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Depressive Symptoms, Antidepressant Medication Use, and Inflammatory Markers in the Diabetes Prevention Program

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Abstract

Objective—Antidepressant medication use (ADM) has been shown to predict diabetes. This paper assessed the role of inflammatory markers in this relationship within the Diabetes Prevention Program (DPP).

Methods—DPP participants randomized to Metformin (MET), Lifestyle Intervention (ILS) or placebo (PLB) were assessed for depression (BDI; Beck Depression Inventory) annually; ADM use semi-annually; serum inflammatory markers (CRP, IL-6) at baseline and Year 1; and diagnosis of T2DM semi-annually (over 3.2 years).

Results—At baseline (N=3,187), mean BMI was 34 kg/m^2 (S.D. 6) and the median BDI score was 3 [interquartile range: 1–7]. 181 (5.7%) reported ADM use and 328 (10%) had BDI scores of ≥11. CRP and IL-6 levels did not differ by treatment group.

Baseline ADM, but not BDI score, was associated with higher levels of baseline CRP adjusted for demographic, anthropometric variables, and other medications (20% higher, p=0.01). Year 1 CRP decreased for non-ADM users in the MET (−13.2%) and ILS (−34%) groups and ADM users in the ILS group (−29%). No associations were found with IL-6.

CRP and continuous use of ADM predicted incident T2DM in the PLB group. In the ILS group, continuous and intermittent ADM, but not CRP, predicted T2DM. In the MET group, CRP predicted incident T2DM. CRP did not mediate the risk of T2DM with ADM use in any group.

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Conclusions—ADM was significantly associated with elevated CRP and incident T2DM. In the PLB group, ADM and CRP independently predicted onset of T2DM, however CRP did not significantly mediate the effect of ADM.

Keywords

Depression; antidepressant medications; inflammatory markers; diabetes

INTRODUCTION

Clinically significant depressive symptoms affect one in four adults with diabetes [1]. Among persons with type 2 diabetes (T2DM), elevated depressive symptoms are associated with hyperglycemia [2], increased severity of diabetes complications [3–4], worsened medication adherence [5–7], higher medical costs [8], increased functional disability [9–10], and early mortality [11–12].

A bidirectional relationship between diabetes and depression as a clinical syndrome has been documented, in which lifetime history of diagnosed depression confers a 37–60% increased risk for the development of T2DM [13–17]. Two recent studies have demonstrated predictive relationships between antidepressant medication (ADM) use and depressive symptoms to the onset of T2DM. The Women's Health Initiative evaluated the contribution of ADM use and depressive symptoms as predictors of incident T2DM [18]. Both elevated depressive symptoms and ADM use were associated with increased incidence of T2DM.

The Diabetes Prevention Program (DPP) documented antidepressant medication (ADM) use at study entry as a risk factor for the onset of type 2 diabetes (T2DM) among participants randomized to placebo (PLB) and lifestyle intervention (ILS) group arms [19, 20]. Intermittent or continuous antidepressant medication exposure also predicted onset of T2DM in the ILS arm when adjusted for covariates (race/ethnicity, age, sex, education, fasting plasma glucose at baseline, weight at baseline and weight change during the study). These relationships were not observed in the metformin (MET) arm. Depressive symptoms, measured using the Beck Depression Inventory (BDI), did not predict the onset of T2DM in any of the treatment groups.

One potential explanatory mechanism for the observed predictive relationship between antidepressant medications, depressive symptoms and the onset of T2DM is chronic, low-grade systemic inflammation. Inflammatory markers such as C-reactive protein (CRP) and interleukin-6 (IL-6) have been shown to be associated with BMI and weight loss in those at-risk for the development of diabetes [21]. In the DPP cohort, CRP levels differed by type of diabetes prevention intervention and sex over a 12-month follow-up period [22]. CRP has also been shown to be elevated in people diagnosed with diabetes [23–25] and depression [26–28].

