The Prospective Association Between Inflammation and Depressive Symptoms in Type 2 Diabetes Stratified by Sex

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OBJECTIVE

We tested whether inflammation is associated with worsening depressive symptoms in type 2 diabetes and examined whether sex moderated this association.

RESEARCH DESIGN AND METHODS

In a prospective cohort study of people with newly diagnosed type 2 diabetes, we measured depressive symptoms over a 2-year follow-up using the Patient Health Questionnaire-9 (PHQ-9). The independent variable was a composite inflammation burden score at diagnosis of diabetes, derived from hs-CRP, white cell count, interleukin (IL)-1β, IL-1 receptor antagonist, monocyte chemotactic protein-1, and vascular endothelial growth factor concentrations. General linear models assessed *1*) the association between overall inflammation burden and estimated marginal mean PHQ-9 score (ln transformed) at 2 years and *2*) whether sex interacted with elevated inflammation burden (above-median score) in predicting change in PHQ-9 score. Models were adjusted for age, ethnicity, BMI, blood pressure, cholesterol, HbA_{1c}, antidepressants, anti-inflammatory medications, and baseline ln PHQ-9 score.

RESULTS

Of 1,174 people with complete inflammation data, mean (SD) age was 56.7 (11.0) years and 46.1% were of nonwhite ethnicity and 44.1% female. After full adjustment, inflammation burden was not associated with worsening ln PHQ-9 score (P = 0.65). However, female sex interacted with elevated inflammation in predicting higher 2-year ln PHQ-9 score (β = 0.32, P = 0.005), showing that the difference by inflammation burden in females was 0.32 larger than in males. In post hoc comparisons, ln PHQ-9 score was higher in females than males with elevated inflammation (P = 0.003) but not with low inflammation (P = 0.34) burden.

CONCLUSIONS

In type 2 diabetes, female sex confers specific vulnerability to the effects of inflammation on depressive symptoms.

Depressive symptoms are reported by 10–30% of people with type 2 diabetes—twice as often as in the general population—and are associated with 1.5- to 3.0-fold increased frequency of diabetes complications and premature mortality (1–3). A psychological model for the association is that depressive symptoms reflect the burden of diabetes and depressive symptoms, in turn leading to poor diabetes outcomes through poor self-care (4). This model, however, provides limited

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opportunities to understand disease mechanisms and improve outcomes. For example, in cohort studies, depressive symptoms are not always associated with worsening in glycemic control over time (5), suggesting that depression does not consistently lead to worsening diabetes self-care. In neuroimaging research, the brain changes typical of depression—such as hippocampal atrophy—mirror those seen in type 2 diabetes (6,7). Moreover, the link is bidirectional: whereas type 2 diabetes is associated with increased risk of incident depressive symptoms, the converse association is even stronger (8).

A unifying explanation for these observations is that depressive symptoms and type 2 diabetes are not distinct conditions but, rather, may be linked by shared disease mechanisms, such as elevated inflammation (9). In support of this, proinflammatory cytokines and elevated acute phase proteins are associated with onset of depression and type 2 diabetes, respectively (10,11), while some anti-inflammatory therapies have demonstrated benefit in the two conditions separately (12,13). To date, research testing inflammation as a link between depression and type 2 diabetes has been scarce. In cross-sectional studies in people with type 2 diabetes, those with comorbid depressive symptoms had higher concentrations of acute-phase proteins and cytokines, even after adjustment for confounders such as BMI, smoking, and age (14–16). However, no prospective cohort study has tested the association between inflammation and the course of depressive symptoms over time in people with type 2 diabetes, so potential causality cannot yet be inferred.

Like depressive symptoms, female sex is associated with increased risk of cardiovascular complications in people with type 2 diabetes, even accounting for sex differences in other major cardiovascular risk factors (17). Depressive symptoms are also nearly twice as prevalent in females as in males with established type 2 diabetes (18). In depression research, female sex appears to increase vulnerability to the effects of inflammation on the brain (19), and anti-inflammatory diabetes treatments may improve depressive symptoms more significantly in females (20). Collectively, this suggests that inflammation could lead predominantly to depressive symptoms in females with type 2 diabetes and, further, could provide an explanation for the poor overall prognosis of diabetes in females.

