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)

*Yasuaki Hayashino, Tsuyoshi Mashitani, Satoru Tsujii, and Hitoshi Ishii, for the Diabetes Distress and Care Registry at Tenri Study Group**

Diabetes Care 2014;37:2459–2465 | DOI: 10.2337/dc13-2312

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 HbA_{1c} levels were 66.0 years, 24.6 kg/m^2, 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/m^2, 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).

Department of Endocrinology, Tenri Hospital, Tenri, Japan

Corresponding author: Yasuaki Hayashino, hayasino-y@umin.net.

Received 3 October 2013 and accepted 26 May 2014.

**Members of the Diabetes Distress and Care Registry at Tenri Study Group are listed in* APPENDIX.

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 classic 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

Patients

Patient data were derived from the second-year survey of a diabetes registry at Tenri Hospital, a regional tertiary care teaching hospital in Japan. The details of this registry have previously been described (17–19). In brief, this study is a cohort study aiming at evaluating the cross-sectional and prospective association between psychosocioeconomic factors, biomarkers, and the incidence of micro- and macrovascular complications in patients with diabetes. The registry recruited patients diagnosed with diabetes who had visited the outpatient clinic of our hospital between October 2009 and December 2011. The second-year survey was performed from January to December 2011. We excluded patients with prediabetes diagnosed by an oral glucose tolerance test, gestational diabetes mellitus, type 1 diabetes, or diabetes induced by steroid use or other endocrinological diseases, and we finally used data of patients diagnosed with type 2 diabetes. At registration, the attending physician confirmed the diagnosis according to the Classification and Diagnostic Criteria of Diabetes Mellitus by the Japan Diabetes Society. 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 Patient Health Questionnaire-9 (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 HbA_{1c} and hs-CRP levels. HbA_{1c} 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).

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 PHQ-9. Shortly thereafter, technicians performed measurement of hs-CRP levels with separated serum samples using a latex immunoassay 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 be not more than 0.01 [ΔE/min]) and Hitachi LABOSPECT 008 automatic analyzer (Hitachi Products, Hitachi City, Japan).

Depression

The diagnosis of depression at the time of participation in this study was made using the PHQ-9 as a screening tool (22,23). The PHQ-9 has been validated as being appropriate for screening for depression in patients with diabetes (24) and includes nine items assessing nine symptoms of depression as defined by the DSM-IV (25,26). Internal consistency of the PHQ-9 has been shown to be high (Cronbach α of 0.89) (26). Results from interviews showed that individuals who scored high ($\geq$10) on the PHQ-9 were between 7 and 13.6

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 χ^2 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 reference category 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, were used with an entry 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; HbA_{1c} 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/m^2), and the logistic regression model used was model 3 (described above). We selected the cutoff point of BMI as 25 kg/m^2 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 HbA_{1c} levels into the two following categories: those with HbA_{1c} 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 HbA_{1c} levels was determined based on the Japan Diabetes Association recommendation and the National Institute for Health and Clinical Excellence criteria for excellent glycemic control (27). We tested for statistical interaction by adding interaction terms between CRP category and BMI or HbA_{1c} 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, HbA_{1c} level, and BMI were 66.0 years, 7.4% (57.8 mmol/mol), and 24.6 kg/m^2, 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 HbA_{1c} 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/m^2, no significant association was found between hs-CRP quintiles and major depression; however, among patients with a BMI of ≥25 kg/m^2, 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 HbA_{1c} 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/m^2. 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