Separate studies have examined levels of inflammatory markers along different dimensions of the clinical manifestation of this comorbidity. In the Multiethnic Study of Atherosclerosis, Golden and colleagues [29] examined whether IL-6 and CRP were associated with depression (defined as either the presence of antidepressant medications or a CES-D score ≥

16) in participants with impaired fasting glucose (IFG), untreated diabetes or treated diabetes. Inflammatory marker levels were associated with depression in the treated diabetes group, but were not significantly associated with depression in the IFG or untreated diabetes groups in this cross-sectional study.

In the Health, Aging and Body Composition study [30], Doyle and colleagues examined whether interleukin-6 (IL-6) and C-reactive protein (CRP) concentrations were higher in individuals with T2DM and elevated depressive symptoms combined compared to individuals with either T2DM or depressive symptoms alone in an older (70–79 years) adult sample. IL-6 levels were significantly higher among those with diabetes and elevated depressive symptoms compared to those with depressive symptoms alone, diabetes alone, or neither. Higher levels of CRP were observed in those with both co-morbidities compared to depression alone and healthy controls.

These studies raise new questions about the relationships among diabetes, depressive symptoms and inflammatory markers. For example, it is unknown whether depressive symptoms and ADM use have the same relationship to inflammatory markers; or whether severity of depressive symptoms is associated with inflammatory marker levels. In the DPP, ADM use predicted onset of T2DM but depressive symptoms did not; whereas in the Women's Health Initiative Study both ADM and depressive symptoms predicted T2DM. Moreover, differences in the classification of depression (i.e. ADM use and/or depressive symptoms) may account for variations in results across studies.

The Diabetes Prevention Program study is well-suited to explore relationships between antidepressant medication use, inflammatory cytokines and the onset of type 2 diabetes. Using this well-characterized sample of adults at risk for T2DM, we addressed the following aims:

1. To evaluate the cross-sectional association of antidepressant medication use and depressive symptoms with inflammatory markers (IL-6 and CRP) at baseline and at one-year follow-up time points in the DPP study cohort.
2. To evaluate differences within and across DPP treatment groups i.e. lifestyle intervention (ILS), placebo (PLB) and metformin (MET) in inflammatory markers, depressive symptoms and antidepressant medication use.
3. To evaluate whether inflammatory markers may mediate the previously observed relationship between antidepressant medications and onset of T2DM.

Research Design and Methods

Designed as an efficacy trial to evaluate metformin and lifestyle interventions compared with placebo in the prevention of type 2 diabetes, the DPP enrolled N=3234 adults who were at high risk for type 2 diabetes [31] between 1996 and 1999. The study protocol was approved by the Institutional Review Boards of all participating sites (N=27) and participants completed the informed consent process prior to enrollment. Participants were randomized to one of three conditions: lifestyle intervention (ILS), metformin (MET) or placebo (PLB). At the time of the trial, metformin was not approved by the Federal Drug

Administration for diabetes prevention. In July 2001, masked DPP treatment was discontinued after it was demonstrated that the lifestyle intervention was superior in reducing the risk of developing diabetes. At each study visit, participants were asked to bring all prescribed medications, including ADMs, to clinic visits where the medications were recorded by generic name, brand name or both [31]. Detailed methods are described elsewhere [31]. The current paper represents a secondary data analysis of the DPP cohort.

Measures

Demographic characteristics were determined at baseline via a self-administered questionnaire including age at randomization, sex, ethnicity, marital status, income, and education.

Beck Depression Inventory (BDI) is a 21-item self-report questionnaire used to assess symptoms of depression that correspond to DSM-IVTR diagnostic criteria. The measure was administered annually at each assessment. The BDI has excellent short-term test-retest reliability (r = 0.93) and inter-item correlations (ranging from r = 0.91 to r = 0.95) when used in general populations [32]. Scores have been categorized by Beck for interpretation: 0–10 represents normal levels of depressive symptoms; 11–16 is mild mood disturbance; 17–20 is ‘borderline’ clinical depression; 21–30 is moderate depression; 31–39 is severe depression; and 40 and above is ‘extreme’ depression [32].