Using an incident type 2 diabetes cohort, we therefore aimed to test the hypotheses that elevated inflammation is associated with worsening depressive symptoms in people with type 2 diabetes and, secondly, that this association is stronger in females than in males.

RESEARCH DESIGN AND METHODS

Setting and Study Design

The South London Diabetes (SOUL-D) study is a population-based prospective cohort of people with newly diagnosed type 2 diabetes recruited within 6 months of diagnosis and followed over 2 years (21). The study was set in the inner-city boroughs of Lambeth, Southwark, and Lewisham in South London, which collectively have ~0.75 million residents from diverse ethnic and socioeconomic backgrounds. All general practices (GPs) in these boroughs were invited to participate. Local protocols for diagnosis of type 2 diabetes followed World Health Organization criteria (22). Ethics 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). All participants gave written informed consent, including for access to their medical records. Details of inclusion criteria and recruitment timetable have previously been published (21).

Outcome

The outcome at 2-year follow-up was depressive symptoms, as measured by total Patient Health Questionnaire-9 (PHQ-9) score. Due to positive skew, we ln transformed PHQ-9 scores. As discussed previously, the PHQ-9 is a nine-item questionnaire based on the DSM-IV diagnostic criteria for clinical depression, which has been validated for use in people with type 2 diabetes (23). Missing PHQ-9 data (where <20% of responses were missing) were imputed using case mean substitution, discussed in detail previously (5).

Independent Variable

The independent variable was a composite measure of inflammation burden based on six markers of inflammation: hs-CRP, interleukin-1β (IL-1β), IL-1 receptor antagonist (IL-1RA), monocyte chemotactic protein-1 (MCP-1), vascular endothelial growth factor (VEGF), and white blood cell count (WBC). As well as measuring a range of inflammatory pathways—including acute-phase, cytokine, and chemokine responses—these markers were selected because of their positive individual associations with depressive symptoms in the baseline SOUL-D cohort (14). As in previous research (24), a composite inflammation burden score was calculated by transforming each measure into a z-distribution, with mean 0 and SD 1, before averaging the individual biomarker *z* scores. This approach minimizes multiple testing and reduces the influence of the biological variability of each measure. Serum hs-CRP was measured using an Advia 2400 analyzer (Siemens Diagnostics, Frimley, U.K.) with detection limit 0.1 mg/L; WBC was measured using an Advia 2120 analyzer (Siemens Diagnostics); and IL-1β, IL-1RA, VEGF, and MCP-1 were measured from serum samples centrifuged from venous blood samples taken after an overnight fast, 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.

Confounders

We considered the following potential confounders a priori: age, ethnicity (white vs. nonwhite), BMI, blood pressure, smoking status, HbA_{1c} (measured by affinity chromatography [Primus Ultra2; Primus Corporation, Kansas City, KS]), serum total cholesterol (measured using the Siemens Advia 2400 Analyzer, detection limit 0.01 mmol/L), and prescription of any anti-inflammatory medications (systemic steroids, nonsteroidal anti-inflammatory drugs [NSAIDs]), and antidepressant medications.

Statistical Analyses

Baseline Analysis

Data were analyzed using IBM SPSS, version 25.0. We compared the following baseline characteristics of the cohort stratified by low or elevated inflammation burden at baseline:

sociodemographic variables (age, self-report ethnicity [African/Caribbean, white, South Asian/other]), baseline biomedical variables (smoking status, total cholesterol, BMI, HbA_{1c}, inflammatory markers, anti-inflammatory medications, antidepressant medications, blood pressure, inflammatory marker concentrations), and baseline PHQ-9 score. For continuous variables, we used Student *t* test for normally distributed data and the Mann-Whitney *U* test for skewed data, and for categorical variables we used χ^2 tests. Results were presented as mean (SD) or median (interquartile range) for skewed data, unless otherwise stated. Compared with those included in the analysis, we assessed the characteristics of people missing inflammation data at baseline.

Prospective Association Between Inflammation Burden and Depressive Symptoms

The prospective analysis comprised unadjusted and adjusted general linear models in which the outcome was 2-year PHQ-9 score (ln transformed). We firstly tested whether elevated inflammation burden (total inflammation *z* score) was associated with elevated PHQ-9 score at follow-up in the whole cohort after adjustment for baseline PHQ-9 score. We next adjusted the model for the range of potential confounders. Associations were reported using the standardized β-coefficient and its associated *P* value.

