Chemical Industries, Ltd., Osaka, Japan; for sensitivity, when saline is used, the absorbance change should not be more than 0.01 [ΔE/min]) and Hitachi LABOSPECT 008 automatic analyzer (Hitachi Products, Hitachi City, Japan).

Depression

The ethics committee of Tenri Hospital approved this study. In 2011, of all 4,332 eligible patients with diabetes (40.5% female patients with type 1 [4.6%] and type 2 [92.3%] diabetes with mean [SD] age 65.6 [12.1] years), 4,197 provided consent to participate in the study; 3,671 were confirmed to have type 2 diabetes. We excluded 30 patients with missing data of hs-CRP levels and 67 patients who did not complete the PHQ-9. The remaining 3,573 patients who met the inclusion criteria were included in the study.

Data Collection

On the survey date, patients underwent routine medical history inquiry, physical examinations, and laboratory tests. Clinical research coordinators used patient medical charts to collect information on demographics such as age, sex, body weight, duration of diabetes, medical history including micro- and macrovascular complications, and treatment modalities. Laboratory tests included the evaluation of HbA1c and hs-CRP levels. HbA1c levels were expressed in accordance with the National Glycohemoglobin Standardization Program as recommended by the Japanese Diabetes Society (20).

Physical exercise was measured using the short version of the International Physical Activity Questionnaire (IPAQ), a self-reporting instrument that asks for an estimate of total weekly physical activity (walking/vigorous and moderate-intensity activity) during the previous week. Physical activity levels were categorized into three (low, moderate, and high) categories following the scoring rule of IPAQ (21).
times more likely to be diagnosed with depression by the mental health professional. On the other hand, individuals scoring low (≤4) on the PHQ-9 had a less than a 1 in 25 chance of having depression. We used the below criteria to define major depression according to the DSM-IV classification. Major depression was diagnosed if five or more of the nine depressive symptom criteria were present for at least “more than half the days” in the past 2 weeks and one of the symptoms was depressed mood or anhedonia (22,23).

**Statistical Analysis**
Continuous variables were expressed as mean (SD). Intergroup differences were evaluated using the unpaired Student t test for normally distributed variables, the Mann-Whitney U test for variables with skewed distribution, and χ² analysis for categorical variables. Because the distribution of CRP levels was right skewed, CRP levels were categorized into quintiles. A logistic regression analysis was used to estimate the odds ratio (OR) (95% CI) for major depression with a presence of CRP levels of the third quintile. The two following statistical models were used: model 1 was an age- and sex-adjusted model; model 2 was adjusted for age, sex, and exercise (low, moderate, and high); variables in model 3, selected using backward stepwise selection, was used with an entry and removal probability of 0.05 and removal probabilities of 0.2. The initial model for backward stepwise selection was comprised of age; sex; duration of diabetes; type of diabetes therapy; smoking; BMI, HbA1c levels; history of cardiovascular disease, cancer, and arthritis (osteoarthritis or collagen vascular disease including rheumatoid arthritis); nonsteroidal anti-inflammatory drug use, diabetic retinopathy; and diabetic nephropathy.

Subsequently, we examined the stratified analysis by BMI or glycemic control. In the stratified analysis by BMI, we divided patients based on BMI into two categories (BMI of <25 or ≥25 kg/m²), and the logistic regression model used was model 3 (described above). We selected the cutoff point of BMI as 25 kg/m² because the Japan Society for the Study of Obesity defines obesity in this manner. In the stratified analysis by glycemic control, we divided patients based on HbA1c levels into the two following categories: those with HbA1c levels of <7.5 or ≥7.5% (<58 or ≥58 mmol/mol), and the logistic regression model used was model 2. The cutoff point of HbA1c levels was determined based on the Japan Diabetes Association recommendation and the National Institute for Clinical Excellence criteria for excellent glycemic control (27). We tested for statistical interaction by adding interaction terms between CRP category and BMI or HbA1c category to a multivariable-adjusted logistic regression model. All P values were two sided; P values of <0.05 were considered statistically significant, except those for interaction analyses where we used P < 0.10. All analyses were performed using Stata/SE, version 12.1 (Stata Corporation, College Station, TX).

