

Depression Symptoms and Antidepressant Medicine Use in Diabetes Prevention Program Participants

THE DIABETES PREVENTION PROGRAM
RESEARCH GROUP*

OBJECTIVE — To assess depression markers (symptoms and antidepressant medicine use) in Diabetes Prevention Program (DPP) participants and to determine whether changes in depression markers during the course of the study were associated with treatment arm, weight change, physical activity level, or participant demographic characteristics.

RESEARCH DESIGN AND METHODS — DPP participants ($n = 3,187$) in three treatment arms (intensive lifestyle, metformin, and placebo) completed the Beck Depression Inventory (BDI) and reported on use of antidepressant medicines at randomization and subsequently at each annual visit (average duration in study 3.2 years).

RESULTS — On study entry, 10.3% of participants had BDI scores ≥ 11 , which was used as a threshold for mild depression, 5.7% took antidepressant medicines, and 0.9% had both depression markers. During the DPP, the proportion of participants with elevated BDI scores declined (from 10.3% at baseline to 8.4% at year 3), while the proportion taking antidepressant medicines increased (from 5.7% at baseline to 8.7% at year 3), leaving the proportion with either marker unchanged. These time trends were not significantly associated with the DPP treatment arm. Depression markers throughout the study were associated with some participant demographic factors, adjusted for other factors. Men were less likely to have elevated depression scores and less likely to use antidepressant medicine at baseline (9.0% of men and 17.9% of women had at least one marker of depression) and throughout the study ($P < 0.0001$). Those with more education were less likely to have elevated symptom scores ($P = 0.0007$) but more likely to be taking antidepressant medicine ($P = 0.002$). Non-Hispanic white participants were less likely than African Americans to have BDI scores ≥ 11 ($P = 0.03$), but white participants were more likely to be taking antidepressant medicine than any other racial/ethnic group ($P < 0.0001$).

CONCLUSIONS — DPP participation was not associated with changes in levels of depression. Countervailing trends in the proportion of DPP participants with elevated depression symptoms and the proportion taking antidepressant medicine resulted in no significant change in the proportion with either marker. The finding that those taking antidepressant medicine often do not have elevated depression symptoms indicates the value of assessing both markers when estimating overall depression rates.

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Abbreviations: BDI, Beck Depression Inventory; DPP, Diabetes Prevention Program; IGT, impaired glucose tolerance; MET, metabolic equivalent; MDD, major depressive disorder; SSRI, selective serotonin reuptake inhibitor.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Depression is more common among people with diabetes than in the general population (1,2). The causal relationships between depression and glucose metabolism are not well understood, but some associations have been documented. People with diabetes who are depressed have higher HbA_{1c} levels (3), more diabetes complications (4,5), and much higher general health care costs than people with diabetes who are not depressed (6,7). Treating depression in people with diabetes may be associated with improved glucose control (8,9), but this has not been seen in patients with lower HbA_{1c} levels (10,11). Effective treatment is provided to <25% of depressed diabetic patients (12).

Recent studies suggest that depression and glucose dysregulation may be linked before the onset of type 2 diabetes. Some suggest that depression could increase a person's risk of developing type 2 diabetes (13–15), either by influencing behaviors such as eating and physical activity or via increased sympathoadrenal and hypothalamic-pituitary-adrenal axis activity (16,17). The Diabetes Prevention Program (DPP) offered an opportunity to study depression markers in a population at increased risk for developing type 2 diabetes because they are overweight and have impaired glucose tolerance (IGT).

The associations among depression, activity level, and weight are not clear. Some have found a positive association between weight and depression (18–20), though this may be true only for women (21). Others have reported contrasting findings regarding the association between activity level and depression (22,23). If changes in activity level and weight are associated with changes in depression markers, DPP participants in the intensive lifestyle arm could experience greater changes in these markers than those in the placebo and metformin arms. The effects of DPP interventions on depression markers could influence the likelihood that interventions similar to the DPP will be widely adopted.