Interaction Between Inflammation and Sex on Course of Depressive Symptoms

We next used general linear models to test the interaction between sex and inflammation burden on 2-year PHQ-9 score. We firstly measured the β-coefficient of the interaction, which presents the difference in PHQ-9 score between low and elevated inflammation status in females compared with males. We next interrogated the directionality of any interaction using the estimated marginal mean (EMM) difference in PHQ-9 score at follow-up by comparing the differences in PHQ-9 score between females and males within the low and elevated inflammation groups. EMMs are presented at mean values for each covariate (rather than resetting them to 0, as in linear regression models), which provides a clinically relevant measure of the association between inflammation and depression course in a typical patient (in this case, a patient with average baseline depression score and average score or average proportion for other covariates and categorical variables, respectively). The unadjusted interaction model comprised the outcome 2-year PHQ-9 score (ln transformed) and the independent variables of sex, inflammation status, sex * inflammation status, and baseline PHQ-9 score. We next adjusted the model for the full range of confounders. Interactions were also displayed graphically.

Sensitivity Analyses

To account for missing data, we performed multiple imputation analyses with 20 multiply imputed data sets. Incomplete variables were imputed under fully conditional specification using an iterative Markov chain Monte Carlo estimation method. All variables were included in the imputation process, including interactions between PHQ-9 score (ln transformed) and sex at both time points. The parameters of interest were estimated in each imputed data set separately and combined using Rubin's rules (25). Finally, to account for participants who may have had elevated inflammation due to an acute infection, we conducted a further sensitivity analysis excluding those with hs-CRP concentration >10 mg/L at baseline (26).

RESULTS

Ninety-six of 136 (70.6%) GPs agreed to participate. From their diabetes registers, a target population of 3,008 patients with newly diagnosed type 2 diabetes was identified, of whom 2,406 people were potentially eligible and invited to participate—of whom 1,735 people consented. Of these, 1,174 (67.7%) provided complete data on all six inflammatory markers and were included in the current analysis. The mean (SD) age of this subset was 56.7 (11.0) years, 44.1% were female, and 46.1% were of nonwhite ethnicity.

Compared with those included in the analysis, those with missing inflammation data were younger (mean [SD] age 55.0 [11.0] vs. 56.7 [11.0] years, P = 0.003); had slightly higher BMI (32.5 [6.7] vs. 31.8 [6.4] kg/m^2, P = 0.032), slightly lower total cholesterol (4.50 [1.1] vs. 4.62 [1.1] mmol/L, P = 0.044), and higher baseline depressive symptoms (median 3 [interquartile range 1–7] vs. 2 [0–6], P = 0.009); were more often of nonwhite ethnicity (65.0% vs. 48.7%, $P < 0.001$) and smokers at baseline (24.5% vs. 19.0%, P = 0.011); and were less likely to be prescribed NSAIDs/steroids (23.2% vs. 30.0%, P = 0.003), or antidepressants at baseline (1.2% vs. 7.3%, $P < 0.001$). However, there were no differences in proportion of female sex (P = 0.14), baseline HbA_{1c} (P = 0.21), systolic blood pressure (P = 0.47), or diastolic blood pressure (P = 0.89) (test statistics not shown).

Baseline Comparisons

Compared with those with low inflammation burden, people with elevated inflammation burden were older, had higher BMI, higher total cholesterol, higher hs-CRP, higher baseline PHQ-9 score, were more often of African/Caribbean ethnicity than white, were more often smokers at baseline, and were more often prescribed antidepressant medication. There were no differences by inflammation burden in sex, South Asian ethnicity, blood pressure, glycemic control, and prescription of anti-inflammatory medication (Table 1).