Physical Exam, Medical History and Inflammatory Markers—Medical history data were obtained by interview annually to evaluate smoking and prescribed medication regimen including antidepressant medications. Body mass index (BMI) was calculated from height at baseline and weight measured at annual visits. Fasting blood samples for later measurement of glucose, insulin, and triglycerides, CRP and IL-6 were collected at baseline and Year 1. Insulin resistance was evaluated using the Homeostasis Model (HOMA-IR), calculated from glucose and insulin values [33]. Oral glucose tolerance testing to monitor onset of T2DM was performed annually.

Statistical Analyses

Analyses were conducted using SAS 9.01 (The SAS Institute, Cary, NC). CRP and IL-6 were not normally distributed so both were log-transformed for all analyses. The associations between depressive symptoms (ADM use, or BDI score ≥11) and CRP or IL-6 were assessed in multivariate linear models, adjusted for age, sex, race/ethnicity, BMI, triglycerides, smoking, HOMA-IR, fasting glucose, statins and anti-inflammatory medications. Physical activity was evaluated as a potential covariate but was not significantly related to CRP when BMI and sex were used as covariates. It was not included in the final models in the interests of parsimony.

Multivariate linear regression was also performed to predict Year 1 CRP and IL-6 levels using baseline values of ADM and depression scores. Depressive symptoms were examined as a continuous measure (BDI total score) and then separately as a categorical variable using thresholds of BDI (≥11) [32]. Antidepressant medication (ADM) use was coded as absent/present at baseline. Analyses were conducted within each randomized treatment group as

well as across treatment groups. Linear models were used to assess the change of the inflammatory marker from baseline to year 1 and model based means, also called least square means are reported. Cox's proportional hazard models were used to assess risk of developing diabetes during the masked phase of the DPP study (Years 1 through 3). Consistent with other DPP analyses [19, 20] in the time-dependent (i.e. variables might change value at each visit time) covariate analyses predicting diabetes risk, ADM use was defined as absent, intermittent (present at some but not all visits) or continuous (reported by participants at all visits). To examine mediation effects, hazard ratios and confidence intervals were compared between models that included the inflammatory marker (CRP or IL6) to those without the markers [34]. Models were adjusted for age, race, sex, BMI, triglycerides, smoking, HOMA-IR, baseline weight, change in weight, treatment arm and concurrent medications including statins, estrogens, systemic steroids, aspirin, and NSAIDs, which may induce changes in inflammatory marker levels.

Results

This analysis was based on the 3,187 of 3,234 enrolled DPP participants who completed the Beck Depression Inventory (BDI) at baseline. Baseline demographic characteristics for these participants are shown in Table 1, and are similar among the treatment groups. Overall, sixty-eight percent of the participants were women, 66% were married, 74% attained high school education or greater The mean age was 50.6 years (S.D. 10.7), and the mean BMI was 34.0 kg/m^2 (S.D. 6.7).

Baseline Analyses

At DPP baseline, 10% of the sample reported no ADM use and BDI scores at or above the clinically meaningful threshold (i.e. BDI ≥ 11); 4.8% reported ADM use with BDI < 11; and 16% reported both ADM use and BDI > 11. No statistical differences were observed across classes of antidepressant medications with a minority of participants (N=37) prescribed an ADM class other than a selective serotonin reuptake inhibitor or serotonin norepinephrine reuptake inhibitor.

We initially examined ADM and BDI with CRP but found that the interaction term was not statistically significant. Examination of each predictor independently indicated that ADM use was significantly associated with elevated CRP, median = 0.61 mg/dl for ADM use versus 0.36 mg/dl for non ADM use, p<0.0001 (Table 2). When adjusted for demographic, anthropometric and concurrent medications, CRP levels were significantly higher in the ADM use group compared to non-ADM use (20.0% higher, p=0.01). When adjusted for these same covariates, CRP levels were not related to depressive symptoms, whether the BDI score was examined as a continuous or categorical variable (i.e. cut-score ≥ 11). IL-6 was not associated with either ADM nor depressive symptoms coded as continuous or categorical.

