



The Association Between Depressive Symptoms and Systemic Inflammation in People With Type 2 Diabetes: Findings From the South London Diabetes Study

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OBJECTIVE

The prevalence of depression and depressive symptoms is increased twofold in people with type 2 diabetes compared with the general population and is associated with worse biomedical outcomes and increased mortality. Type 2 diabetes, cardiovascular disease, and depression in nondiabetes subjects are independently associated with raised concentrations of circulating inflammatory markers, but it is not known if a similar association is observed in type 2 diabetes. We tested the hypothesis that higher depressive symptom scores in newly diagnosed type 2 diabetes patients were associated with higher concentrations of inflammatory markers.

RESEARCH DESIGN AND METHODS

Depressive symptoms in adults with newly diagnosed type 2 diabetes recruited from primary care were assessed using the Patient Health Questionnaire-9. Twelve markers of inflammation (C-reactive protein [hs-CRP], interleukin-4 [IL-4], IL-6, IL-10, vascular endothelial growth factor [VEGF], tumor necrosis factor- α [TNF- α], IL-1 β , IL-1 receptor antagonist [IL-1RA], monocyte chemoattractant protein-1 [MCP-1], white blood cell count [WBC], adiponectin, and triglyceride [TG]) were measured. Covariates included sociodemographic factors, adiposity, macrovascular disease, HbA_{1c}, and prescribed medication. The association between each inflammatory marker and depressive symptom score was estimated by multiple linear regression.

RESULTS

The baseline cohort consisted of 1,790 participants. After adjusting for covariates, CRP ($B = 0.13$, $P < 0.001$), IL-1 β ($B = 0.06$, $P = 0.047$), IL-1RA ($B = 0.13$, $P < 0.001$), MCP-1 ($B = 0.11$, $P = 0.001$), WBC ($B = 0.13$, $P < 0.001$), and TG ($B = 0.10$, $P < 0.001$) were associated with depressive symptoms.

CONCLUSIONS

Increased inflammation may be involved in the pathogenesis of depressive symptoms in type 2 diabetes and contribute to the increased risk of complications and mortality in this group.

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The prevalence of depression and depressive symptoms is twice as common in individuals with type 2 diabetes compared with those without diabetes (1,2). When depression and depressive symptoms are present, they are associated with worse glycemic control (3), an increased risk of microvascular and macrovascular diabetes complications (4), and an increased risk of premature mortality (5). In prospective studies, the presence of depressive symptoms is associated with a 37–60% increased risk of incident type 2 diabetes, and there is a smaller reverse association of a 15–24% risk of incident depressive symptoms in those with type 2 diabetes (6–9).

The mechanisms for this bidirectional relationship between depressive symptoms and diabetes are not well understood (10). We are investigating activated innate immunity as the common antecedent for the parallel development of diabetes and depression, and for cardiovascular disease (which is a common comorbidity of diabetes and depression), since there is evidence for the involvement of innate immunity in the pathogenesis of all three.

Depression in the general population, when defined by diagnostic clinical interview, has a small but significant association with a systemic, cytokine-mediated, chronic inflammatory state (a marker of activation of innate immunity) that differs according to subtype of depression (11–13). Insulin resistance, type 2 diabetes, and cardiovascular diseases are also associated with a chronic low-grade inflammatory response due to activated innate immunity (14–16). Prospective studies have shown that raised circulating concentrations of inflammatory markers, including acute-phase proteins such as C-reactive protein (CRP) and proinflammatory cytokines such as interleukin-6 (IL-6), are associated with the onset of type 2 diabetes in cohorts with initially normal glucose tolerance (17,18). Activated innate immunity is also a strong independent risk factor for cardiovascular events and mortality in the general population and in those with established type 2 diabetes (16,19,20). There have been similar observations of associations between inflammation and cardiovascular disease; in a cohort of people with depression, those with asymptomatic cardiovascular disease had increased concentrations of

markers of systemic inflammation (21). Furthermore, childhood adversity, a major risk factor for adult depression, is prospectively associated with higher concentrations of CRP in early adult life (22). Depressive symptoms are associated with raised white blood cell count (WBC) in people with established cardiovascular disease (23). In a small selected inpatient depression sample ($n = 70$), adiponectin and IL-6 were associated with metabolic status (24), and in a secondary analysis of an elderly U.S. cohort, a nested sample of established diabetes ($n = 14$), depressive symptoms were positively associated with IL-6 (25).

Despite these proposed mechanisms, in people with newly diagnosed type 2 diabetes, it is not known if there is an association between systemic inflammation and depressive symptoms. We tested the hypothesis that the presence of depressive symptoms was associated with increased concentrations of circulating inflammatory markers in a cohort of newly diagnosed type 2 diabetes patients. We selected newly diagnosed cases of type 2 diabetes as this represents a window of opportunity to identify patients at high risk of poor prognosis with the potential of early intervention.

