Depression as a Predictor of Weight Regain Among Successful Weight Losers in the Diabetes Prevention Program

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OBJECTIVE—To determine whether depression symptoms or antidepressant medication use predicts weight regain in overweight individuals with impaired glucose tolerance (IGT) who are successful with initial weight loss.

RESEARCH DESIGN AND METHODS—A total of 1,442 participants who successfully lost at least 3% of their baseline body weight after 12 months of participation in the randomized controlled Diabetes Prevention Program (DPP) continued in their assigned treatment group (metformin, intensive lifestyle, or placebo) and were followed into the Diabetes Prevention Program Outcome Study (DPPOS). Weight regain was defined as a return to baseline DPP body weight. Participant weight and antidepressant medication use were assessed every 6 months. Depression symptoms (Beck Depression Inventory [BDI] score ≥ 11) were assessed every 12 months.

RESULTS—Only 2.7% of the overall cohort had moderate to severe depression symptoms at baseline; most of the participants with BDI score ≥ 11 had only mild symptoms during the period of observation. In unadjusted analyses, both depression symptoms (hazard ratio 1.31 [95% CI 1.03–1.67], $P = 0.03$) and antidepressant medication use at either the previous visit (1.72 [1.37–2.15], $P < 0.0001$) or cumulatively as percent of visits (1.005 [1.002–1.008], $P = 0.0003$) were predictors of subsequent weight regain. After adjustment for multiple covariates, antidepressant use remained a significant predictor of weight regain ($P < 0.0001$ for the previous study visit; $P = 0.0005$ for the cumulative measure), while depression symptoms did not.

CONCLUSIONS—In individuals with IGT who do not have severe depression and who initially lose weight, antidepressant use may increase the risk of weight regain.

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Depression is common in obese individuals (1–4) and is 50–100% more prevalent in those with diabetes than in the general population (3,4). Depression symptoms are associated with an increased risk of type 2 diabetes (5,6), and antidepressant medication use may also be associated with the development of diabetes in high-risk individuals (7–9). Both depression symptoms and antidepressant medications have been associated with overweight/obesity in individuals with or at increased risk of type 2 diabetes (7,10).

Depression is known to impair adherence to treatment recommendations in several chronic illnesses, including diabetes (11,12). This raises the possibility that problems with motivation and concentration, two cardinal symptoms of depression, could interfere with adherence to weight-loss efforts such as those shown to reduce the risk of developing type 2 diabetes in the Diabetes Prevention Program (DPP) (13) and the Finnish Diabetes Prevention Study (14). An analysis of a subset of DPP participants showed that higher baseline levels of depression symptoms were associated with lower levels of baseline physical activity (15). Another analysis from the original DPP cohort suggested that baseline depression symptoms did not adversely impact the chances of successful initial weight loss among participants randomized to the intensive lifestyle arm (16). It is not known whether depression symptoms at baseline affected weight in the metformin or placebo arms of the DPP clinical trial.

Weight regain is common after successful weight loss. To our knowledge, no studies have examined mood or antidepressant use as predictors of weight regain in individuals with prediabetes or diabetes who were previously successful in losing weight. In this study, we explored the association between weight gain and depression symptoms or antidepressant use in participants who successfully lost at least 3% of their baseline body weight after 1 year of the DPP. We examined the associations between depression symptoms or antidepressant use and weight

regain 6 months subsequently. We also examined the associations between cumulative depression symptoms or antidepressant use over the course of the DPPOS and weight regain. Our hypotheses were that depression symptoms would predict weight regain and that antidepressant use would predict weight regain. These associations would suggest the importance of regular monitoring for depression in successful weight loss participants in order to intervene early to decrease the risk of weight regain and for close follow-up for weight regain in individuals taking antidepressants.