Follow-up

A total of 803 (68.4%) of people provided both inflammation and 2-year PHQ-9 data. Compared with those followed up, people with missing data were younger (mean [SD] age 55.1 [11.6] vs. 57.4 [10.7] years, P = 0.001), more likely to be female (49.1% vs. 41.8%, P = 0.021), more likely to be of nonwhite ethnicity (52.8% vs. 43.0%, P = 0.002), more likely to have low inflammation burden (56.1% vs. 46.6%, P = 0.002), had higher baseline HbA_{1c} (mean [SD] 7.14% [1.5%] vs. 6.90% [1.4%], P = 0.006), and had higher baseline diastolic blood pressure (84.0 [11.2] vs. 82.6 [10.4] mmHg, P = 0.04). However, there were no differences by attrition in proportion of smokers (P = 0.64), prescription of NSAIDs/steroids at baseline (P = 0.34), prescription of antidepressants at baseline (P = 0.73), baseline BMI (P = 0.13), baseline systolic blood pressure (P = 0.55), baseline total cholesterol (P = 0.98) or baseline total PHQ-9 score (P = 0.84) (test statistics not shown).

Table 1—Baseline characteristics of the SOUL-D cohort stratified by inflammation burden at baseline

Variable	Total cohort[a]	Elevated inflammation burden (n = 592)[a]	Low inflammation burden (n = 582)[a]	P[b]
Sociodemographic variables				
Age, years	56.7 (11.0)	57.6 (10.9)	55.7 (11.0)	0.003
Sex, *n* (%)				
Male	656 (55.9)	323 (54.6)	333 (57.2)	—
Female	518 (44.1)	269 (45.4)	249 (42.8)	0.36
Ethnicity, *n* (%)				
White	633 (54.0)	394 (66.6)	239 (41.1)	—
African/Caribbean	417 (35.5)	124 (20.9)	293 (50.3)	<0.001[c]
South Asian/other	124 (10.6)	74 (12.5)	50 (8.6)	0.59[c]
Baseline vascular risk factors				
Smoking status, *n* (%)				
Smoker	216 (18.9)	152 (26.3)	64 (11.4)	—
Nonsmoker	924 (81.1)	427 (73.7)	497 (88.6)	<0.001
BMI, kg/m^2	31.8 (6.4)	32.6 (6.8)	30.9 (5.8)	<0.001
Systolic BP, mmHg	136.1 (17.4)	136.3 (17.5)	136.0 (17.3)	0.78
Diastolic BP, mmHg	83.0 (10.5)	83.1 (10.6)	82.8 (10.4)	0.61
HbA_{1c}, %	6.98 (1.4)	7.02 (1.4)	6.91 (1.4)	0.35
HbA_{1c}, mmol/mol	52.8 (10.6)	53.2 (10.6)	52.0 (10.5)	0.35
Total cholesterol, mmol/L	4.62 (1.1)	4.70 (1.1)	4.53 (1.0)	0.007
Baseline inflammatory variables				
Prescribed NSAIDs/opioids, *n* (%)				
Yes	348 (30.0)	187 (31.9)	161 (28.0)	—
No	814 (70.0)	400 (68.1)	414 (72.0)	0.15
hs-CRP	2.7 (1.1–6.3)	4.6 (1.9–9.0)	1.6 (0.8–3.9)	<0.001
IL-1β	1.02 (0.73–1.87)	1.16 (0.79–2.64)	0.91 (0.69–1.54)	<0.001
IL-1RA	437.0 (290.0–695.8)	620.2 (399.4–916.0)	323.8 (223.1–473.4)	<0.001
MCP-1	102.3 (59.6–152.2)	138.7 (92.3–189.2)	72.3 (49.9–109.9)	<0.001
VEGF	76.0 (45.6–118.1)	114.4 (82.1–163.7)	48.9 (33.1–71.7)	<0.001
WBC	7.6 (6.4–9.0)	8.6 (7.4–10.1)	6.7 (5.7–7.7)	<0.001
Baseline psychological variables				
PHQ-9 score	2 (0–6)	3 (1–7)	2 (0–6)	<0.001
Prescribed antidepressants, *n* (%)				
Yes	84 (7.2)	53 (8.9)	31 (5.3)	—
No	1,089 (92.8)	538 (91.1)	551 (94.7)	0.016

BP, blood pressure. [a]Inflammation burden comprises baseline concentrations of WBC, IL-1β, IL-1RA, hs-CRP, MCP-1, and VEGF. Each concentration is z-transformed, and all six measures are averaged to calculate an overall score. This is split by the median value to define elevated and low inflammation burden. [b]Parametric continuous data are presented as mean (SD) and compared using Student *t* test; nonparametric continuous data are presented as median (interquartile range) and compared using Mann-Whitney *U* test; categorical variables are presented as frequency, *n* (%), and compared using χ^2 tests. [c]Compared with white ethnicity.