RESEARCH DESIGN AND METHODS

Design

The study used a population-based, cross-sectional design with the baseline participants in the South London Diabetes Study (SOUL-D), which is a prospective cohort study designed to test the relative effects of psychological and social factors on biomedical outcomes in people with newly diagnosed type 2 diabetes. Ethical approval was granted by the King's College Hospital Research Ethics Committee (reference 08/H0808/1) and by Lambeth, Southwark, and Lewisham Primary Care Trusts (reference RDLSLB 410), and all participants provided written informed consent.

Setting and Sampling Frame

The study was set in the inner-city boroughs of Lambeth, Southwark, and Lewisham in South London, which collectively have ~0.75 million U.K. residents from diverse socioeconomic and ethnic background, with 66% white, 20% African/Caribbean, and 14% South Asian and other (26). All 138 general

practices (primary care clinics in the U.K.'s National Health Service) in these boroughs were invited to participate, and this constituted the sampling frame. Every 6 months, each diabetes register was searched for patients with a new diagnosis of type 2 diabetes.

Study Population and Case Definition

People with a first (<6 months) diagnosis of type 2 diabetes according to World Health Organization's criteria (27), aged between 18 and 75 years at diagnosis, were identified from diabetes registers of participating general practices and invited to participate. Recruitment was conducted between May 2008 and September 2012; further details of the sampling methodology have been described in detail elsewhere (26).

Assessment of Confounders

The following data were measured and coded using general practice records: age, sex, history of macrovascular disease (myocardial infarction, coronary artery bypass graft, cerebrovascular accident, and carotid or limb revascularization), and current prescribed medications with a possible anti-inflammatory action (statins, fibrates, systemic steroids, non-steroidal anti-inflammatory drugs, and COX-2 inhibitors). A physical examination was performed to measure systolic and diastolic blood pressures (mmHg) and BMI (kg/m^2), and a questionnaire was used to determine smoking status and self-report ethnicity based on 2001 U.K. census methods (26).

Main Explanatory Variables

We selected 12 inflammatory markers identified a priori as associated with type 2 diabetes and/or depression (11–15,18–20,23,28,29). Serum CRP was measured by a high-sensitivity CRP (hs-CRP) assay using an Advia 2400 analyzer (Siemens Diagnostics, Frimley, U.K.). The detection limit of the assay was 0.1 mg/L. WBC was measured using an Advia 2120 analyzer (Siemens Diagnostics); these tests were carried out using freshly drawn venous blood samples stored at room temperature until analyzed. Adiponectin was measured using ELISA kits (R&D Systems Europe, Oxon, U.K.). The detection limit of the assay was 0.246 mg/L. IL-4, IL-6, IL-10, vascular endothelial growth factor (VEGF), tumor necrosis factor- α (TNF- α), IL-1 β , IL-1 receptor antagonist (IL-1RA), and monocyte

chemotactic protein-1 (MCP-1) were all measured from serum samples centrifuged from venous blood samples taken after an overnight fast and stored between -40 and -80°C using cytokine-array biochip kits (Randox, Belfast, U.K.) and analyzed using the Randox Evidence Investigator. The inter- and intra-assay coefficients of variation for all analytes measured using these kits are <15 and $<10\%$, respectively. We measured fasting lipids using a Siemens Advia 2400 analyzer. The detection limits of the assays were as follows: triglyceride (TG) 0.01 mmol/L (the 12th inflammatory marker), total cholesterol 0.01 mmol/L, and HDL cholesterol 0.1 mmol/L; LDL cholesterol was calculated via the Friedewald formula. Glycated hemoglobin (HbA_{1c}) was measured by affinity chromatography using the Primus Ultra 2 analyzer (Primus Corporation, Kansas City, MO). Fasting lipid tests were performed using freshly drawn venous blood samples stored at room temperature until analyzed. Fasting blood samples were drawn in the morning at the patients' respective general practices or their local phlebotomy service and were centrifuged, analyzed, aliquoted, and then frozen (for the cytokine analyses) on the same day.

Main Outcome Variable

The presence of depressive symptoms at baseline was measured using the Patient Health Questionnaire-9 (PHQ-9). This is a self-report measure that was developed for primary care to aid clinicians in identifying probable cases of depression. A cutoff score of ≥ 10 is the optimal threshold for identifying probable cases of depression, with a sensitivity of 73% and specificity of 98% (30,31), whereas those with a score <10 were defined as nondepressed participants. The PHQ-9 has acceptable validity in diabetes populations (32).