Some demographic factors, including

age, sex, race/ethnicity, and education, appear to be associated with depression in the general population (1,24–27) and among people with diabetes (28), although we found no studies of antidepressant medicine use among patients with diabetes. The large multiethnic DPP cohort offers an opportunity to determine whether the effects of DPP participation on depression markers vary by demographic factors in a population with IGT. We found no studies of any depression marker in people with IGT.

In this study, we address the following questions. 1) Did the proportion of DPP participants with depression markers (elevated symptom scores and antidepressant medicine use) change during the course of the study? 2) Did these changes differ by treatment arm? 3) Did these changes differ by participant demographic characteristics? 4) Were these changes associated with changes in weight or activity level?

RESEARCH DESIGN AND METHODS

The DPP was conducted at 27 centers and involved persons at high risk for developing type 2 diabetes. Methods (29,30) and results (31) have been described in detail elsewhere, and the protocol is available at <http://www.bsc.gwu.edu/dpp>. The institutional review board at each center approved the protocol, and all participants gave written informed consent.

A total of 3,234 participants enrolled in the DPP, but only 3,187 completed the depression symptoms questionnaire at baseline. This analysis is based on these 3,187 participants. Participants were at least 25 years of age, had a BMI of ≥ 24 kg/m² (≥ 22 kg/m² in Asians), and a plasma glucose concentration of 95–125 mg/dl (5.3–6.9 mmol) in the fasting state (≤ 125 mg/dl in American Indians) and 140–199 mg/dl (7.8–11.0 mmol) 2 h after a 75-g oral glucose load. Individuals were excluded if in the previous weeks they had taken antidepressant medicines that might contribute to weight loss, such as bupropion or a selective serotonin reuptake inhibitor (SSRI) at more than the lowest usual dose (i.e., > 20 mg fluoxetine or the equivalent) (32). Potential participants were also excluded if they had illnesses or conditions that could seriously reduce their ability to participate in the study (including major psychiatric disorders) or were unable to successfully

complete the 3-week run-in period, during which participants took placebo medicines and recorded eating and activity. Recruitment was designed to randomize approximately half the participants from racial/ethnic minority groups.

Interventions

Eligible participants were randomly assigned to one of three interventions: standard lifestyle recommendations plus metformin (Glucophage) at a dose of 850 mg twice daily (metformin arm), standard lifestyle recommendations plus a placebo pill twice daily (placebo arm), or an intensive lifestyle modification program (intensive lifestyle arm). Goals for participants assigned to the lifestyle intervention were to achieve and maintain a weight reduction of at least 7% of initial body weight through a healthy low-fat diet and to engage in physical activity of moderate intensity, such as brisk walking, for at least 150 min/week (33).

Outcomes

As part of a comprehensive protocol, DPP participants completed the Beck Depression Inventory (BDI) (34) before randomization and subsequently at each annual visit. Scores for the BDI were masked to clinic staff, but a question on the BDI concerning thoughts of suicide was screened by staff during the visit at which the BDI was completed. If the participant's response to this question was "I have thoughts of killing myself but I would not carry them out," "I would like to kill myself," or "I would kill myself if I had the chance," the program coordinator consulted with the clinic behavioral scientist and/or principal investigator to decide what action to take.

Participants brought all prescription medicines to each clinic visit, from which the current use of antidepressant medicines was assessed. We report follow-up through July 2001, after which the primary results were announced and the interventions unmasked. This was 4 months longer than the results reported previously (31), resulting in a total mean follow-up of 3.2 years per participant.

We measured depression in three ways: BDI scores ≥ 11 , current use of antidepressant medicines, and either BDI score ≥ 11 or current use of antidepressant medicines. We included the third measure because we wanted an estimate of all participants who could be consid-

ered depressed, regardless of whether they were treated. Other researchers have chosen BDI scores ranging from 10 to 16 to define depression (35–38), generally as a function of the importance placed on depression recognition. We chose a score toward the low end of the severity range as our symptom threshold because we believed few severely depressed participants would pass the screening process for eligibility in the DPP.