**RESULTS**

**Patient Characteristics**
Table 1 shows the demographic characteristics and laboratory data of patients according to the presence or absence of major depression. Overall, mean age, HbA1c level, and BMI were 66.0 years, 7.4% (57.8 mmol/mol), and 24.6 kg/m², respectively. Patients with major depression tended to be relatively young (P < 0.001) and female (P < 0.001) with a high BMI (P < 0.001), high HbA1c levels (P < 0.001), and high hs-CRP levels (P = 0.0098); had more diabetic nephropathy (P = 0.043), required more insulin therapy (P = 0.001), and exercised less (P < 0.001); and the distribution of smoking category was statistically different between two groups (P < 0.001).

The ORs for the association between CRP quintile and major depression are shown in Table 2. In the age- and sex-adjusted model (model 1), the OR for major depression was 1.86 (95% CI 1.01–3.42; P = 0.045) in the highest CRP quintile compared with that in the reference category of CRP levels (third quintile). However, this association diminished after adding exercise to the model (OR 1.70 [95% CI 0.92–3.13]; P = 0.089). Further adjustment (model 3) disappeared this association (OR 1.58 [95% CI 0.85–2.94]; P = 0.148) in the highest CRP quintile.

Subsequently, we proceeded to examine the stratified analysis by BMI or glycemic control (Table 3). In patients with a BMI of <25 kg/m², no significant association was found between hs-CRP quintiles and major depression; however, among patients with a BMI of ≥25 kg/m², a significant association was observed between the highest hs-CRP quintile and major depression (OR 2.69 [95% CI 1.09–7.08]; P = 0.032) in comparison with the reference category of CRP (third quintile). We did not observe a significant association between hs-CRP and major depression in either of HbA1c subgroups.

**CONCLUSIONS**

In the nonstratified analysis, the hs-CRP level was associated with a high prevalence of major depression in the age- and sex-adjusted model; however, multivariable adjustment diminished this association. This finding is consistent with that of a previous study in which a crude association between inflammatory markers, including CRP, diminished after adjustment for clinical and demographic covariates in patients with type 1 diabetes (6). In our study, high hs-CRP levels were associated with a high prevalence of major depression in patients with type 2 diabetes if BMI was ≥25 kg/m². Recently, Doyle et al. (16) examined the association between inflammation and elevated depressive symptoms, and they found that higher CRP levels were observed in patients with diabetes with depression than in those without. Because subjects in this study were an obese population, our results also seem to be consistent with this study. Our results show that the association between hs-CRP and diabetes is valid even in an Asian population, but it might not be extended to nonobese subjects. We did not observe a significant association between hs-CRP and major depression even after stratifying glycemic control levels.

Recent evidence has suggested that depression is a risk factor for developing type 2 diabetes and vice versa (5), and it was speculated that common biological pathways may underlie the association between depression and diabetes (28), one of which is inflammation. A number of prospective studies have suggested that high levels of inflammatory markers predict the incidence of type 2 diabetes (29–31). Several studies have suggested a cross-sectional association between depression and inflammation. Depression has been associated with higher levels of
Inflammatory markers (white blood cells, CRP, and interleukin [IL]-6) (32,33), and higher depression screen scores were significantly associated with higher CRP levels (34). In addition, the association between depression and inflammation has been shown to be bidirectional. In a cohort of 263 participants, the baseline depression screen score was positively associated with a subsequent increase in IL-6 levels (35).