Changes in CRP and IL-6 from Baseline to Year 1 of DPP

Multivariate regression analyses were performed to identify changes in CRP and IL-6 concentrations from baseline to the Year 1 follow-up assessment by baseline ADM use

across the three DPP groups (see Table 3). We initially added BDI to the models and found no statistically significant interaction terms of the change in CRP and IL-6. Each term was then used independently. In the ILS group, CRP decreased in both those with and without ADM use at baseline. CRP decreased in those without ADM use at baseline in the MET group. No significant change in CRP was observed in the placebo group in either the ADM or no ADM use group.

Similar regression analyses were performed using IL-6 as the dependent variable. There were no significant changes in IL-6 concentrations from baseline to the Year 1 follow-up assessment were observed by ADM use or DPP groups (data not shown).

Mediation Analyses

Hazard ratios were compared to assess CRP as a mediator on the effect of intermittent and continuous ADM use over time to predict onset of T2DM over the 3.2 year follow-up period (shown in Table 4). In the PLB group, both continuous ADM use and CRP predicted the onset of T2DM suggesting that in the absence of an active medication or lifestyle intervention, ADM and CRP are concomitant risk factors for the onset of T2DM. CRP, however, did not mediate the effect of ADM in T2DM. ADM had similar hazard ratios in regression models with and without CRP (Table 4). In the ILS group, continuous and intermittent ADM use predicted T2DM onset, but CRP was not a significant mediator of this relationship. In the MET group, time-dependent CRP (1.2 HR; 95% CI: 1.0–1.4) significantly predicted onset of T2DM but continuous and intermittent ADM did not. A test for heterogeneity across treatment groups in log CRP was not statistically significant indicating no significant differences across treatment groups.

Discussion

The current study evaluated the association of inflammatory markers, antidepressant medication (ADM) use and depressive symptoms, and whether these inflammatory markers explained the prediction of diabetes incidence by ADM in a well-characterized sample of adults with impaired glucose tolerance. ADM use was associated with higher levels of CRP at baseline and changes in CRP levels from baseline to Year 1 follow-up assessment in the ILS group. There were no significant changes in CRP levels observed from baseline to Year 1 assessment in the PLB group. The MET group had significant decreases in CRP levels only among those without ADM use at baseline. CRP was a significant independent predictor of incident T2DM in the PLB group but did not mediate the effect of ADM use in any of the treatment groups.

These findings contribute to the literature in several ways. First, patients randomized to the ILS group who were taking ADM at baseline had a larger reduction in CRP, which was significant compared to patients assigned to the MET group who were taking ADMs at baseline. The extent the observed reduction in CRP for patients in the ILS group can be attributed to either ADM use, being assigned to the ILS group, or some complex interaction between these two variables cannot be determined in the context of the original study design. Patients assigned to the MET group who were taking ADMs at baseline had a smaller reduction in CRP compared to patients in the ILS group taking ADMs. Metformin treatment

alone showed a significant reduction in CRP, suggesting an anti-inflammatory benefit for patients randomized to metformin treatment without ADM use.

Second, the findings from this study are consistent with and extend the growing body of research on the cytokine theory of depression [37] which has examined the associations among elevated inflammatory markers, depressive symptoms, and the effect of ADMs on reducing inflammation independent of any antidepressant effect(s) [38]. The current investigation is the first to examine these associations within a sample of patients having impaired glucose tolerance. According to the cytokine theory of depression, the presence of psychological stress up-regulates the production of pro-inflammatory cytokines and acute-phase reactants, such as CRP, within specific neurological systems (e.g., serotonin & norepinephrine re-uptake inhibition &/or hypothalamic-pituitary-adrenal axis dysfunction) that are associated with depressive symptoms [37]. In addition, inflammatory cytokines can reduce the concentration of monoamine precursors through the activation of enzymes such as indoleamine 2,3-dixygenase, which break down tryptophan, the primary amino acid precursor for serotonin, into kynurenine (i.e., a neurotoxic metabolite). In support of the cytokine hypothesis, numerous studies have shown that antidepressant treatments for MDD, particularly with SSRIs, have produced a significant reduction in CRP levels, irrespective of the resolution of depressive symptoms [39]. Findings from this investigation support this result since significant reductions in CRP among patients using ADMs were found in the ILS group. However, this finding should be interpreted with caution, since patients on ADMs in the study were taking SSRI and tricyclic antidepressant medications. It may be difficult to compare our findings to investigations examining the anti-inflammatory effect of single SSRI usage on inflammatory markers, even though a large proportion (78%) of patients reported SSRI use at baseline. Duration of ADM use is another factor that could contribute to the observed findings. Recent reviews have noted that antidepressant medications can decrease and increase inflammatory activity (e.g. IL-6 and CRP), depending on different levels of inflammation at the time of medication introduction [40]. Dose, duration and interactions of ADMs with other biological systems can contribute to inflammatory marker levels [40]. Due to the nature of the DPP study design, duration of ADM use at baseline was not collected, so we are unable to account for the effects of length of exposure of ADM on inflammatory marker levels observed in the study.