Self-reported levels of leisure physical activity were assessed annually with the Modifiable Activity Questionnaire (39). Physical activity level was calculated as the product of the duration and frequency of each activity (in hours per week), weighted by an estimate of the metabolic equivalent (MET) of that activity, and summed for all activities performed, with the result expressed as the average MET hours per week for the previous year.

Analysis

Demographic factors (age at randomization, sex, race/ethnicity, and education) were examined for differences in the proportion of participants with depression markers at entry to the study using Pearson's χ^2 test. Multiple logistic regression modeling with all demographic variables as covariates was performed to rule out confounders. Repeated-measures modeling using generalized estimating equations (40) was used to evaluate trends in the proportion of participants with depression markers over time, as well as differences in time trends among treatment arms or by participant demographic factors. Generalized estimating equations were also used to evaluate the association between weight loss, leisure activity change, and having depression markers. Type III score test was used for the P value, and Wald CI was reported. SAS was used for all analyses (version 8.2; SAS Institute, Cary, NC).

RESULTS— Table 1 shows demographic characteristics and depression marker levels for DPP participants at randomization. Among the 3,187 participants, 328 (10.3%) had BDI scores indicating at least mild depression (≥ 11), 86 (2.7%, data not shown) had BDI scores indicating moderate to severe depression (≥ 16), and 181 (5.7%) were taking antidepressant medicines. On entry to the study, only 29 (0.9%) DPP participants had both depression markers.

Table 1—Depression symptoms and antidepressant medicine use of DPP participants by baseline characteristics

	Total (n)*	BDI \geq 11 (%)	Antidepressant medicine use (%)	BDI \geq 11 or antidepressant medicine use (%)
Total participants	3,187	328 (10.3)	181 (5.7)	480 (15.1)
Age (years)				
25–44	983	115 (11.7)	47 (4.8)	155 (15.8)
45–59	1,567	160 (10.2)	102 (6.5)	244 (15.6)
\geq 60	637	53 (8.3)	32 (5.0)	81 (12.7)
P value†		0.0907	0.1349	0.1789
P value‡		0.5859	0.1805	0.6315
Sex				
Female	2,158	255 (11.8)	160 (7.4)	387 (18.0)
Male	1,029	73 (7.1)	21 (2.0)	93 (9.0)
P value†		<0.0001	<0.0001	<0.0001
P value‡		0.0022	<0.0001	<0.0001
Race/ethnicity				
Caucasian	1,746	132 (7.6)	144 (8.2)	254 (14.5)
African American	636	81 (12.7)	11 (1.7)	89 (14.0)
Hispanic American	498	67 (13.5)	18 (3.6)	82 (16.5)
American Indian	165	33 (20.0)	6 (3.6)	38 (23.0)
Asian	142	15 (10.6)	2 (1.4)	17 (12.0)
P value†		<0.0001	<0.0001	0.0272
P value‡		0.0001	<0.0001	0.2606
Education (years)				
<12	822	122 (14.8)	33 (4.0)	147 (17.9)
13–16	1,534	152 (9.9)	91 (5.9)	227 (14.8)
\geq 17	831	54 (6.5)	57 (6.9)	106 (12.8)
P value†		<0.0001	0.037	0.0132
P value‡		<0.0001	0.0484	0.1160

Data are n (%) unless otherwise indicated. *All participants had complete information regarding antidepressant medicine use. However, some participants did not complete the Beck questionnaire. Numbers reported here are those who have completed BDI data and are included in the analyses. †P value from χ^2 test. ‡P value from multivariate logistic regression with the other three variables shown in the table adjusted.