RESEARCH DESIGN AND METHODS

The DPP was a randomized controlled clinical trial designed to compare the effects of lifestyle modification (achievement of ≥150 min of exercise per week and 7% weight loss) or metformin on delaying the onset of type 2 diabetes in overweight or obese adults who had impaired glucose tolerance and impaired fasting glucose (17,18). Participants with major psychiatric disorders and those taking greater than moderate doses of antidepressants were excluded (19). The first phase of the DPP study concluded after a mean 2.8 years of follow-up, with the finding that both lifestyle and metformin treatment resulted in significantly reduced risk of progression to type 2 diabetes compared with placebo (13). The study then continued in 2001 as the Diabetes Prevention Program Outcomes Study (DPPOS), designed to assess the effects of lifestyle or metformin on preventing long term macro- and microvascular complications of diabetes. In the DPPOS, participants continued in their assigned DPP treatment group: metformin, intensive lifestyle modification, or placebo. While weight loss per se was not a goal for participants in the metformin or placebo groups, all three treatment groups received exercise and weight loss advice in DPPOS and were eligible to attend quarterly lifestyle education sessions. Lifestyle intervention participants were also offered additional semiannual weight loss–specific campaigns. While the mechanism of weight loss in the metformin group may differ than other groups, all three treatment groups were included in this analysis because the objective was to see what the presence of depression symptoms did to the risk of weight regain among those who successfully lost weight regardless of the intervention or mechanism.

Data were collected longitudinally throughout the DPP/DPPOS. Participants' weight was collected every 6 months during both DPP and DPPOS through October 2008. As the weight regain event happened throughout the course of the study, the weight regain outcome was defined as a time-to-event variable at the subject level. Concurrent medication data were collected every 6 months in DPP/DPPOS. Nutrition data were collected at DPP baseline and year 1 and DPPOS years 1, 2, and year 5. Psychological and behavioral questionnaires were administrated annually in both DPP and DPPOS (17,18). Analyses in this paper are limited to successful weight losers, defined as participants randomized to the lifestyle, metformin, or placebo arms who achieved at least the median or greater weight loss (3% of baseline body weight) at the 12-month visit after randomization. The primary outcome of this analysis was weight regain (i.e., failure to maintain weight loss), defined as time to the first measured occurrence of a regain to the DPP baseline weight. We took a participant-centric perspective in selecting return to baseline weight, rather than a set kilogram definition, of weight regain, as we believe the former approach more closely mirrors concerns regarding how those who attempt weight loss and clinicians gauge the success of their efforts in real-world settings.

Data collection in this analysis, spanning the DPP and DPPOS, continued for a mean of 10 years. Participant data were censored at the point of weight regain. Cox proportional hazard models were used to examine the association between the key predictors (depression symptoms and antidepressant use) and the main outcome of weight regain. We hypothesized that both variables would predict weight regain. "Depression symptoms" was defined categorically as a Beck Depression Inventory (BDI) score ≥11. The BDI is a 21-item questionnaire, widely used clinically and in research, that has been shown to reliably detect mild, moderate, and severe levels of depression; the cut point of ≥11 indicates at least mild depression symptoms (19). Presence or absence of antidepressant use (selective serotonin uptake inhibitors, tricyclic antidepressants, serotonin/ norepinephrine reuptake inhibitors, and dopamine agonists) was derived from concurrent medication data.

Because depression symptoms and antidepressant use were measured repeatedly

throughout the study, we used time-dependent covariate analyses to model the relationship between depression and weight regain. Predictors in the models included depression symptoms 6 months prior to assessment of weight regain, percent of time having depression symptoms at previous DPP/DPPOS visits, taking an antidepressant 6 months earlier, and percent of time taking an antidepressant at previous DPP/DPPOS visits. For variables measured only at annual visits, such as depression scores, missing values at the semiannual visits were imputed using the previous annual visit data. Other nonstructural missing values were very sporadic and imputed using the last-value-carried-forward approach. Again using time-to-event analyses, we then sequentially assessed for the effect of several covariates potentially related to weight gain, including *1*) baseline treatment group (lifestyle, metformin, and placebo); *2*) age, sex, and ethnicity; *3*) marital status, income level, and education level; *4*) BMI at randomization and percent weight loss at the 12-month DPP visit; *5*) baseline activity and nutrient intake at DPP entry and at entry into the analysis and time-dependent leisure activity; *6*) medical comorbidity (assessed by number of chronic medications at the visit before weight regain), total number of serious adverse events before weight regain, incident diagnosis of diabetes, and initiation of diabetes medications other than metformin during follow-up; *7*) diabetes status plus antiglycemic medication use; *8*) average leisure activity throughout the study period; and *9*) DPP baseline participant self-rating of general health using the General and Physical Functioning questions of the SF-36 and mild or greater levels of anxiety. (Serious adverse medical events include conditions resulting in hospitalization for >24 hours, prolongation of a current hospitalization, permanent or severe disability, death, or congenital abnormality in pregnancy; are life threatening; or are involved in an accidental or intentional medication overdose.) Anxiety was assessed with the Beck Anxiety Inventory, a 21-item self-administered questionnaire shown to reliably detect mild levels of anxiety at a score ≥8 (20). Participants were not asked the indication (depression vs. anxiety) for antidepressant use at DPPOS visits; however, only 16% of participants had mild or greater levels of anxiety, and depression and anxiety symptoms are often comorbid (21). To examine the possibility that the association between depression

symptoms or antidepressant use and weight regain varied by the degree of initial weight loss, we examined the interaction between percentage of initial weight loss (3–7%, or approximately 7–15 pounds, versus ≥ 7%) and the depression variables. The SAS system was used for all analyses (version 9.3; SAS Institute, Cary, NC).