Finally, we observed that CRP contributes to the risk of T2DM (as shown in the PLB group) but does not explain the relationship between ADM use and incident T2DM.

There were no statistically significant relationships between IL-6 and depressive symptoms or ADM. This finding may be consistent with studies of depressed psychiatric inpatients in which IL-6 levels returned to control levels following medication treatment [35].

Depressive symptoms, whether expressed as a continuous total score or categorically, were not related to CRP or IL-6 at baseline or Year 1 follow-up, when adjusted for other covariates. This finding differs from Doyle [30] in which CRP and IL-6 were elevated in participants with CES-D scores ≥ 20. Depressive symptom levels in the DPP sample were limited overall (median BDI score = 3) due to the exclusion of people with significant depression at enrollment in this efficacy trial. The contrast in findings between the Health

ABC study and this study suggest that greater depression symptom severity may be necessary to observe an association with CRP and IL-6 levels.

In the placebo group, CRP and ADM use each independently predicted onset of T2DM, notably after weight and changes in weight over time were accounted for in the models. In the lifestyle group where participants lost 5–7% of their body weight, CRP did not independently predict incident T2DM. In the metformin group, CRP was a significant predictor of incident T2DM. Tests for CRP as a mediator between ADM use and incident T2DM were not significant across treatment groups. In this pre-diabetes sample, it is unknown whether this negative finding is a function of a lack of association between CRP and ADM use or whether levels of CRP were not at a level that would demonstrate a relationship. The finding of ADM use as a predictor of incident T2DM was consistent with prior analyses of this data set [19, 20].

Limitations of this study include a heterogeneous use of antidepressant medications (SSRIs and TCA medications) representative of clinical practice patterns at the time of the study. Although it is possible that different classes of medications could influence the observed outcomes differently, in this sample, 78% of ADM use was an SSRI medication [36]. The study is also limited by the lack of available data on the length of use of ADMs by participants prior to baseline data collection. Due to the nature of the original study design (i.e. diabetes prevention), ADM use was not randomly assigned which limits our ability to control for the effects of ADM exposure (both dose and duration) on the outcome variables. In addition, a limited number of individuals experienced clinically significant depressive symptoms whether they were currently treated with ADMs or without medications. Thus the impact of greater levels of depression on inflammatory markers could not be assessed. It is possible that levels of depressive symptoms were greater in those participants who were prescribed ADMs prior to enrollment in the DPP but this data was not collected for the purposes of the DPP trial.

The strengths of this study include a carefully studied group of individuals whose diagnosis of T2DM was captured within 6 months of onset; the ability to distinguish between depressive symptoms and ADM use; strong psychometric properties in the measurement of depressive symptoms, precise data collection about medications and adjustment in the analyses for medications that affect inflammation; and the use of a non-institutionalized, non-psychiatric community sample.