We found strong baseline associations between depression markers and all demographic factors except age (Table 1). At baseline, controlling for other demographic factors, men were less likely than women to have BDI scores \geq 11 ($P = 0.002$), less likely to be taking antidepressant medicines ($P < 0.0001$), and less likely to have either depression marker ($P < 0.0001$). Participants with more education were less likely to have elevated BDI scores ($P < 0.0001$) and more likely to be taking antidepressants ($P = 0.05$). Race/ethnicity was associated with both elevated BDI scores ($P = 0.0001$) and antidepressant medicine use ($P < 0.0001$). Pairwise comparison (data not shown) found that non-Hispanic white participants were less likely to have elevated BDI scores than African-American, Hispanic-American, and American-Indian participants ($P < 0.006$) and more likely to take antidepressant medicines than those in any other racial/ethnic group ($P < 0.004$,

except $P < 0.05$ compared with American Indians and Asians). Hispanic-American participants were more likely to take antidepressants than African-American participants ($P = 0.01$). At the end of study, 93% of participants remained active, and this was not associated with baseline depression marker status.

Changes in depression markers during the DPP

The proportion of DPP participants with BDI scores \geq 11 decreased during the study (from 10.3% at baseline to 8.4% at year 3, $P = 0.0016$), whereas the proportion using antidepressant medicines increased (from 5.7% at baseline to 8.7% at year 3, $P < 0.0001$). The proportion of participants who had at least one of these two markers did not change significantly over time, reflecting the countervailing effects of the two component measures. These changes are shown by treatment arm in Table 2 for both sexes. There was

no significant interaction between DPP treatment arm and any of these time trends for either sex, indicating that the trends were similar for the three treatment arms, although at the 3rd year of follow-up there were marginally significant treatment arm differences in the proportion of female participants with either depression marker ($P = 0.0635$). The rate in the intensive lifestyle arm was lower than that in the placebo arm at that point ($P < 0.02$). In a separate analysis (data not shown), weight loss during the DPP was associated with a small but significant reduction in the risk of elevated depression (odds ratio [OR] 0.975/kg [95% CI 0.960–0.990], $P = 0.002$), and increased leisure activity was associated with a small but significant reduction in the risk of elevated symptoms (0.960/5 MET h/week [0.920–1.001], $P = 0.012$), a trend toward reduced antidepressant use (0.976/5 MET h/week [0.950–1.002], $P = 0.058$), and a small but significant

Table 2—Depression markers during the DPP by sex and treatment arm

	n	BDI ≥ 11 (%)*			Antidepressant medicine use (%)*			BDI ≥ 11 or antidepressant medicine use (%)†		
		Placebo	Metformin	Intensive lifestyle	Placebo	Metformin	Intensive lifestyle	Placebo	Metformin	Intensive lifestyle
Men										
Baseline	1,029	7.3	6.4	7.6	1.8	1.9	2.4	9.1	8.1	10.0
Year 1	948	6.1	5.3	6.0	2.4	3.5	3.2	7.5	8.6	7.9
Year 2	848	6.0	4.3	3.7	3.2	4.0	3.7	8.9	8.0	6.7
Year 3	512	5.8	5.2	5.5	5.2	5.7	3.8	9.0	9.8	7.7
Year 4	166	4.5	5.3	4.6	4.5	3.5	4.6	6.8	7.0	7.7
Women										
Baseline	2,158	12.4	11.5	11.4	6.4	9.0	6.9	18.1	19.7	16.1
Year 1	1,980	10.2	8.1	9.2	8.1	7.8	7.4	17.1	14.7	15.0
Year 2	1,819	11.3	10.7	9.2	10.0	10.9	8.3	19.6	18.7	15.5
Year 3	1,038	12.7	9.0	8.0	11.2	12.0	8.8	21.8	18.6	15.0
Year 4	331	8.9	10.7	6.3	13.9	11.7	7.9	18.8	20.4	13.4

*There was no statistically significant treatment difference for percentage of subjects with BDI ≥ 11 or percentage of subjects taking antidepressant medicines at any time point for either male or female participants. †For the combined category, there is a marginal difference in the three treatment arms at year 3 (P value = 0.0635) for the female participants.

reduction in either marker (0.965/5 MET h/week [0.939–0.992], $P = 0.002$). There were no significant interactions between these trends and treatment arm.