Statistical Analyses

Data were analyzed using SPSS 21.0 (released 2012, IBM SPSS Statistics, version 21.0; IBM Corp, Armonk, NY). The main characteristics of the study population are summarized as mean (SD) where data were normally distributed or median (interquartile range [IQR]) where data were skewed, or as a count (percentage) for categorical variables, all stratified by PHQ-9 depression case status. Unadjusted statistical analyses were

conducted using Student *t* test for normally distributed continuous data, Mann-Whitney *U* test for nonnormally distributed continuous data, and Spearman ranked correlation coefficient (r_s) to compare bivariate associations. The χ^2 test was used for comparisons of categorical data. A natural log was used to transform skewed data for inflammatory markers and PHQ-9 score in multiple regressions. Multiple linear regressions were used to assess the relationship between depressive symptom score as the dependent variable and those inflammatory markers that had significant association in the unadjusted analyses as independent variables; covariates were added to the model in sequential steps using a hierarchical method and only retained if they were significantly associated with the outcome or an important clinical confounder, such as ethnicity. Simes' improved Bonferroni method was used to correct for multiple testing for pairwise comparisons of inflammatory marker differences between groups and association between inflammatory marker concentrations and PHQ-9 score. An assessment of the residuals did not suggest major violations of the assumptions of a multiple regression. Left-censored data for concentrations of inflammatory markers (where the actual concentration was below the minimum detection threshold) accounted for $<2\%$ of values. Left-censored values were replaced with values equal to half the minimum detected value for each cytokine. For five cases (0.5% of the sample), the value for MCP-1 concentration was right censored (i.e., the value was known only to be more than the maximum detection threshold of the assay). In the unadjusted analyses of MCP-1 (which used ranked data), these five cases were included and right-censored data were substituted for the maximum detectable value. These five cases were omitted from the adjusted multiple linear regression analysis because of the small number of cases with right-censored values. A sensitivity analysis that included the cases with right-censored values showed they had no effect on the results of the multiple linear regression.

RESULTS

Of 139 general practices invited, 96 (70%) agreed to participate, from which 1,790 participants with newly diagnosed

type 2 diabetes were recruited. There were $>25\%$ missing answers from PHQ-9 scores in 21 (1.2%) participants, so these were excluded and the analyses were conducted on $n = 1,769$ (98.8%). Analyses of inflammatory markers were conducted on a subset of the cohort for whom we had a stored serum sample, $n = 1,227$ (69%). Compared with those with a frozen stored sample, those who had missing or unanalyzable blood samples ($n = 542$) were younger (mean age 57 [11] vs. 55 [11] years, $P < 0.001$) and more likely to be of black African or Caribbean ethnicity (36 vs. 50% , $P < 0.001$), but there were no statistically significant differences in sex (55 vs. 56% male, $P = 0.83$), PHQ-9 depression cases (13.6 vs. 17.8% , $P = 0.08$), or glycemic control (DCCT HbA_{1c} 6.97% [1.4] vs. 7.09% [1.6]; IFCC HbA_{1c} 52.7 mmol/mol [15.2] vs. 54.0 mmol/mol [17.3]; $P = 0.148$). The median age for female participants was 57 years (IQR 50–64), suggesting that the majority were probably postmenopausal.

Table 1 reports the demographic characteristics, depressive symptom score, and concentrations of inflammatory markers in the type 2 diabetes patients stratified by PHQ-9 depression case status. The prevalence of depression cases, defined as a PHQ-9 score ≥ 10 , was 14.6% ($n = 258$). Depression case subjects were nearly 5 years younger, had a higher BMI, were more likely to be female, and had a significantly greater prevalence of macrovascular disease.

Median circulating concentrations of the inflammatory markers hs-CRP, IL-1RA, WBC, and TG were significantly higher in depression case subjects compared with nondepressed participants, and these differences remained significant after Simes' improved Bonferroni correction for multiple testing (Table 1). There were no statistically significant differences in LDL cholesterol, HDL cholesterol, total cholesterol, IL-4, IL-6, IL-10, VEGF, TNF- α , IL-1 β , MCP-1, or adiponectin concentrations in depression case subjects compared with nondepressed participants, although there was a trend toward lower concentrations of adiponectin in the former group.