These findings add to an emerging understanding of the relationship of inflammatory markers with depression, antidepressant medication and type 2 diabetes in a sample of adults at risk for T2DM without clinical depression. Taken together, the research on diabetes, depression and inflammation supports the role of inflammation as a contributing factor for depression and diabetes. There is evidence for the role of inflammation in the development and exacerbation of T2DM [23, 24]; differences in marker levels among clinically depressed adults compared to controls [30]; and ADM use as a risk factor for the onset of T2DM [19, 20]. These findings suggest that CRP does not mediate the relationship between ADM use and diabetes in the context of low levels of depressive symptoms. However, these findings suggest that individuals prescribed ADMs who are at risk for T2DM would be well-served

to engage in both lifestyle change (i.e. weight loss) and metformin use to reduce risk factors associated with inflammation and ADM use for the progression of T2DM.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

ADM	Antidepressant medications
BDI	Beck Depression Inventory
BMI	Body Mass Index
CRP	C-Reactive Protein
DPP	Diabetes Prevention Program
IL-6	Interlueken-6
ILS	Lifestyle Intervention treatment group
MET	Metformin treatment group
PBL	Placebo treatment group
T2DM	type 2 diabetes mellitus

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Table 1

Baseline Characteristics of Study Participants by Intervention Group

Characteristics		**Total**	**Placebo**	**Metformin**	**Lifestyle**
	N	**3187**	**1060**	**1062**	**1065**
Age at randomization	Median(IQR)	49.9 (43.0, 57.6)	49.6 (43.3, 57.4)	50.4 (44.0, 57.3)	49.6 (42.2, 58.3)
Sex	Male	1029 (32%)	329 (31%)	360 (34%)	340 (32%)
	Female	2158 (68%)	731 (69%)	702 (66 %)	725 (68%)
Race/ethnicity	White	1746 (55%)	575 (54%)	597 (56%)	574 (54%)
	African American	636 (20%)	217 (20%)	218 (21%)	201 (19%)
	Hispanic	498 (16%)	164 (15%)	160 (15%)	174 (16%)
	American Indian	165 (5%)	55 (5%)	51(5%)	59 (6%)
	Asian	142 (5%)	49 (5%)	36 (3%)	57 (5%)
Income[#]	<50,000	1622 (55%)	553 (57%)	517 (53%)	552 (56%)
	50,000+	1312 (45%)	419 (43%)	460 (47%)	433 (44%)
Marital Status	Living together/Married	2099 (66%)	707 (67%)	688 (65%)	704 (66%)
	Others	1088 (34%)	353 (33%)	374 (35%)	361 (34%)
Education Level	12 yrs or less	822 (26%)	280 (26%)	267 (25%)	275 (26%)
	13–16 yrs	1534 (48%)	511 (48%)	508 (48%)	515 (48%)
	17+ yrs	831 (26%)	269 (25%)	287 (27%)	275 (26%)
Leisure activity(met-hours)	Median(IQR)	9.9 (3.9, 20.7)	10.0 (4.0, 21.2)	10.0 (4.0, 20.8)	9.5 (3.9, 19.6)
BMI (kg/m^2)	Median(IQR)	32.8 (29.0, 37.4)	33.2 (28.9, 37.8)	32.7 (29.1, 37.3)	32.6 (28.9, 37.2)
BDI score	Median(IQR)	3.0 (1.0, 7.0)	3.0 (1.0, 7.0)	3.0 (1.0, 7.0)	3.0 (1.0, 7.0)
BDI>=11	Yes	328 (10%)	115 (11%)	104 (10%)	109 (10%)
	No	2859 (90%)	945 (89%)	958 (90%)	956 (90%)
Taking Antidepressant	Yes	181 (6%)	53 (5%)	70 (7%)	58 (5%)
	No	3006 (94%)	1007 (95%)	992 (93%)	1007 (95%)
Antidepressant Class					
SSRI		141 (78%)	41 (77%)	55 (79%)	45 (78%)
Tricyclics		40 (22%)	12 (23%)	15 (21%)	13 (22%)
CRP (mg/dl)	Median(IQR)	0.37 (0.17–0.76)	0.38 (0.17, 0.78)	0.35 (0.17, 0.73)	0.38 (0.17, 0.76)
IL6 (pg/ml)	Median(IQR)	1.93 (1.28–2.96)	1.95 (1.31, 2.97)	1.87 (1.25, 2.95)	1.95 (1.29, 2.98)

Data presented as mean (SD) or %.

P -values are based on χ^2 tests for categorical variables and Kruskal-Wallis test for continuous variables. BMI = Body Mass Index; BDI = Beck Depression Inventory total score; CRP = C-reactive protein; and IL6= Interleukin 6.