Figure 1 shows changes in depression markers during the course of the DPP as a function of baseline depression marker status. Figure 1A shows that the majority ($n = 2,707$) of participants had neither marker at baseline; by the year 3 follow-up, $\sim 5\%$ of those participants had BDI scores ≥ 11 , and a similar proportion were taking antidepressant medicines. Participants who had baseline BDI scores ≥ 11 (Fig. 1B) were more likely to start taking antidepressant medicines during the DPP than participants with lower baseline BDI scores (Fig. 1A; OR 2.63, $P < 0.0001$). Most participants who had BDI scores ≥ 11 at baseline did not have elevated scores by the year 1 follow-up (Fig. 1B and D), regardless of baseline antidepressant medicine use. Similarly, many participants who were taking antidepressant medicine at baseline were no longer taking it by the year 1 follow-up, regardless of baseline BDI score (Fig. 1C and D).

Figure 2 shows that during the DPP, antidepressant medicine use increased more among male than among female participants ($P = 0.009$). There were also significant interactions between trends in the proportion with either depression marker and both race/ethnicity ($P < 0.0001$) and education ($P = 0.002$). The

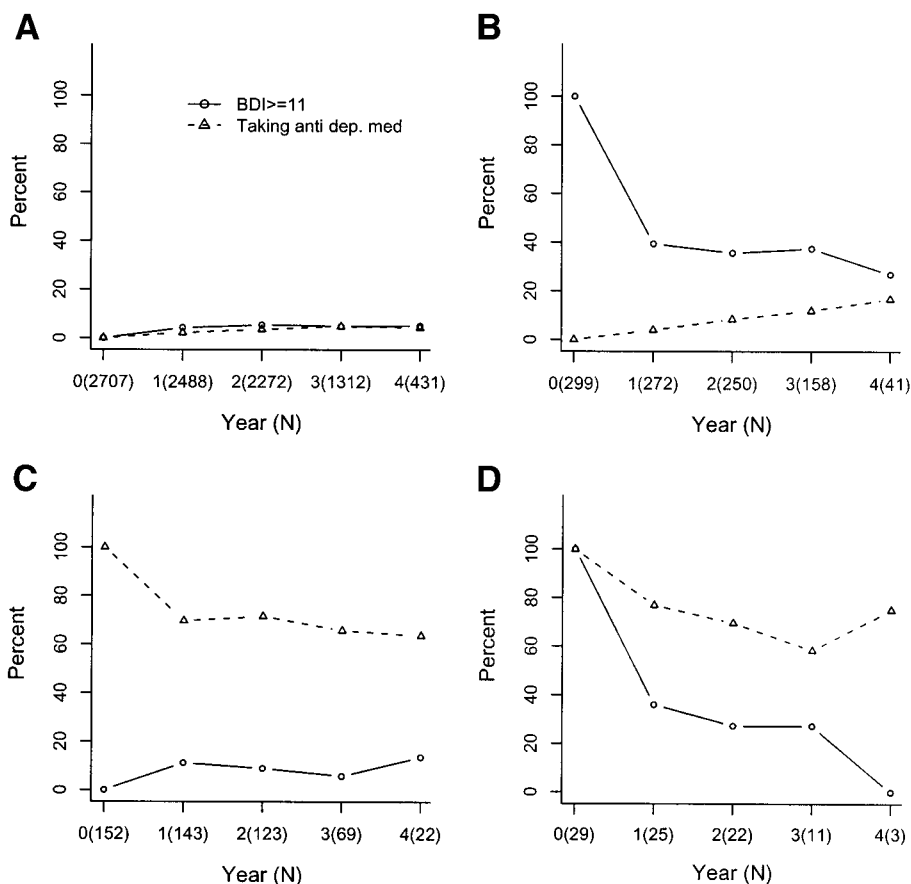


Figure 1—Change in two depression markers (BDI ≥ 11 and taking antidepressant medicine) by baseline depression status. A: Participants who were negative for both depression markers at baseline. B: Participants with baseline BDI ≥ 11 who were not taking antidepressant medicine. C: Participants with BDI < 11 and taking antidepressant medicine. D: Participants who were positive for both depression markers.

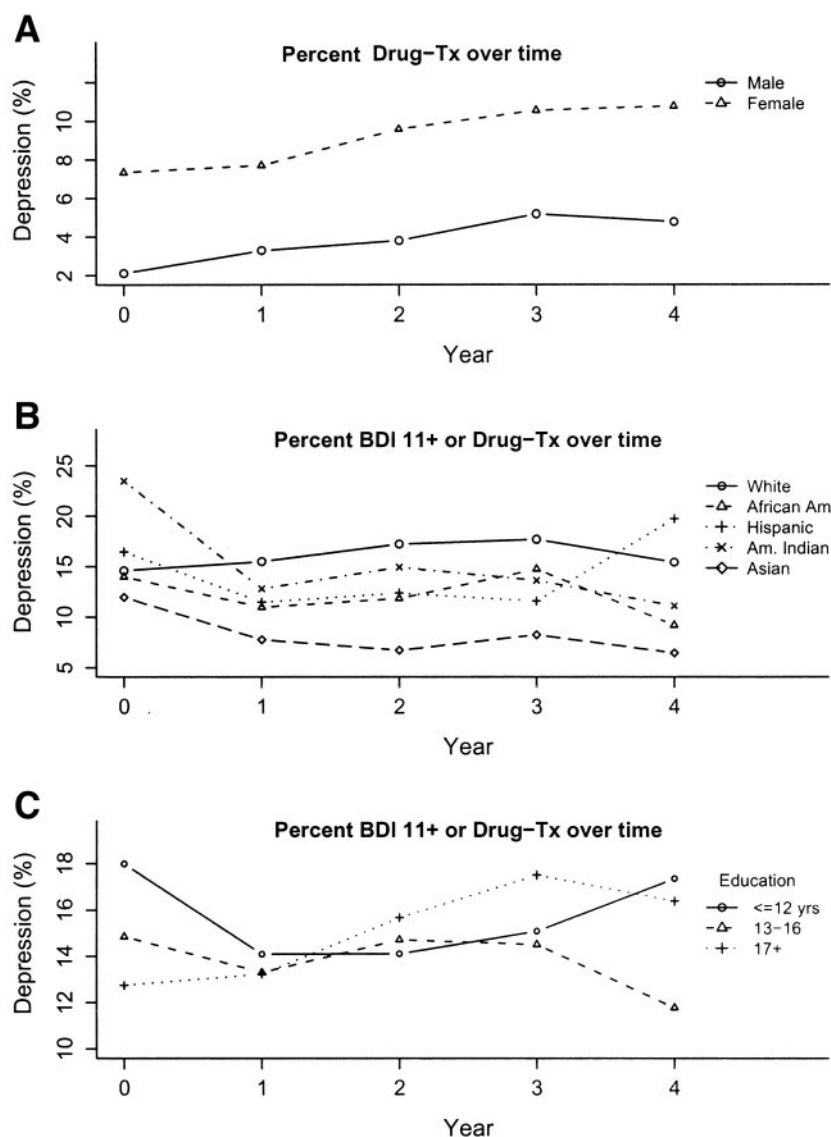


Figure 2—Time trend in depression markers by demographic factors sex (A), race/ethnicity (B), and education (C). Time trend in antidepressant medication varied by sex (A, $P = 0.009$). Time trend in either depression marker use varied by race/ethnicity (B, $P < 0.0001$) and education (C, $P = 0.001$).

proportion with either depression marker increased among non-Hispanic whites relative to other racial/ethnic groups and among those with ≥ 17 years of education relative to those with less education.