Symptoms of depression, measured as a continuous PHQ-9 score, were positively correlated with the inflammatory

Table 1—Baseline characteristics of depression case subjects (PHQ-9 ≥ 10) and nondepressed (PHQ-9 < 10) participants with type 2 diabetes in the South London Diabetes Study

Baseline variable	Total (n = 1,769)	No depression (n = 1,511)	Depression (n = 258)	P value
Mean age, years	56.1 (11.04)	56.6 (11.05)	53.0 (10.40)	<0.001*
Sex (%)				
Male	976 (55.2)	855 (56.6)	121 (46.9)	0.004*
Female	793 (44.8)	656 (43.4)	137 (53.1)	
Ethnicity (%)				
White	878 (49.6)	750 (49.6)	128 (49.6)	0.128
Black	710 (40.1)	615 (40.7)	95 (36.8)	
Asian/other	181 (10.2)	146 (9.7)	35 (13.6)	
Mean % HbA _{1c} (mean HbA _{1c} , mmol/mol)	7.00 (1.45) (53.1)	6.98 (1.46) (52.8)	7.13 (1.43) (54.5)	0.139
Lipids				
Median TG, mmol/L	1.40 (0.90–2.00)	1.40 (0.90–1.90)	1.50 (1.00–2.20)	0.003*
Mean LDL, mmol/L	2.63 (0.91)	2.63 (0.90)	2.65 (0.98)	0.792
Mean HDL, mmol/L	1.22 (0.34)	1.22 (0.33)	1.20 (0.39)	0.589
Mean total cholesterol, mmol/L	4.57 (1.09)	4.56 (1.06)	4.69 (1.23)	0.097
Mean BMI, kg/m ²	32.0 (6.50)	31.8 (6.34)	33.4 (7.23)	0.001*
Macrovascular disease (%)				
None	1,584 (90.8)	1,365 (91.5)	219 (86.2)	0.007*
More than 1	161 (9.2)	126 (8.5)	35 (13.8)	
Inflammatory markers				
Median hs-CRP, mg/L	2.90 (1.20–6.40)	2.70 (1.10–6.20)	3.25 (1.40–8.70)	0.002*
Median IL-4, ng/L	1.34 (1.11–1.68)	1.34 (1.10–1.68)	1.35 (1.17–1.68)	0.380
Median IL-6, ng/L	1.35 (0.68–3.42)	1.32 (0.67–3.41)	1.40 (0.75–3.63)	0.420
Median IL-10, ng/L	0.45 (0.34–0.63)	0.44 (0.34–0.63)	0.47 (0.35–0.68)	0.144
Median VEGF, ng/L	75.3 (44.8–119.3)	74.6 (44.9–118.2)	83.3 (44.9–128.7)	0.589
Median TNF- α , ng/L	0.89 (0.39–1.86)	0.89 (0.39–1.88)	0.91 (0.43–1.76)	0.771
Median IL-1 β , ng/L	1.02 (0.73–1.87)	1.01 (0.72–1.85)	1.12 (0.76–2.06)	0.191
Median IL-1RA, ng/L	437.2 (292.0–694.8)	430.0 (282.9–672.4)	488.8 (337.3–785.3)	0.003*
Median MCP-1, ng/L	103.3 (60.2–152.9)	101.7 (59.3–151.1)	112.1 (62.8–162.6)	0.134
Median WBC, $\times 10^9$ /L	6.51 (5.31–7.97)	6.44 (5.25–7.86)	6.91 (5.74–8.56)	<0.001*
Median adiponectin, mg/L	4.94 (3.28–7.50)	5.01 (3.29–7.61)	4.65 (3.27–6.65)	0.097

Data are n (%), mean (SD), or median (IQR) as appropriate. Missing or incomplete values were as follows: HbA_{1c} = 117 cases, lipids = 245 cases, BMI = 3 cases, macrovascular history = 24 cases, hs-CRP = 308 cases, WBC = 183 cases, and adiponectin = 304 cases. Values for IL-4, IL-6, IL-10, VEGF, TNF- α , IL-1 β , IL-1RA, and MCP-1 were for a subset of the first 1,227 case subjects for whom we had a stored serum sample. *Significant after Simes' improved Bonferroni correction for multiple testing.

markers hs-CRP, VEGF, IL-1 β , IL-1RA, MCP-1, WBC, and TG and were negatively correlated with adiponectin; these differences remained significant after Simes' improved Bonferroni correction for multiple testing (Table 2). The mean HbA_{1c} concentration was not statistically different between depression case subjects and nondepressed participants.

Table 3 reports the results of the final models of multiple linear regression analyses; these were used to compare concentrations of circulating markers of inflammation with levels of depressive symptoms (PHQ-9 score) while adjusting for sociodemographic factors, HbA_{1c}, adiposity (BMI), smoking history, history of macrovascular disease, and prescription of medication. Only those inflammatory markers that were associated with PHQ-9 score in unadjusted Spearman ρ tests were included in the multiple linear regression analyses, namely, hs-CRP, VEGF, IL-1 β , IL-1RA,

MCP-1, WBC, TG, and adiponectin. After adjusting for all covariates, there remained a significant association between six inflammatory markers (hs-CRP, IL-1 β , IL-1RA, MCP-1, WBC, and TG) and depressive symptom score.