Table 1—Baseline characteristics according to depressive status

	All	Nondepressed	Major depression	*P*
N	3,573	3,451	122	
Age, years	66.0 (11.4)	66.1 (11.2)	62.4 (14.5)	<0.001
Female, %	38.9	38.3	55.7	<0.001
BMI, kg/m^2	24.6 (4.2)	24.5 (4.2)	26.0 (5.5)	<0.001
Duration of diabetes, years	14.6 (10.1)	14.6 (10.1)	15.2 (9.5)	0.461
HbA_{1c}				<0.001
NSGP, %	7.4 (1.2)	7.4 (1.2)	8.0 (1.7)	
IFCC, mmol/mol	57.8 (13.1)	57.6 (12.8)	63.5 (18.6)	
hs-CRP, mg/dL†	0.08 (0.01–0.17)	0.07 (0.01–0.16)	0.1 (0.01–0.29)	0.0098
Diabetic retinopathy, %	41.9	41.6	49.5	0.128
Diabetic nephropathy, %	54.4	54.1	63.6	0.043
Diabetes therapy, %				0.001
Diet only	14.6	14.9	5.7	
Oral medication only	45.5	45.7	40.2	
Insulin	39.9	39.4	54.1	
Physical activity, %‡				<0.001
Low	39.5	38.7	60.7	
Moderate	29.0	29.2	24.6	
High	31.5	32.1	14.7	
Smoking, %				<0.001
Never	43.3	42.9	54.6	
Past	40.5	41.1	23.1	
Current	16.3	16.2	19.7	
Cardiovascular disease, %	16.5	16.4	20.3	0.313
Cancer, %	9.8	9.9	8.2	0.545
Arthritis, %§	0.22	0.20	0.82	0.157
NSAID use, %	24.1	23.9	39.5	0.155

Data are means (SD) unless otherwise indicated. IFCC, International Federation of Clinical Chemistry and Laboratory Medicine; 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.

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 the 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

Table 2—Association between hs-CRP and major depression

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

*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).

Table 3—Association between hs-CRP and major depression stratified by BMI or HbA_{1c} level*

	hs-CRP quintiles (interquartile range), mg/dL					*P* for interaction
	1 (0.01–0.01)	2 (0.05–0.06)	3 (0.07–0.09)	4 (0.12–0.18)	5 (0.31–0.80)	
BMI <25 kg/m^2						0.148
Number of subjects	862	263	324	362	352	
Number with major depression	23	7	10	8	12	
OR (95% CI) for depression (model 3)	0.96 (0.45–2.07)	0.78 (0.28–2.21)	1.00 (Ref.)	0.63 (0.24–1.64)	0.81 (0.32–2.01)	
BMI ≥25 kg/m^2						
Number of subjects	291	180	260	357	322	
Number with major depression	10	7	6	18	24	
OR (95% CI) for depression (model 3)	1.67 (0.59–4.69)	1.95 (0.63–5.98)	1.00 (Ref.)	2.09 (0.81–5.39)	2.69 (1.09–7.08)	
HbA_{1c} $<7.5\%$ (58 mmol/mol)						
Number of subjects	829	261	347	406	381	0.309
Number with major depression	20	7	11	10	14	
OR (95% CI) for depression (model 3)	0.83 (0.39–1.77)	0.90 (0.34–2.40)	1.00 (Ref.)	0.70 (0.29–1.69)	1.10 (0.49–2.51)	
HbA_{1c} $\geq7.5\%$ (58 mmol/mol)						
Number of subjects	324	182	237	313	293	
Number with major depression	13	6	5	16	20	
OR (95% CI) for depression (model 3)	1.94 (0.67–5.61)	1.58 (0.47–5.39)	1.00 (Ref.)	2.01 (0.71–5.69)	2.27 (0.81–6.36)	

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).

age-group, our result is consistent with their result with respect to the fact that we did not find a significant association in the nonstratified analysis. Our study determined that several factors such as obesity and glycemic control may modify the association between inflammation and depression. However, it is unclear whether these factors or other unevaluated factors such as insulin insensitivity are the real effect modifiers; thus, further studies are required.