CONCLUSIONS

Effects of DPP participation on depression markers

On entry to the DPP, 10.3% of participants had elevated depression scores. In other studies of national samples, 6.1% of individuals without diabetes and 9.3% of individuals with diabetes had major depressive

disorder (MDD) based on the results of structured clinical interviews (1,24). Structured clinical interviews have been shown to identify fewer cases of depression than screening tools like the BDI (2), so the proportion of DPP participants who would have qualified for a diagnosis of MDD based on symptoms was probably close to that for the general population of people without diabetes. We found that in addition to the 10.3% of participants who entered the DPP with elevated BDI scores, 5.7% were taking antidepressant medicine, and 0.9% had both depression markers.

During the course of the study, the

proportion of participants taking antidepressant medicines went up while the proportion with elevated depression symptoms went down, leaving the proportion of DPP participants with either depression marker unchanged. Changes over time in the proportion of DPP participants with either depression marker did not vary significantly by treatment arm for participants of either sex.

If we had considered only symptoms, we might have concluded that the DPP interventions resulted in decreased depression. Including antidepressant medicine use as a depression marker suggests no effect of the DPP on the prevalence of depression. Increased antidepressant use by DPP participants appears to parallel trends in the general population. During the decade that ended in 1997, antidepressant medicine use in the U.S. tripled (27) and rates presumably continued to rise during the years of the DPP, which ended in 2001. This dramatic increase in antidepressant medicine use was substantially fueled by the popularity of selective serotonin reuptake inhibitors (SSRIs). SSRIs were not available in 1988, but by 1997 they were prescribed for 58% of all patients treated for depression, including those treated without medication (27). DPP participation might have also encouraged health care-seeking behavior or resulted in medical referrals, either of which could lead to greater use of antidepressant medicines.

Treatment arm differences in depression markers during the study/association between depression markers and changes in weight and activity

We found no significant interactions between depression marker time trends and DPP treatment arm for either men or women, although at annual visits for years 2 and 3 the proportion of participants in the intensive lifestyle arm with either depression marker was lower than that in the placebo arm. Weight loss was associated with a small but significant reduction in the likelihood of elevated depression symptoms, and increased leisure activity had similar associations with all depression markers. The magnitude of these associations was small, so it is difficult to estimate their clinical significance. The fact that these associations did not differ by treatment arm suggests that they are

not unique to participants in a structured lifestyle intervention.

Changes in depression markers during the study as a function of baseline depression marker status

Among DPP participants not taking antidepressant medicine at randomization, those with elevated baseline BDI scores were more likely to start taking these medications during the study, but only a small minority of those with elevated baseline scores began taking these medicines while they were in the DPP. While this suggests that many participants who might have benefited from antidepressant medicines were not receiving them, we also found evidence that elevated BDI scores were a transitory phenomenon, perhaps not requiring treatment: most participants with elevated baseline BDI scores had lower scores by their year 1 follow-up, regardless of their baseline antidepressant medicine use.

Association between demographic factors and depression markers

Other studies have reported that depression is less common among men, both in the general population (24) and among those with diabetes (1,28), and we found that male DPP participants were less likely to have elevated symptom scores throughout the study. A population-based study reported relatively small sex differences in antidepressant medication rates among psychiatric patients (41). In contrast, men in the DPP were less likely to take antidepressant medicines throughout the study. Differences in provider treatment practices or differences in insurance coverage for medication costs could account for differences in findings.