Prospective Association Between Inflammation Burden and Course of Depressive Symptoms

Before or after full adjustment, there was no association between inflammation burden at baseline and higher PHQ-9 score at 2 years in the whole cohort (Table 2).

Unadjusted Interaction Between Inflammation Burden and Sex on Course of Depressive Symptoms

In the unadjusted general linear model, female sex interacted significantly with elevated inflammation burden in predicting higher PHQ-9 score (β = 0.36, P = 0.001), meaning that the difference between low and elevated inflammation status was 0.36 larger in females compared with males (Table 2). A post hoc analysis of the interactions revealed no differences in depressive symptoms between males and females with low inflammation burden (EMM difference = 0.07, P = 0.37), while depressive symptoms were significantly higher in females than males in the subgroup with elevated inflammation burden (EMM difference = 0.29, $P < 0.001$) (Table 3 and Fig. 1*A*).

Adjusted Interaction Between Inflammation Burden and Sex on Depressive Symptoms

After adjustment for the full range of confounders, including baseline depressive symptoms, the interaction remained significant (β = 0.32, P = 0.005): the difference between low and elevated inflammation burden in females was 0.32 larger than in males (Table 2). Post hoc pairwise comparisons again showed that there was no significant difference between males and females in the low inflammation group (EMM difference = 0.08, P = 0.34), whereas females had higher depressive symptoms than males in the elevated inflammation group (EMM difference = 0.23, P = 0.003), conditioned on average values of covariates (Table 3 and Fig. 1*B*).

Sensitivity Analyses

Using multiple imputation for missing data did not alter the conclusions: the unadjusted interaction (β = 0.36, $P < 0.001$) and fully adjusted interaction (β = 0.31, $P < 0.001$) between female sex and elevated inflammation remained strongly significant. Supplementary

Table 2—Multivariate analysis testing the associations among inflammation burden, sex, and 2-year depressive symptoms in the SOUL-D cohort

Independent variables	Adjusted for baseline PHQ-9 score only	Fully adjusted[a]
Model 1: inflammation as independent variable		
Overall inflammation burden, continuous	0.05 (−0.03 to 0.14), P = 0.23	0.02 (−0.07 to 0.11), P = 0.65
Inflammation burden, binary (1 = elevated, 0 = low)	0.09 (−0.02 to 0.19), P = 0.11	0.06 (−0.05 to 0.18), P = 0.30
Model 2: inflammation, sex, and their interaction as independent variables		
Inflammation burden (1 = elevated, 0 = low)	−0.06 (−0.20 to 0.08), P = 0.37	−0.07 (−0.22 to 0.08), P = 0.35
Sex (1 = female, 0 = male)	−0.07 (−0.23 to 0.09), P = 0.37	−0.08 (−0.25 to 0.09), P = 0.34
Interaction (female sex ∗ elevated inflammation burden)	0.36 (0.15–0.57), P = 0.001	0.32 (0.10–0.53), P = 0.005
Total number in model	797	706

Data are β (95% CI), P value, unless otherwise indicated. Multivariable general linear models with outcome 2-year PHQ-9 score (ln transformed). Reference groups are low inflammation burden, male sex, and low inflammation ∗ male sex. [a]Adjusted for baseline PHQ-9 score (log transformed), age, nonwhite ethnicity, BMI, baseline systolic blood pressure, baseline smoking status, baseline serum cholesterol, baseline HbA_{1c}, prescription of anti-inflammatory medication, and prescription of antidepressant medication.

Table 1 shows the full breakdown of unadjusted and adjusted interactions after multiple imputation. Exclusion of the 147 people with baseline hs-CRP >10 mg/L—potentially indicating acute infection—likewise did not alter the conclusions: the fully adjusted interaction remained significant (β = 0.31, P = 0.009), and females had higher depressive symptoms than males in the subgroup with elevated inflammation (EMM difference = 0.24, P = 0.007).