Conversely, in a cohort of >3,339 participants with >12 years of follow-up, baseline inflammatory marker levels (CRP and IL-6) were associated with a subsequent risk of depression at follow-up (36). However, this association was not observed in patients with type 2 diabetes. A recently conducted meta-analysis revealed that the relative risk of type 2 diabetes was 1.26 (95% CI 1.16–1.37) per 1 log mg/L increment in CRP levels (37). Hood et al. (6) evaluated the association between numerous inflammatory markers and depression in young patients (mean age 15.2 years) with type 2 diabetes using Center for Epidemiologic Studies Depression Scale. Even in a crude analysis, they did not identify a significant association between depression and inflammation in patients with diabetes. Although our study was conducted on a different age-group, our

Table 1—Baseline characteristics according to depressive status

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Nondepressed</th>
<th>Major depression</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>3,573</td>
<td>3,451</td>
<td>122</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>66.0 (11.4)</td>
<td>66.1 (11.2)</td>
<td>62.4 (14.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female, %</td>
<td>38.9</td>
<td>38.3</td>
<td>55.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.6 (4.2)</td>
<td>24.5 (4.2)</td>
<td>26.0 (5.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of diabetes, years</td>
<td>14.6 (10.1)</td>
<td>14.6 (10.1)</td>
<td>15.2 (9.5)</td>
<td>0.461</td>
</tr>
<tr>
<td>HbA₁c</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSGSP, %</td>
<td>7.4 (1.2)</td>
<td>7.4 (1.2)</td>
<td>8.0 (1.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IFCC mmol/mol</td>
<td>57.8 (13.1)</td>
<td>57.6 (12.8)</td>
<td>63.5 (18.6)</td>
<td></td>
</tr>
<tr>
<td>hs-CRP, mg/dL †</td>
<td>0.08 (0.01–0.17)</td>
<td>0.07 (0.01–0.16)</td>
<td>0.1 (0.01–0.29)</td>
<td>0.0098</td>
</tr>
<tr>
<td>Diabetic retinopathy, %</td>
<td>41.9</td>
<td>41.6</td>
<td>49.5</td>
<td>0.128</td>
</tr>
<tr>
<td>Diabetic nephropathy, %</td>
<td>54.4</td>
<td>54.1</td>
<td>63.6</td>
<td>0.043</td>
</tr>
<tr>
<td>Diabetes therapy, %</td>
<td></td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Diet only</td>
<td>14.6</td>
<td>14.9</td>
<td>5.7</td>
<td></td>
</tr>
<tr>
<td>Oral medication only</td>
<td>45.5</td>
<td>45.7</td>
<td>40.2</td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>39.9</td>
<td>39.4</td>
<td>54.1</td>
<td></td>
</tr>
<tr>
<td>Physical activity, %‡</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low</td>
<td>39.5</td>
<td>38.7</td>
<td>60.7</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>29.0</td>
<td>29.2</td>
<td>24.6</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>31.5</td>
<td>32.1</td>
<td>14.7</td>
<td></td>
</tr>
<tr>
<td>Smoking, %</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Never</td>
<td>43.3</td>
<td>42.9</td>
<td>54.6</td>
<td></td>
</tr>
<tr>
<td>Past</td>
<td>40.5</td>
<td>41.1</td>
<td>23.1</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>16.3</td>
<td>16.2</td>
<td>19.7</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease, %</td>
<td>16.5</td>
<td>16.4</td>
<td>20.3</td>
<td>0.313</td>
</tr>
<tr>
<td>Cancer, %</td>
<td>9.8</td>
<td>9.9</td>
<td>8.2</td>
<td>0.545</td>
</tr>
<tr>
<td>Arthritis, %§</td>
<td>0.22</td>
<td>0.20</td>
<td>0.82</td>
<td>0.157</td>
</tr>
<tr>
<td>NSAID use, %</td>
<td>24.1</td>
<td>23.9</td>
<td>39.5</td>
<td>0.155</td>
</tr>
</tbody>
</table>

Data are means (SD) unless otherwise indicated. IFCC, International Federation of Clinical Chemistry; NGSP, National Glycohemoglobin Standardization Program; NSAIDs, nonsteroidal anti-inflammatory drugs. †Median (interquartile range) is reported. ‡Physical activity levels were categorized into three (low, moderate, high) categories following the scoring rule of the IPAQ (21). §Osteoarthritis or collagen vascular disease including rheumatoid arthritis.