Other studies have reported that depression is less common among those with more education in the general population (24–26) and perhaps also among people with diabetes who have more education (28), although a population-based study that included people with diabetes found no association between depression and education (1). We found that throughout the study, participants with more education were less likely to have elevated depression symptom scores and more likely to be taking antidepressant medicines, although the proportion with either marker increased during the course of the study among those with the

most education, whereas it remained unchanged among those with less education.

Some studies in the general population and a population-based study that included people with diabetes found no differences in depression markers among non-Hispanic whites, African Americans, and Hispanic Americans (1,25,26), although one study in the general population reported lower rates of lifetime MDD among African Americans than among non-Hispanic whites or Hispanic Americans (24). We found that throughout the DPP, non-Hispanic white participants were less likely to have elevated scores than African Americans and Hispanic Americans and that they were more likely to be taking antidepressant medicine than any other racial/ethnic group. During the course of the study, the proportion with either depression marker increased among non-Hispanic whites but remained unchanged among other racial/ethnic groups.

Strengths and limitations of the current study

Strengths of the current study include the large multiethnic population, including groups in which depression has rarely been studied, the definitive identification of IGT, and the fact that data were collected regarding antidepressant medication and depression symptoms. Limitations include the fact that the study cohort is probably not representative of all individuals with IGT because self-selection and screening procedures make it very likely that severely and even moderately depressed individuals were underrepresented. Also, we did not confirm that all patients using antidepressants were taking them for depression. These medicines are prescribed to treat other conditions. Some SSRIs are used to treat panic disorder, obsessive compulsive disorder, post-traumatic stress disorder, social anxiety disorder, and bulimia nervosa (42), but patients with these disorders probably represent a small proportion of those taking SSRIs. On entry to the DPP, 68% of participants taking antidepressants were taking SSRIs. At the 3rd year follow-up, this proportion was 76%. Tricyclic antidepressants are sometimes prescribed for relief of neuropathic symptoms in patients with diabetes, but DPP participants did not have diabetes at the outset of the study.

Implications

The current study suggests that it is possible to engage willing participants in an intensive effort to prevent or delay the development of type 2 diabetes without increasing depression. In fact, we found that participants who were more active or who lost weight also had small but significant reductions in their risk for some depression markers during the course of the study, independent of their treatment arm. These findings reinforce earlier reports that activity and weight are associated with depression (18–20,43,44), and they suggest a positive psychological impact of intensive efforts to prevent type 2 diabetes.

Our study also reveals relatively low levels of reported depression treatment among most racial/ethnic minorities and among those with less education. We found some signs that these differences diminished during the course of the study, but they remained large and should be further investigated and addressed for reasons of equity and because depression in people with IGT may be associated with negative physical health outcomes, as in people with diabetes.

The current findings offer guidance for future research. Our finding that there was essentially no overlap between the group of participants with BDI scores ≥ 11 and those taking antidepressant medicine reinforces the importance of considering the latter as a marker of depression. Estimates of depression rates based on either BDI or medication alone are likely to be too low. The lack of overlap between those with elevated symptoms and those taking antidepressant medicine also raises questions about possible differences between the two groups in health outcomes and how these outcomes might differ from those for patients receiving psychotherapy for depression. Considering both depression markers also provides a basis for understanding the clinical complexity of patients treated for depression. Patients who are positive for both markers likely have partially treated depression, those who take antidepressant medicine but do not have elevated symptoms have fully treated depression or are taking antidepressants for other indications, patients with elevated symptoms who are not taking antidepressant agents have untreated depression or depression that has not responded to psychotherapy, and patients

with neither depression marker are not depressed or their depression has been treated successfully with psychotherapy.

We did not collect data on psychotherapy in this study. Future studies should do so. Future studies should also determine with certainty that antidepressant medicines are being taken to treat depression rather than other conditions, and they should include subjects who are more representative of the population of individuals with IGT than those enrolled in the DPP.

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