CONCLUSIONS

In a prospective cohort study of people with newly diagnosed type 2 diabetes recruited from primary care, elevated inflammation at diagnosis of type 2 diabetes—as estimated using a composite measure of acute-phase, cytokine, and chemokine markers—was not associated with worsening depressive symptoms over 2 years. However, elevated inflammation burden was associated with greater worsening depressive symptoms in females compared with males. These findings remained robust to adjustment for a range of proinflammatory and anti-inflammatory confounders, including BMI and smoking status.

Comparison With Previous Literature

Depressive symptoms are commonly reported in people with type 2 diabetes and are associated with poor biomedical outcomes (1,2). In addition to psychological and behavioral factors, there is increasing evidence that biological mechanisms may provide a link between depressive symptoms and type 2 diabetes. In particular, previous studies have demonstrated a cross-sectional association between elevated inflammation and depressive symptoms in people with type 2 diabetes (14,15), although no cohort study has tested this prospectively. Our study therefore marks a clear advance in the literature by demonstrating that inflammation is associated with preferential worsening in depressive symptoms in females compared with males with type 2 diabetes.

Although depressive symptoms are nearly twice as prevalent in females with type 2 diabetes compared with males (18), the reasons for this predominance are poorly understood. A possible explanation is that females are more likely to report depressive symptoms than males, for example, due to different social processes influencing presentation of psychological distress for the different sexes. However, this is not supported by the similar reporting of depressive symptoms between males and females with low burden of inflammation in our study. Likewise, adjustment for increased BMI—another possible reason

Table 3—General linear models testing the sex differences in 2-year depressive symptoms stratified by low and high inflammation burden in the SOUL-D cohort

	(I) Sex	(J) Sex	Mean difference (I − J)	SE	P value	95% CI lower bound	95% CI upper bound
Pairwise comparisons between males and females within low and elevated inflammation groups: adjusted for baseline depressive symptoms only[a]							
Low inflammation burden	Male	Female	−0.07	0.08	0.37	−0.23	0.09
Elevated inflammation burden	Male	Female	−0.29	0.07	<0.001	−0.43	−0.14
Pairwise comparisons between males and females within low and elevated inflammation groups: fully adjusted[b]							
Low inflammation burden	Male	Female	0.08	0.09	0.34	−0.09	0.25
Elevated inflammation burden	Male	Female	−0.23	0.08	0.003	−0.39	−0.08

Outcome is EMM PHQ-9 score (ln transformed) at 2 years. [a]Adjusted only for baseline PHQ-9 score (ln transformed). [b]Adjusted for baseline PHQ-9 score (ln transformed), age, nonwhite ethnicity, BMI, baseline systolic blood pressure, baseline smoking status, baseline serum cholesterol, baseline HbA_{1c}, prescription of anti-inflammatory medication, and prescription of antidepressant medication.