RESULTS—Baseline characteristics of DPP participants who lost ≥3% of their baseline body weight as of the 12-month DPP visit and those who did not are shown in Table 1. Of the original 3,234 DPP enrollees, 1,452 (44.9%) had lost at least 3% of their baseline body weight at the time of the 12-month DPP visit, which was the point of maximum weight loss for most participants. Seventy-one percent of DPP lifestyle participants achieved ≥3% weight loss compared with 42% of participants randomized to metformin and 21% of participants randomized to placebo ($P < 0.001$). Participants who lost ≥3% weight were older at DPP baseline (50.9 compared with 49.1 years of age, $P < 0.0001$) and had a lower baseline BMI (32.4 vs. 33.2 kg/m^2, $P = 0.0028$). Non-Hispanic white participants were somewhat more successful losing 3% of baseline weight compared with participants in other ethnic groups ($P < 0.01$), and married participants were slightly more successful compared with those who were not married ($P < 0.05$). Baseline antidepressant use, depression symptoms, anxiety symptoms, caloric intake, and leisure activity did not differ between participants losing weight and those not losing weight. Ten participants had no subsequent visits and were excluded from further analysis. Therefore, 1,442 participants are included in this analysis: 762 (52.8%) of successful weight losers were lifestyle participants, 452 (31.4%) were metformin participants, and 228 (15.8%) participated in the placebo arm. The median weight loss in the three groups was 8.5% (25th–75th percentile 6.1–12.0), 6.0% (4.3–8.9), and 5.7% (4.1–8.1), respectively. Among the 1,442 study participants who lost ≥3% of their baseline body weight as of the 12-month DPP visit, 826 (57%) regained their baseline weight, which occurred, on average, after 5.1 years of follow-up. Weight regain occurred in 124 (55.6%) lifestyle participants, 245 (54.2%) metformin participants, and 157 (68.9%) placebo participants. The crude incidence rate of weight regain to baseline in the three groups was 10.3 per 100 person-years for lifestyle, 10.3 for metformin, and 17.9 for the placebo group ($P < 0.0001$). As shown in Fig. 1, the difference between placebo and the other two groups was significant ($P < 0.0001$) beginning at the 6-month visit after the start of this analysis. Treatment group and weight loss at year one were independently associated with weight regain (data not shown).

Overall, 25.6% of the cohort in this analysis experienced elevated depression symptoms and 23.4% reported antidepressant use at least once during the assessment period. The majority of depressed participants had mild symptoms (BDI 11–15); only 36% of participants with depression symptoms (2.7% of the overall cohort) had more severe depression symptoms (BDI score of ≥16), limiting our power to conduct subset analyses on the most severely depressed (likely major depressive disorder) participants. The percentage of participants with categorically defined depression symptoms at a given study assessment point fluctuated throughout the study, while the percentage of participants taking antidepressant medication at a study assessment point trended upward toward 11–12% (Fig. 2)—a finding consistent with secular prevalence and trends (22). Less than 7.4% of participants simultaneously reported both depression symptoms and antidepressant use at any visit during the assessment period.

In unadjusted models, both depression symptoms (hazard ratio 1.31 [95%

Table 1—*Comparison of participants who lost ≥3% baseline weight vs. those who did not*