Table 2—Association between hs-CRP and major depression

<table>
<thead>
<tr>
<th>hs-CRP quintiles (interquartile range), mg/dL</th>
<th>1 (0.01–0.01)</th>
<th>2 (0.05–0.06)</th>
<th>3 (0.07–0.09)</th>
<th>4 (0.12–0.18)</th>
<th>5 (0.31–0.80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>1,153</td>
<td>443</td>
<td>584</td>
<td>719</td>
<td>674</td>
</tr>
<tr>
<td>Number with major depression</td>
<td>33</td>
<td>13</td>
<td>16</td>
<td>26</td>
<td>34</td>
</tr>
<tr>
<td>OR (95% CI) for major depression</td>
<td>1.09 (0.59–2.00)</td>
<td>1.14 (0.54–2.40)</td>
<td>1.00 (Ref.)</td>
<td>1.33 (0.70–2.50)</td>
<td>1.86 (1.01–3.42)</td>
</tr>
<tr>
<td>Age- and sex-adjusted model (model 1)</td>
<td>1.16 (0.63–2.13)</td>
<td>1.14 (0.54–2.40)</td>
<td>1.00 (Ref.)</td>
<td>1.26 (0.67–2.39)</td>
<td>1.70 (0.92–3.13)</td>
</tr>
<tr>
<td>Multivariable-adjusted model (model 2)†</td>
<td>1.21 (0.66–2.24)</td>
<td>1.14 (0.54–2.43)</td>
<td>1.00 (Ref.)</td>
<td>1.19 (0.63–2.25)</td>
<td>1.58 (0.85–2.94)</td>
</tr>
</tbody>
</table>

*Model 2 adjusted for age, sex, and exercise. †Model 3 adjusted for age, sex, smoking, type of diabetes therapy, diabetic nephropathy, arthritis, nonsteroidal anti-inflammatory drug use, and exercise (low, middle, and high intensity) (21).
result is consistent with their result with respect to the fact that we did not find a significant association in the nonstrati-
fied analysis. Our study determined that several factors such as obesity and
glycemic control may modify the associ-
ation between inflammation and de-
pression. However, it is unclear whether these factors or other unevaluated
factors such as insulin insensitivity
are the real effect modifiers; thus, fur-
ther studies are required.

The association between high hs-CRP
levels and major depression was attenu-
ated after adjustment for exercise, and the
significant association was observed in
the high-BMI group, which is an inter-
esting finding. Obesity is strongly asso-
ciated with chronic inflammation. The
association between obesity and inflam-
mation was first reported by Hotamisili-
gil, Sharigill, and Spiegelman (38), and
since then, adipose tissue has been rec-
nized as an important source of a
number of cytokines. It is well-known
that exercise reduces the risk of develop-
ing type 2 diabetes, improves glycemic
control in patients with diabetes
(39–41), and improves the symptoms of
depression (42). Recently, our meta-
analysis revealed that long-term exer-
cise reduced CRP levels in patients with
diabetes (43). Based on these previ-
ous reports, our results suggest that
inflammatory cytokines specifically
from adipose tissue may play an impor-
tant role in the association between
type 2 diabetes and major depression, and
exercise seems to be a strong con-
founder in this association between in-
flammation and depression in these
patients.

Some limitations were observed in
the current study. The first, most
obvious, limitation of the study was its
cross-sectional design. Therefore, firm
conclusions regarding the directions of
the causality of the association between
hs-CRP levels and depression in the cur-
rent analysis cannot be drawn; however,
based on biological evidences, we
hypothesize a bidirectional association.
Second, we used self-reported mea-
sures to define major depression, which
may have resulted in misclassification.
However, this misclassification most
likely occurred evenly across hs-CRP cat-
egories and resulted in nondifferential
misclassification. Nondifferential mis-
classification inevitably leads to a
reduced strength of estimated expo-
sure-disease associations (44). Thus,
we may have ultimately underestimated
the association between hs-CRP levels
and major depression. Third, residual
confounders may exist in the associa-
tion with depression, such as socioeco-
nomic status or marital status; however,
we did not have sufficient data on these
variables. Forth, we did not have en-
ough data on whether patients suf-
fered from acute infections, so we could
not adjust for that. Despite this, we did
not ask patients to participate in the
survey if patients had a febrile condition
that day because patients have to be in
a good enough condition to answer the
self-administered questionnaire; thus,
not adjusting for febrile condition might
not influence our results so much. Fi-
nally, data were derived from the regis-
try of a single diabetes center, thereby
raising concerns regarding generaliza-
tions derived from the results, particu-
larly for the multiethnic North American
and European populations.