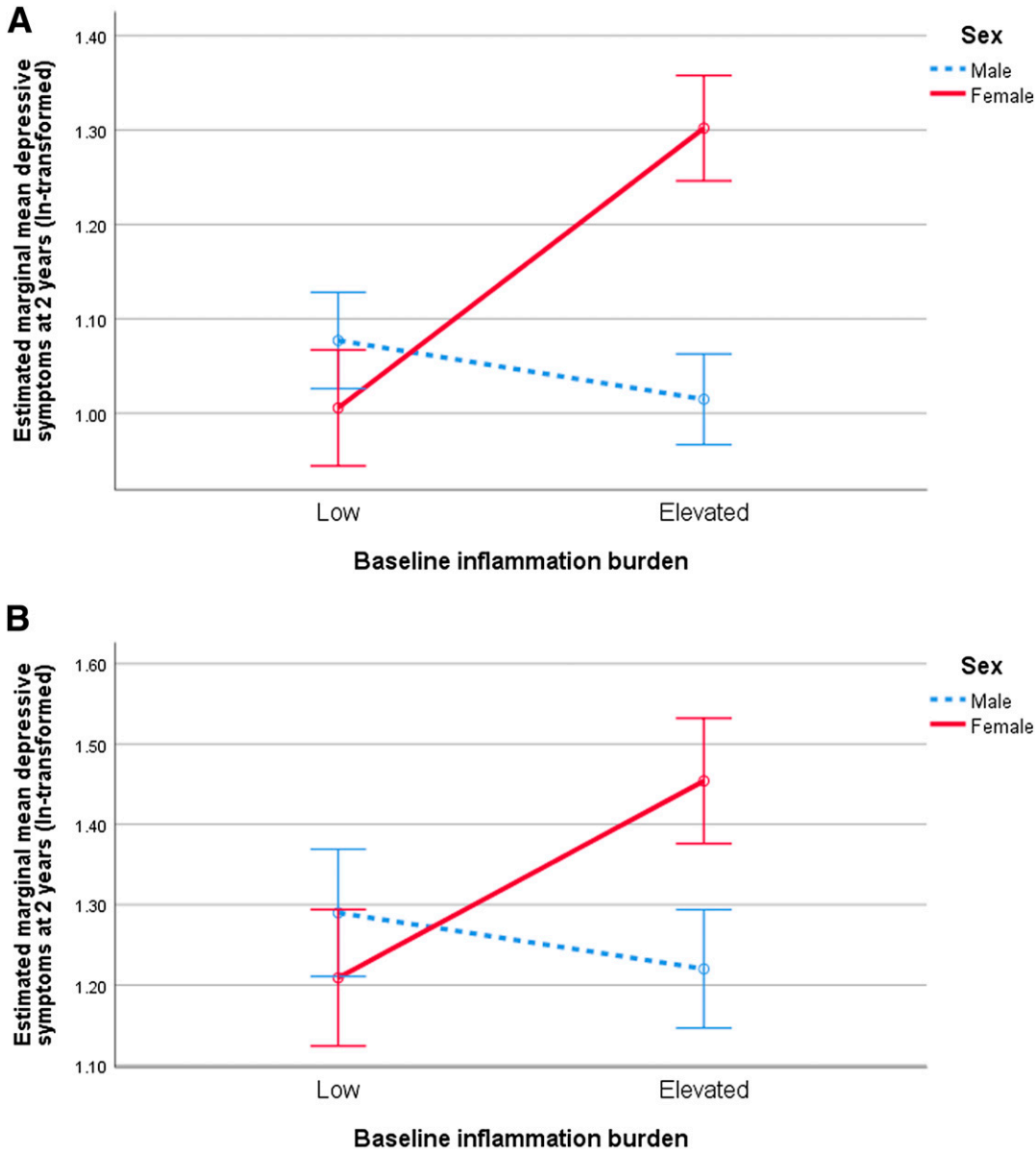

Figure 1—General linear model testing the interaction between sex and inflammation burden on the 2-year course of depressive symptoms in the SOUL-D cohort. *A*: Adjusted only for baseline depressive symptoms. Baseline PHQ-9 score (ln-transformed) is entered into the model at the mean value of 1.19. Error bars: ±1 SE of the mean. *B*: Adjusted for baseline depressive symptoms and the full range of confounders. Nonwhite ethnicity, smoking status, anti-inflammatory medications, and antidepressant medications are entered into the model as fixed factors. Covariates are evaluated at the following mean values: baseline PHQ-9 score (ln-transformed) = 1.17, age = 57.6 years, BMI = 31.6 kg/m^2, systolic blood pressure = 135.9 mmHg, total cholesterol = 4.61 mmol/L, HbA_{1c} = 6.90%. Error bars: ±1 SE of the mean.

for female vulnerability to depression (27)—did not attenuate our findings.

Echoing prospective findings from the general population (28,29), our results suggest that worse depressive symptoms in females with type 2 diabetes could result from elevated inflammation. This is likely to occur through dialogue with dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis. Specifically, activation of the HPA axis by stress should normally lead to an increase in glucocorticoid sensitivity, enabling cortisol to inhibit and thus regulate inflammatory responses. Whereas males demonstrate this response consistently, stress appears to exert the opposite effect in females, leading to decreased glucocorticoid sensitivity and exaggerated inflammatory responses (30). Notably, females in our sample were typically of postmenopausal age, by which time HPA axis dysfunction has become most pronounced, probably due to loss of modulation by gonadal steroids (31). The presence of a dysfunctional HPA axis thereby exposes females to exaggerated effects on inflammation, leading to increased risk of cardiovascular disease in the periphery and potentially an increased risk of depression centrally (32,33). Central effects may occur through proinflammatory cytokines activating the enzyme indoleamine 2,3-dioxygenease, which diverts tryptophan metabolism from serotonin

toward neurotoxic metabolites in the brain (33).