The association between high hs-CRP levels and major depression was attenuated after adjustment for exercise, and the significant association was observed in the high-BMI group, which is an interesting finding. Obesity is strongly associated with chronic inflammation. The association between obesity and inflammation was first reported by Hotamisligil et al. (38), and since then, adipose tissue has been recognized as an important source of a number of cytokines. It is well-known that exercise reduces the risk of developing 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 exercise reduced CRP levels in patients with diabetes (43). Based on these previous reports, our results suggest that inflammatory cytokines specifically from adipose tissue may play an important role in the association between type 2 diabetes and major depression, and exercise seems to be a strong confounder in this association between inflammation 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 current analysis cannot be drawn; however, based on biological evidences, we hypothesize a bidirectional association. Second, we used self-reported measures to define major depression, which may have resulted in misclassification. However, this misclassification most likely occurred evenly across hs-CRP categories and resulted in nondifferential misclassification. Nondifferential misclassification inevitably leads to a reduced strength of estimated exposure-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 association with depression, such as socioeconomic status or marital status; however, we did not have sufficient data on these variables. Fourth, we did not have enough data on whether patients suffered 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. Finally, data were derived from the registry of a single diabetes center, thereby raising concerns regarding generalizations derived from the results, particularly for the multi-ethnic North American and European populations.

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

Acknowledgments. The authors especially thank Yukari Moritsuji, Yuki Fujita, Noriko Nakamura, and Yoko Sakamoto (Department of Endocrinology, Tenri Hospital) for their clerical support. The authors thank Dr. Fumihiko Nakamura and Noriko Hatanaka (Department of Clinical Pathology, Tenri Hospital) for their support in describing the CRP measurement method. The authors thank Enago (www.enago.jp) for English language review.

Funding. This study was partially supported by the Manpei Suzuki Diabetes Foundation and JSPS KAKENHI (grant 25460641).

The funders played no role in the study design or conduct; data collection, analysis, or interpretation; or the preparation, review, or approval of the manuscript.

Author Contributions. Y.H. searched the literature, conceived the study, analyzed the data, interpreted the results, wrote the first draft of most sections of the report, obtained funding, collected the data, revised the report, and participated in writing of the report. Y.H. was project coordinator. T.M., S.T., and H.I. organized and supervised the study, interpreted the results, and revised the report. Y.H. and T.M. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Appendix

Members of the Diabetes Distress and Care Registry at Tenri Study Group are Hitoshi Ishii, Shintaro Okamura, Tsuyoshi Mashitani, Miyuki Furuya, Masako Kitatani, Satoshi Matsunaga, Hirohito Kuwata (Department of Endocrinology, Tenri Hospital); Satoru Tsujii (Diabetes Center, Tenri Hospital); Yasuaki Hayashino (Department of Endocrinology, Tenri Hospital, Department of Epidemiology and Healthcare Research, Kyoto University Graduate School of Medicine); Yaeko Kondo (Department of Diabetes and Clinical 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); and Masami Tanaka (Division of Endocrinology, Metabolism and Nephrology, Department of Internal Medicine, Keio University School of Medicine).