CONCLUSIONS

In a large population-based, newly diagnosed type 2 diabetes cohort, we found that depression case subjects as defined by the PHQ-9 were younger, more overweight, had more macrovascular disease, and had higher circulating concentrations of several established inflammatory markers. After adjusting for relevant potential confounding variables, including adiposity, age, sex, ethnicity, smoking, HbA_{1c}, diabetes complications, and medications with anti-inflammatory action, the association between depressive symptoms and hs-CRP, IL-1 β , IL-1RA, MCP-1, WBC, and TG remained significant.

A strength of our study is that we chose a priori a large range of inflammatory markers that have been implicated

Table 2—Unadjusted Spearman ranked correlation for association between inflammatory marker concentration and PHQ-9 score

Inflammatory marker	r_s	P value
hs-CRP	0.15	<0.001*
IL-4	0.06	0.056
IL-6	0.05	0.075
IL-10	0.05	0.105
VEGF	0.07	0.012*
TNF- α	0.02	0.404
IL-1 β	0.09	0.003*
IL-1RA	0.16	<0.001*
MCP-1	0.08	0.005*
WBC	0.13	<0.001*
TG	0.11	<0.001*
Adiponectin	-0.07	0.010*

*Significant after Simes' improved Bonferroni correction for multiple testing.

Table 3—Adjusted† final multiple linear regression models for the independent association between PHQ-9 score‡ and each inflammatory marker‡

Model	R ²	Inflammatory marker	Age	Sex	BMI	MVD	HbA _{1c}	
hs-CRP	0.07	B (SE)	0.15 (0.03)	−0.02 (0.003)	0.20 (0.05)	0.003 (0.004)	0.27 (0.09)	0.003 (0.002)
		Standardized b	0.13	−0.17	0.10	0.02	0.08	0.04
		P	<0.001*	<0.001*	<0.001*	0.435	0.004*	0.111
VEGF	0.05	B (SE)	0.07 (0.04)	−0.02 (0.003)	0.14 (0.06)	0.007 (0.005)	0.21 (0.10)	0.004 (0.002)
		Standardized b	0.05	−0.17	0.07	0.05	0.07	0.06
		P	0.073	<0.001*	0.016*	0.110	0.030*	0.056
IL-1β	0.05	B (SE)	0.08 (0.04)	−0.02 (0.003)	0.15 (0.06)	0.008 (0.005)	0.22 (0.10)	0.004 (0.002)
		Standardized b	0.06	−0.17	0.08	0.05	0.07	0.06
		P	0.047*	<0.001*	0.010*	0.078	0.025*	0.043*
IL-1RA	0.06	B (SE)	0.20 (0.05)	−0.02 (0.003)	0.11 (0.06)	0.003 (0.005)	0.19 (0.10)	0.003 (0.002)
		Standardized b	0.13	−0.17	0.06	0.02	0.06	0.05
		P	<0.001*	<0.001*	0.056*	0.464	0.057	0.125
MCP-1	0.06	B (SE)	0.16 (0.05)	−0.02 (0.003)	0.16 (0.06)	0.008 (0.005)	0.21 (0.10)	0.003 (0.002)
		Standardized b	0.11	−0.18	0.08	0.05	0.07	0.05
		P	0.001*	<0.001*	0.006*	0.097	0.032*	0.068
WBC	0.07	B (SE)	0.47 (0.10)	−0.02 (0.002)	0.24 (0.05)	0.008 (0.004)	0.24 (0.09)	0.003 (0.002)
		Standardized b	0.13	−0.18	0.12	0.05	0.07	0.04
		P	<0.001*	<0.001*	<0.001*	0.041*	0.008*	0.093
TG	0.07	B (SE)	0.29 (0.08)	−0.02 (0.002)	0.25 (0.05)	0.010 (0.004)	0.25 (0.09)	0.003 (0.002)
		Standardized b	0.10	−0.17	0.13	0.07	0.07	0.04
		P	<0.001*	<0.001*	<0.001*	0.011*	0.005*	0.113
Adiponectin	0.06	B (SE)	−0.08 (0.05)	−0.01 (0.003)	0.26 (0.06)	0.009 (0.004)	0.27 (0.09)	0.003 (0.002)
		Standardized b	−0.05	−0.16	0.13	0.06	0.08	0.05
		P	0.096	<0.001*	<0.001*	0.036*	0.003*	0.063

*Significant after Simes' improved Bonferroni correction for multiple testing. †Adjusted for age, sex, ethnicity, HbA_{1c}, BMI, smoking, history of macrovascular disease (MVD), and prescribed medications. Only age, sex, BMI, MVD, and HbA_{1c} are displayed here as these were the explanatory covariates. ‡These variables were ln transformed.