In conclusion, we observed that hs-
CRP levels were associated with a high
prevalence of major depression in pa-
ients with type 2 diabetes with a BMI
of ≥25 kg/m². This association was sig-
nificant after adjustment for possible
confounders. The causality of this asso-
ciation remains unclear and requires
evaluation in a future prospective study.

Appendix
Members of the Diabetes Distress and
Care Registry at Tenri Study Group are
Hitoshi Ishii, Shintaro Okamura,
Tsuysoshi Mashtiani, Miyuki Furuya,
Masako Kitatani, Satoshi Matsunaga,
Hirohito Kuwata (Department of Endo-
crinology, Tenri Hospital); Satoru Tsujii
(Diabetes Center, Tenri Hospital);
Yasuaki Hayashino (Department of En-
docrinology, Tenri Hospital, Department
of Epidemiology and Healthcare Re-
search, Kyoto University Graduate
School of Medicine); Yaeko Kondo (De-
partment of Diabetes and Clinical

Table 3—Association Between hs-CRP and major depression stratified by BMI or HbA1c level*

<table>
<thead>
<tr>
<th></th>
<th>h-CRP quintiles (interquartile range), mg/dL</th>
<th>P for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1Q (0.01–0.01)</td>
<td>2Q (0.05–0.06)</td>
</tr>
<tr>
<td>BMI &lt; 25 kg/m²*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of subjects</td>
<td>862</td>
<td>263</td>
</tr>
<tr>
<td>Number with major depression</td>
<td>23</td>
<td>7</td>
</tr>
<tr>
<td>OR for depression (model 3)</td>
<td>0.96 (0.45–2.07)</td>
<td>0.78 (0.28–2.21)</td>
</tr>
<tr>
<td>BMI ≥ 25 kg/m²*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of subjects</td>
<td>291</td>
<td>180</td>
</tr>
<tr>
<td>Number with major depression</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>OR for depression (model 3)</td>
<td>1.67 (0.59–4.69)</td>
<td>1.95 (0.63–5.98)</td>
</tr>
<tr>
<td>HbA1c &lt; 7.5% (58 mmol/mol)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of subjects</td>
<td>829</td>
<td>261</td>
</tr>
<tr>
<td>Number with major depression</td>
<td>20</td>
<td>7</td>
</tr>
<tr>
<td>OR for depression (model 3)</td>
<td>0.83 (0.39–1.77)</td>
<td>0.90 (0.34–2.40)</td>
</tr>
<tr>
<td>HbA1c ≥7.5% (58 mmol/mol)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of subjects</td>
<td>324</td>
<td>182</td>
</tr>
<tr>
<td>Number with major depression</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>OR for depression (model 3)</td>
<td>1.94 (0.67–5.61)</td>
<td>1.58 (0.47–5.39)</td>
</tr>
</tbody>
</table>

Model 3 adjusted for age, sex, smoking, type of diabetes therapy, diabetic nephropathy, arthritis, nonsteroidal anti-inflammatory drug use, and exercise (low, middle, and high) (21).
Nutrition, Kyoto University); Rei Ueda (Second Department of Internal Medicine, Faculty of Medicine, University of the Ryukyus); Naotaka Fujita (Department of Epidemiology and Healthcare Research, Kyoto University Graduate School of Medicine). Rie Kurokawa (Osaka Medical Center and Research Institute for Maternal and Child Health). Masami Tanaka (Division of Endocrinology, Metabolism and Nephrology, Department of Internal Medicine, Keio University School of Medicine).

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