References

1. Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. Diabetes Care 2001;24:1069–1078
2. Gonzalez JS, Peyrot M, McCarl LA, et al. Depression and diabetes treatment nonadherence: a meta-analysis. Diabetes Care 2008;31:2398–2403
3. de Groot M, Anderson R, Freedland KE, Clouse RE, Lustman PJ. Association of depression and diabetes complications: a meta-analysis. Psychosom Med 2001;63:619–630
4. van Dooren FE, Nefs G, Schram MT, Verhey FR, Denollet J, Pouwer F. Depression and risk of mortality in people with diabetes mellitus: a systematic review and meta-analysis. PLoS ONE 2013;8:e57058
5. Golden SH, Lazo M, Carnethon M, et al. Examining a bidirectional association between depressive symptoms and diabetes. JAMA 2008;299:2751–2759
6. Hood KK, Lawrence JM, Anderson A, et al.; SEARCH for Diabetes in Youth Study Group. Metabolic and inflammatory links to depression in youth with diabetes. Diabetes Care 2012;35:2443–2446
7. Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. Trends Immunol 2006;27:24–31
8. Dantzer R, Kelley KW. Twenty years of research on cytokine-induced sickness behavior. Brain Behav Immun 2007;21:153–160
9. Rabinovitch A. An update on cytokines in the pathogenesis of insulin-dependent diabetes mellitus. Diabetes Metab Rev 1998;14:129–151
10. Greenberg AS, McDaniel ML. Identifying the links between obesity, insulin resistance and beta-cell function: potential role of adipocyte-derived cytokines in the pathogenesis of type 2 diabetes. Eur J Clin Invest 2002;32(Suppl. 3):24–34
11. Pickup JC. Inflammation and activated innate immunity in the pathogenesis of type 2 diabetes. Diabetes Care 2004;27:813–823
12. Dentino AN, Pieper CF, Rao MK, et al. Association of interleukin-6 and other biologic variables with depression in older people living in the community. J Am Geriatr Soc 1999;47:6–11
13. Lutgendorf SK, Garand L, Buckwalter KC, Reimer TT, Hong SY, Lubaroff DM. Life stress, mood disturbance, and elevated interleukin-6 in healthy older women. J Gerontol A Biol Sci Med Sci 1999;54:M434–M439
14. Maes M, Van Bockstaele DR, Gastel A, et al. The effects of psychological stress on leukocyte subset distribution in humans: evidence of immune activation. Neuropsychobiology 1999;39:1–9
15. Reichenberg A, Yirmiya R, Schuld A, et al. Cytokine-associated emotional and cognitive disturbances in humans. Arch Gen Psychiatry 2001;58:445–452
16. Doyle TA, de Groot M, Harris T, et al. Diabetes, depressive symptoms, and inflammation in older adults: results from the health, aging, and body composition study. J Psychosom Res 2013;75:419–424
17. Tsujii S, Hayashino Y, Ishii H; Diabetes Distress and Care Registry at Tenri Study Group. Diabetes distress, but not depressive symptoms, is associated with glycaemic control among Japanese patients with type 2 diabetes: Diabetes Distress and Care Registry at Tenri (DDCRT 1). Diabet Med 2012;29:1451–1455
18. Hayashino Y, Okamura S, Matsunaga S, Tsujii S, Ishii H, Group TTCS; Tenri Cohort Study Group. The association between problem areas in diabetes scale scores and glycemic control is modified by types of diabetes therapy: Diabetes Distress and Care Registry in Tenri (DDCRT 2). Diabetes Res Clin Pract 2012;97:405–410
19. Mashitani T, Hayashino Y, Okamura S, et al. Patient-reported adherence to insulin regimen is associated with glycemic control among Japanese patients with type 2 diabetes: Diabetes Distress and Care Registry at Tenri (DDCRT 3). Diabetes Res Clin Pract 2013;100:189–194
20. Committee of the Japan Diabetes Society on the Diagnostic Criteria of Diabetes Mellitus. Report of the Committee on the Classification and Diagnostic Criteria of Diabetes Mellitus. J Diabetes Invest 2010;1:212–228
21. Craig CL, Marshall AL, Sjöström M, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 2003;35:1381–1395
22. Spitzer RL, Williams JB, Gibbon M. Instruction manual for the structured clinical interview for DSM-III-R. In *Biometrics Research Development*. New York, New York State Psychiatric Institute, 1986, p. 4–13
23. Spitzer RL, Williams JB, Gibbon M, First MB. The Structured Clinical Interview for DSM-III-R (SCID). I: History, rationale, and description. Arch Gen Psychiatry 1992;49:624–629
24. van Steenbergen-Weijenburg KM, de Vroege L, Ploeger RR, et al. Validation of the PHQ-9 as a screening instrument for depression in diabetes patients in specialized outpatient clinics. BMC Health Serv Res 2010;10:235
25. Williams LS, Brizendine EJ, Plue L, et al. Performance of the PHQ-9 as a screening tool for depression after stroke. Stroke 2005;36:635–638
26. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001;16:606–613
27. NHS National Institute for Health and Clinical Excellence (NICE). Type 1 diabetes diagnosis and management of type 1 diabetes in children and young people. Clinical Guideline 15, developed by the National Collaborating Centre for Woman's and Children's Health and the National Collaborating Centre for Chronic Conditions, 2004
28. Champaneri S, Wand GS, Malhotra SS, Casagrande SS, Golden SH. Biological basis of depression in adults with diabetes. Curr Diab Rep 2010;10:396–405
29. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. JAMA 2001;286:327–334
30. Spranger J, Kroke A, Möhlig M, et al. Inflammatory cytokines and the risk to develop type 2 diabetes: results of the prospective population-based European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study. Diabetes 2003;52:812–817
31. Bertoni AG, Burke GL, Owusu JA, et al. Inflammation and the incidence of type 2 diabetes: the Multi-Ethnic Study of Atherosclerosis (MESA). Diabetes Care 2010;33:804–810
32. Brummett BH, Boyle SH, Ortel TL, Becker RC, Siegler IC, Williams RB. Associations of depressive symptoms, trait hostility, and gender with C-reactive protein and interleukin-6 response after emotion recall. Psychosom Med 2010;72:333–339
33. Kobrosly R, van Wijngaarden E. Associations between immunologic, inflammatory, and oxidative stress markers with severity of depressive symptoms: an analysis of the 2005-2006 National Health and Nutrition Examination Survey. Neurotoxicology 2010;31:126–133
34. Elovainio M, Aalto AM, Kivimäki M, et al. Depression and C-reactive protein: population-based Health 2000 Study. Psychosom Med 2009;71:423–430
35. Stewart JC, Rand KL, Muldoon MF, Kamarck TW. A prospective evaluation of the directionality of the depression-inflammation relationship. Brain Behav Immun 2009;23:936–944
36. Gimeno D, Kivimäki M, Brunner EJ, et al. Associations of C-reactive protein and interleukin-6 with cognitive symptoms of depression: 12-year follow-up of the Whitehall II study. Psychol Med 2009;39:413–423
37. Wang X, Bao W, Liu J, et al. Inflammatory markers and risk of type 2 diabetes: a systematic review and meta-analysis. Diabetes Care 2013;36:166–175
38. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis

factor-alpha: direct role in obesity-linked insulin resistance. Science 1993;259:87–91
39. Schellenberg ES, Dryden DM, Vandermeer B, Ha C, Korownyk C. Lifestyle interventions for patients with and at risk for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med 2013;159:543–551
40. Umpierre D, Ribeiro PA, Kramer CK, et al. Physical activity advice only or structured exercise training and association with HbA1c levels in type 2 diabetes: a systematic review and meta-analysis. JAMA 2011;305:1790–1799
41. Hayashino Y, Jackson JL, Fukumori N, Nakamura F, Fukuhara S. Effects of supervised exercise on lipid profiles and blood pressure control in people with type 2 diabetes mellitus: a meta-analysis of randomized controlled trials. Diabetes Res Clin Pract 2012;98:349–360
42. Gellis ZD, Kang-Yi C. Meta-analysis of the effect of cardiac rehabilitation interventions on depression outcomes in adults 64 years of age and older. Am J Cardiol 2012;110:1219–1224
43. Hayashino Y, Jackson JL, Hirata T, et al. Effects of exercise on C-reactive protein, inflammatory cytokine and adipokine in patients with type 2 diabetes: a meta-analysis of randomized controlled trials. Metabolism 2014;63:431–440
44. Dosemeci M, Wacholder S, Lubin JH. Does nondifferential misclassification of exposure always bias a true effect toward the null value? Am J Epidemiol 1990;132:746–748