in the pathogenesis of type 2 diabetes and/or depression or depressive symptoms (11,12,18–20,28,29), to our knowledge one of the largest array of markers measured in any cohort of diabetes. We also chose biomarkers used in routine clinical practice, including circulating hs-CRP, WBC, and TG, which are all components of the acute-phase response in animals and humans and may have clinical applications as useful biomarkers for depressive symptoms (18,23,33). We have used a population-based primary care sample that aims to reduce selection bias. Using a cohort design allowed us to include and adjust for a range of potential confounding variables linking innate immunity, inflammation, and depressive symptoms in type 2 diabetes, including diabetes-related medications that have anti-inflammatory properties, such as statins, systemic steroids, and nonsteroidal anti-inflammatory drugs. As these type 2 diabetes patients were newly diagnosed (<6 months), only 63 (4%) were on insulin therapy. Insulin therapy was equally prescribed in those who were depression case subjects versus those who were not but could

otherwise have been a significant confounder. The cohort is representative of the multiethnic and socially diverse global type 2 diabetes population, and the setting was an inner city where the prevalence of both depression and type 2 diabetes are at their highest (34). We used the continuous PHQ-9 score for our primary hypothesis to improve the power of the analyses and to overcome the limitations in the validity of using a threshold score to define depression.

The main limitation of these data are that they are cross-sectional, so a causative link between inflammatory markers, depressive symptoms, and type 2 diabetes cannot be inferred. When we defined a case of depression using a PHQ-9 cutoff ≥ 10 , we did not confirm a diagnosis of major depression using a clinical interview. Thus we may have overestimated its prevalence because although this cutoff has a high sensitivity, this comes at the expense of a lower specificity in diabetes patients (32). As we have used a continuous PHQ-9 score, it is unclear whether the associations we have reported between depressive symptom score and inflammation exist in both

subthreshold and clinically diagnosed major depressive disorder. We did not adjust for antidepressants because there is no systematic pooled evidence from randomized controlled trials or observation studies to support a direct pro- or anti-inflammatory effect. There is a risk of residual confounding for poor adherence to medication, which we could not measure, although our medication data were derived from current general practitioner prescription records. There was a small risk that comorbid acute or chronic inflammatory conditions may have been included, which could have led to an overestimation of effects, but terminal and advanced conditions were exclusion criteria so the more severely affected case subjects were excluded. We did not adjust for estrogen replacement therapy or any potential inflammatory effects of premenopause, but the majority of our female population was postmenopausal. We did not include diet and physical activity because self-report measures are not sufficiently accurate, but we used BMI, which may be considered a proxy marker for both.

In the general population, inflammation is significantly associated with cardiovascular disease (20), and since inflammation is also a significant biomarker associated with cardiovascular mortality in type 2 diabetes (19), we have hypothesized that activated innate immunity is the common antecedent of a number of chronic noncommunicable diseases such as type 2 diabetes, atherosclerosis, and depressive symptoms (19), which tend to cluster together. It has been suggested that the increased risk of complications in type 2 diabetes with depression and depressive symptoms may be related to poorer glucose control (elevated HbA_{1c}), but in the current study, we did not find significantly raised HbA_{1c} in those who were depression case subjects. This group appears to have developed diabetes at a younger age, which may or may not be due to behavioral effects of depression earlier in the life span. However, as we studied newly diagnosed type 2 diabetes, most patients had not had the opportunity to improve their glycemic control and so the negative impact of the behavioral effects of depression on self-care and glycemic control that others have observed may not have been identifiable at this stage (35). It should be noted that although some collaborative care intervention studies (where therapies for both type 2 diabetes and depression are optimized) have shown improvements in HbA_{1c} (36), as a general rule, glycemic control does not improve when depression alone is treated (37), which argues against the association between depression or depressive symptoms and poor glycemic control being mediated by reduced self-care behaviors alone.

Inflammation may have a role in the pathogenesis of depression and depressive symptoms via numerous mechanisms, including altering the metabolism and activity of monoamine transmitters, effects on neurogenesis and neuroplasticity, and activation of the hypothalamic-pituitary axis (9,13). The increased concentrations of the inflammatory markers we detected in newly diagnosed type 2 diabetes participants with increased depressive symptom scores, independent of HbA_{1c} and BMI, support an alternative hypothesis that activated innate immunity is involved in the etiology of depression

and/or the increased complications associated with it in type 2 diabetes.

We found that IL-1 β , a proinflammatory cytokine, was positively associated with depressive symptoms (the magnitude of the PHQ-9 score), as was IL-1RA, which blocks IL-1 β from binding to its receptor. Where there is increased inflammation and IL-1 β activity in specific tissues, this leads to increased IL-1RA secretion (38). That both these inflammatory markers were similarly associated with depressive symptom score is consistent with the described pathway.