Table 2

Baseline Associations between ADM, BDI Total Score to CRP and IL-6

ADM USE	N	Median CRP* mg/dl (IQR)	N	Median IL6 pg/ml (IQR)
No	3001	0.36 (0.16, 0.73)	2966	1.92 (1.28, 2.95)
Yes	181	0.61 (0.34, 1.0)	179	2.01 (1.26, 3.19)

BDI ≥11	N	Median CRP mg/dl (IQR)	N	Median IL6 pg/ml (IQR)
No	2855	0.36 (0.16, 0.74)	2822	1.88 (1.26, 2.93)
Yes	327	0.44 (0.19, 0.98)	323	2.10 (1.54, 3.40)

ADM=Antidepressant medication use; BDI = Beck Depression Inventory total score; CRP = C-reactive protein; IL6= Interleukin 6; and IQR=Interquartile Range.

* $p = 0.01$ for the association of log transformed CRP and ADM use adjusted for age at randomization, BMI, sex, race/ethnicity, triglycerides, smoking, HOMA-IR, fasting glucose, BDI score, treatment group, anti-inflammatory medications, estrogen, systemic steroids, and statins in the linear regression analysis.

Table 3

Percent Change in CRP from Baseline to Year 1 by ADM Use within DPP Treatment Groups

ADM Use	Placebo LS Means 95% CI N=996	Metformin LS Means 95% CI N=1003	Lifestyle (ILS) LS Means 95% CI N=1006
No N=2830	−2.3% (−9.2%, 5.1%) p=0.53 N=946	−13.2% (−20.0%,−6.0%) p=<0.001 N=934	−31.4% (−36.7%, −25.7%) p<0.001 N=950
Yes N=175	0.40% (−18.8%, 24.0%) p=0.097 N=50	−6.5% (−23.0%, 13.7%) p=0.50 N=69	−28.8% (−42.0%, −12.5%) p=0.001 N=56

ADM = Antidepressant medication use; CRP = C-reactive protein.

P-values reflect the test for whether the change from baseline to year 1 is significantly different from 0 in linear regression model analysis. Models were adjusted for age randomized, BMI, sex, race/ethnicity, triglycerides, smoking, HOMA-IR, fasting glucose, BDI score, anti-inflammatory medications, estrogen, systemic steroids, and statins.

Table 4

Hazard Ratios Predicting Onset of Type 2 Diabetes by Treatment Group

Treatment Group	Predictor Variables	Model 1 Hazard Ratio (95% CI)	Model 2 Hazard Ratio (95% CI)
Placebo N=1036	ADM Intermittent Use vs. No ADM use	1.47 (0.94–2.31)	1.42 (0.90–2.24)
	ADM Continuous Use vs. No ADM use	2.52 (1.31–4.83) *	2.46 (1.28–4.71) *
	Natural Log CRP	-	1.16 (1.01–1.34) *
Metformin N=1049	ADM Intermittent Use vs. No ADM use	1.02 (0.61–1.71)	0.98 (0.58–1.63)
	ADM Continuous Use vs. No ADM use	0.74 (0.29–1.88)	0.71 (0.28–1.80)
	Natural Log CRP	-	1.22 (1.05–1.41) *
Lifestyle N=1052	ADM Intermittent Use vs. No ADM use	2.08 (1.18–3.65) *	2.11 (1.20–3.71) *
	ADM Continuous Use vs. No ADM use	3.26 (1.53–6.93) *	3.06 (1.43–6.57) *
	Natural Log CRP	-	1.11 (0.91–1.35)

ADM = Antidepressant medication use; CRP = C-reactive protein.

* $p<.05$. Model 1 = ADM Use and covariates predicting incident T2DM without log-transformed time-dependent CRP. Model 2 = ADM Use, log-transformed time-dependent CRP and covariates predicting T2DM onset. Models are adjusted for age, sex, race/ethnicity, education, baseline weight, baseline glucose, change in weight, BDI score, anti-inflammatory medications, estrogen, and statins. Additional analysis showed that there was no significant interaction between treatment group and time-dependent log-transformed CRP with onset of diabetes.