Interpretation

Our findings suggest that depressive symptoms and female sex—both poor prognostic factors in type 2 diabetes—are biologically linked by inflammation. The result is an "inflammatory depression" that predominantly affects females, runs a persistent course, and is poorly explained by lifestyle factors such as smoking and obesity. Both female sex and inflammation are strongly associated with cardiovascular risk in type 2 diabetes (17,32), and notably the typical hs-CRP concentration for the elevated inflammation group in our study was in the range for high cardiovascular risk (26). As such, the inflammatory depression of type 2 diabetes in females could be an important and potentially modifiable biomarker of future cardiovascular disease and mortality, which requires testing over longer-term follow-up.

Therapeutically, the strong association between female sex and inflammation suggests a need to "gender" therapy toward reducing the burden of inflammation in females. For example, in managing depression, elevated innate inflammation is associated with poor response to the usual first-line antidepressants: selective serotonin reuptake inhibitors (34). In females with depressive symptoms, clinicians may therefore consider proactive switching to antidepressants that have greater anti-inflammatory properties, such as tricyclic antidepressants (34). Likewise, within the repertoire of current diabetes treatments, females with type 2 diabetes could be treated earlier with therapies known to have greater anti-inflammatory properties. For example, incretin-based therapies and thiazolidinediones have potent effects on inflammation (35,36) and could even be a novel treatment for depression by modifying inflammation (20).

Our results support future trials of anti-inflammatory agents for depressive symptoms in type 2 diabetes. In the general population, anti-inflammatory and HPA axis–modifying therapies have demonstrated inconsistency in improving depressive symptoms (12,37), and our findings suggest that benefit would be maximized by specifically recruiting females to such clinical trials. Future experimental medicine studies are needed to profile the dynamic immune responses conferring vulnerability to female depressive symptoms in type 2 diabetes, thereby providing clearer targets for interventional studies. A better understanding of the bidirectional interplay between the HPA axis and inflammation is required, including factors predisposing one to HPA axis dysfunction, such as changes in gonadal hormones. Finally, life course epidemiological research is needed to delineate the temporal relationship between inflammation, depression, and type 2 diabetes, as well as possible upstream etiologies such as stressful life events.

Strengths and Limitations

Our study is strengthened by its unique multiethnic and socioeconomically diverse cohort, which is representative of the global type 2 diabetes population. By virtue of recruiting all patients within 6 months of diagnosis of type 2 diabetes, confounding effects of diabetes complications on inflammation and depression were minimized. A composite measure of inflammation that included acute-phase, cytokine, and chemokine responses provided a broad yet rigorous test of inflammation. Our data were limited by 32% missing values for inflammation burden at baseline, although there were no sex differences between those missing data and those included. Although a similar attrition rate over 2 years is a further limitation of our study, maximizing follow-up is particularly challenging in an urban population with high rates of social deprivation, multimorbidity, geographical mobility, and a primary care setting in which several GPs closed during the study. Furthermore, multiple imputation of missing data resulted in no significant changes to the study findings. We did not assess for periodontitis, which could be an important cause of inflammation, depression, and type 2 diabetes (38,39). We measured depressive symptoms continuously using a validated self-report questionnaire, which will likely overidentify depressive symptoms compared with a diagnostic interview. However, there is strong evidence that subthreshold depressive symptoms are prognostically important in people with diabetes (40). Finally, longer follow-up is needed to confirm the persistence of inflammatory depression in females, as well as associated biomedical sequelae.

Summary

In the early stages of type 2 diabetes, inflammation shows no overall association with worsening of depressive symptoms over 2-year follow-up. However, inflammation demonstrates a preferential association with worsening depressive symptoms in females compared with males, which is not explained by potential confounders such as obesity. Future studies should test whether inflammation is a modifiable target for reducing the sex gap in psychological and biomedical outcomes in people with type 2 diabetes.

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