Adiponectin, negatively associated with depressive symptom score in our data, is known to have insulin-sensitizing and anti-inflammatory effects and has been reported as decreased in depression (28,29,39). In our data, the association between adiponectin and depressive symptom score was attenuated when adjusting for BMI, which was also a significant explanatory covariate in the final models for the association of PHQ-9 with WBC and TG. This suggests that some of the increased inflammation and the reduced concentrations of adiponectin that we detected in this group are associated with the increased adiposity.

Only the inflammatory markers WBC, hs-CRP, IL-1 β , IL-1RA, MCP-1, and TG were significantly associated with depressive symptom score; whether these markers represent a cluster or subtype of the innate inflammatory response more likely to be associated with depressive symptoms needs to be investigated. We did not detect an association between some markers (such as IL-6 and TNF- α), which have been previously associated with both depression and depressive symptoms, and diabetes (24,25). There are a number of possibilities that could explain this, and there is a risk of overspeculating. It is possible that there are subtypes of depression characterized by different inflammatory profiles. It may be that the concentrations of cytokines such as IL-6 and TNF- α (which are raised in type 2 diabetes and have been associated with its onset) are already raised to a significant level in our whole population and in combination with the other markers (which are associated with depressive symptom score in our cohort) characterize the increased depressive symptoms in our sample.

Our findings have several implications. First, although depression is recognized

as a complication of established type 2 diabetes, we found that even at diagnosis, up to 15% of patients with type 2 diabetes had probable clinical depression. This underlines the importance of recent American Diabetes Association guidelines "Standards of Medical Care in Diabetes—2013" alerting diabetes physicians to the need to screen, identify, and treat depression at the earliest stages of diabetes (40). Second, the association of a higher degree of systemic inflammation with a higher depressive symptom score may explain the increased risk of macrovascular disease and mortality in this group, since inflammation is a known risk factor for cardiovascular disease and mortality in participants with and without diabetes (3,35,37). This may explain why treating depression and depressive symptoms does not necessarily improve diabetes outcomes (4,5), as the increased inflammation and accelerated disease pathology may not be resolved when using conventional pharmacological and psychological treatments for depression.

Our findings support the hypothesis that inflammation in type 2 diabetes may cause the parallel development of depressive symptoms, glucose intolerance, and atherosclerosis (19,20). Moreover, anti-inflammatory therapies may influence both the course of diabetes and depressive symptoms, as has been suggested in the case of cardiovascular disease (19,37); this hypothesis now needs testing. As a cross-sectional association has been observed between depressive symptoms and several inflammatory biomarkers, longitudinal studies are now needed to test the direction of the association between depressive symptoms and inflammation.

We conclude that people with more depressive symptoms and type 2 diabetes have higher circulating concentrations of inflammatory markers than people with diabetes with less depressive symptoms. Studies are now needed to examine whether the concentrations of inflammatory markers at diagnosis of diabetes predict the later development of depressive symptomology.

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References

- Nichols GA, Brown JB. Unadjusted and adjusted prevalence of diagnosed depression in type 2 diabetes. *Diabetes Care* 2003;26:744–749
- 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
- Lustman PJ, Anderson RJ, Freedland KE, de Groot M, Carney RM, Clouse RE. Depression and poor glycemic control: a meta-analytic review of the literature. *Diabetes Care* 2000;23:934–942
- 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
- Katon WJ, Rutter C, Simon G, et al. The association of comorbid depression with mortality in patients with type 2 diabetes. *Diabetes Care* 2005;28:2668–2672
- Knol MJ, Twisk JWR, Beekman ATF, Heine RJ, Snoek FJ, Pouwer F. Depression as a risk factor for the onset of type 2 diabetes mellitus. A meta-analysis. *Diabetologia* 2006;49:837–845
- Mezuk B, Eaton WW, Albrecht S, Golden SH. Depression and type 2 diabetes over the lifespan: a meta-analysis. *Diabetes Care* 2008;31:2383–2390
- Golden SH, Lazo M, Carnethon M, et al. Examining a bidirectional association between depressive symptoms and diabetes. *JAMA* 2008;299:2751–2759
- Nouwen A, Winkley K, Twisk J, et al. Type 2 diabetes mellitus as a risk factor for the onset of depression: a systematic review and meta-analysis. *Diabetologia* 2010;53:2480–2486
- Ismail K. Unraveling the pathogenesis of the depression-diabetes link. In *Depression and Diabetes*. Katon W, Maj M, Sartorius, N, Eds. Chichester, Wiley-Blackwell, 2010, p. 29–61
- Dowlati Y, Herrmann N, Swardfager W, et al. A meta-analysis of cytokines in major depression. *Biol Psychiatry* 2010;67:446–457
- Simon NM, McNamara K, Chow CW, et al. A detailed examination of cytokine abnormalities in major depressive disorder. *Eur Neuropsychopharmacol* 2008;18:230–233
- Lamers F, Vogelzangs N, Merikangas KR, de Jonge P, Beekman AT, Penninx BW. Evidence for a differential role of HPA-axis function, inflammation and metabolic syndrome in melancholic versus atypical depression. *Mol Psychiatry* 2013;18:692–699
- Pickup JC, Mattock MB, Chusney GD, Burt D. NIDDM as a disease of the innate immune system: association of acute-phase reactants and interleukin-6 with metabolic syndrome X. *Diabetologia* 1997;40:1286–1292
- Fernández-Real JM, Pickup JC. Innate immunity, insulin resistance and type 2 diabetes. *Diabetologia* 2012;55:273–278
- Kaptoge S, Di Angelantonio E, Lowe G, et al.; Emerging Risk Factors Collaboration. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. *Lancet* 2010;375:132–140
- Thorand B, Löwel H, Schneider A, et al. C-reactive protein as a predictor for incident diabetes mellitus among middle-aged men: results from the MONICA Augsburg cohort study, 1984–1998. *Arch Intern Med* 2003;163:93–99
- Pickup JC. Inflammation and activated innate immunity in the pathogenesis of type 2 diabetes. *Diabetes Care* 2004;27:813–823
- Pickup JC, Mattock MB. Activation of the innate immune system as a predictor of cardiovascular mortality in type 2 diabetes mellitus. *Diabet Med* 2003;20:723–726
- Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med* 2002;347:1557–1565
- Rajagopalan S, Brook R, Rubenfire M, Pitt E, Young E, Pitt B. Abnormal brachial artery flow-mediated vasodilation in young adults with major depression. *Am J Cardiol* 2001;88:196–198, A7
- Hartwell KJ, Moran-Santa Maria MM, Twal WO, et al. Association of elevated cytokines with childhood adversity in a sample of healthy adults. *J Psychiatr Res* 2013;47:604–610
- Duivis HE, Kupper N, Penninx BW, Na B, de Jonge P, Whooley MA. Depressive symptoms and white blood cell count in coronary heart disease patients: prospective findings from the Heart and Soul Study. *Psychoneuroendocrinology* 2013;38:479–487
- Zeugmann S, Quante A, Heuser I, Schwarzer R, Anghelescu I. Inflammatory biomarkers in 70 depressed inpatients with and without the metabolic syndrome. *J Clin Psychiatry* 2010;71:1007–1016
- 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
- Winkley K, Thomas SM, Sivaprasad S, et al. The clinical characteristics at diagnosis of type 2 diabetes in a multi-ethnic population: the South London Diabetes cohort (SOUL-D). *Diabetologia* 2013;56:1272–1281
- World Health Organization. Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus [article online], 2011. Available from http://www.who.int/diabetes/publications/report-hba1c_2011.pdf. Accessed 13 April 2013
- Leo R, Di Lorenzo G, Tesaro M, et al. Decreased plasma adiponectin concentration in major depression. *Neurosci Lett* 2006;407:211–213
- Kadowaki T, Yamauchi T, Kubota N, Hara K, Ueki K, Tobe K. Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. *J Clin Invest* 2006;116:1784–1792
- Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. *Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire*. *JAMA* 1999;282:1737–1744
- Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001;16:606–613
- Twist K, Stahl D, Amiel SA, Thomas S, Winkley K, Ismail K. Comparison of depressive symptoms in type 2 diabetes using a two-stage survey design. *Psychosom Med* 2013;75:791–797
- Steel DM, Whitehead AS. The major acute phase reactants: C-reactive protein, serum amyloid P component and serum amyloid A protein. *Immunol Today* 1994;15:81–88
- Ayuso-Mateos JL, Vázquez-Barquero JL, Dowrick C, et al.; ODIN Group. Depressive disorders in Europe: prevalence figures from the ODIN study. *Br J Psychiatry* 2001;179:308–316
- Ciechanowski PS, Katon WJ, Russo JE. Depression and diabetes: impact of depressive symptoms on adherence, function, and costs. *Arch Intern Med* 2000;160:3278–3285
- Katon WJ, Lin EHB, Von Korff M, et al. Collaborative care for patients with depression and chronic illnesses. *N Engl J Med* 2010;363:2611–2620
- Ismail K, Winkley K, Stahl D, Chalder T, Edmonds M. A cohort study of people with diabetes and their first foot ulcer: the role of depression on mortality. *Diabetes Care* 2007;30:1473–1479
- Arend WP. The balance between IL-1 and IL-1Ra in disease. *Cytokine Growth Factor Rev* 2002;13:323–340
- Villarreal-Molina MT, Antuna-Puente B. Adiponectin: anti-inflammatory and cardioprotective effects. *Biochimie* 2012;94:2143–2149
- American Diabetes Association. Standards of medical care in diabetes—2013. *Diabetes Care* 2013;36(Suppl. 1):S11–S66