Characteristics at DPP baseline	Weight loss at DPP year 1 visit	
	<3% (n = 1,782)	≥3% (n = 1,452)
Treatment groups*		
Intensive lifestyle	312 (28.9)	767 (71.1)
Metformin	618 (57.6)	455 (42.4)
Placebo	852 (78.7)	230 (21.3)
Age at randomization (years)*	49.1 (42.5–56.7)	50.9 (43.8–59.0)
Sex		
Female	1,219 (55.6)	972 (44.4)
Male	563 (54.0)	480 (46.0)
Race/ethnicity&		
Caucasian	930 (52.6)	838 (47.4)
African American	392 (60.8)	253 (39.2)
Hispanic	282 (55.5)	226 (44.5)
American Indian	98 (57.3)	73 (42.7)
Asian	80 (56.3)	62 (43.7)
Married#		
Yes	1,138 (53.6)	986 (46.4)
No	644 (58.0)	466 (42.0)
Education (years)		
≤12	468 (56.1)	366 (43.9)
13–16	833 (53.5)	723 (46.5)
≥17	481 (57.0)	363 (43.0)
BMI (kg/m^2)&	33.2 (29.1–37.9)	32.4 (28.8–36.7)
Leisure activity (MET h/week)	10.0 (4.1–20.5)	9.6 (3.7–20.7)
Calorie intake (kcal)	1,904 (1,470–2,576)	1,886 (1,436–2,522)
Depression symptoms (BDI ≥11)		
Yes	186 (56.7)	142 (43.3)
No	1,563 (54.7)	1,296 (45.3)
Anxiety symptom (BAI ≥8)		
Yes	286 (55.2)	232 (44.8)
No	1,463 (54.8)	1,206 (45.2)
Antidepressant use		
Yes	92 (56.8)	70 (43.2)
No	1,690 (55.0)	1,382 (45.0)

Data are n (%) or median (interquartile range). BAI, Beck Anxiety Inventory. *$P < 0.0001$. &$P < 0.01$. #$P < 0.05$.
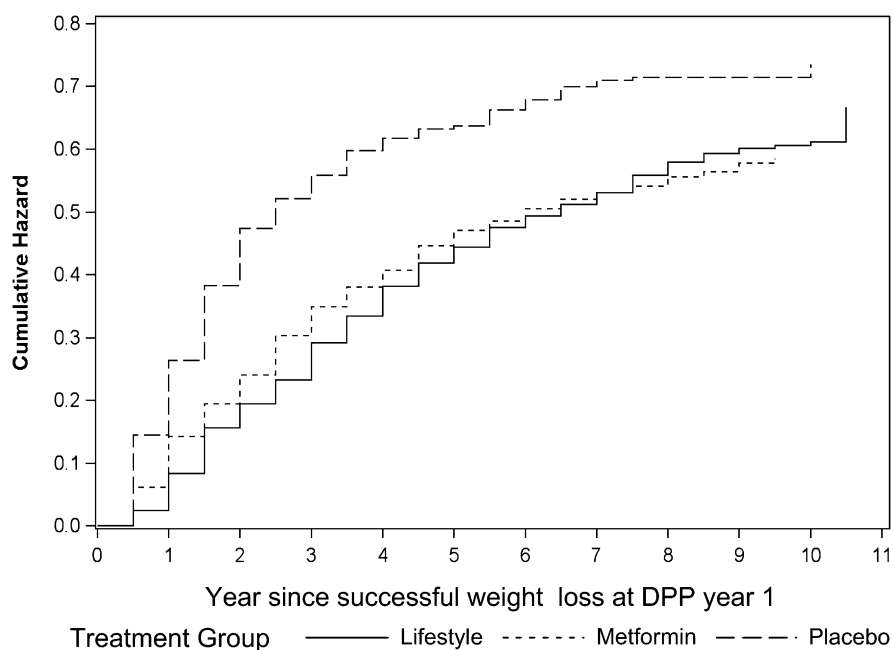
**Figure 1**—*Cumulative incidence of weight regain by DPP treatment group.*

CI 1.03–1.67], P = 0.03) and antidepressant use noted at the study visit 6 months previously (1.72 [1.37–2.15], P < 0.0001) were predictors of weight regain. Cumulative antidepressant use calculated as a percentage of all prior visits was also

noted to predict weight regain (1.005 [1.002–1.008], P = 0.0003), while cumulative depression symptoms calculated as a percentage of all prior study visits was not predictive (1.003 [1.000–1.006], P = 0.09). There were no

significant interactions between depression symptoms and treatment group. After adjustment for all covariates, depression symptoms at the previous visit no longer predicted weight regain; however, use of antidepressant medication at either the previous visit (1.735 [1.338–2.250], P < 0.0001) or any prior study visits as a percent (1.006 [1.002–1.009], P = 0.0005) remained a significant predictor for weight regain. The association of antidepressant use and subsequent weight regain was also noted in the subgroup of selective serotonin reuptake inhibitor (SSRI) participants (1.92 [1.43–2.58], P < 0.0001 for the previous visit; 1.006 [1.003–1.01] for any prior study visit, adjusted for the same covariates as in the antidepressant model). In fact, the antidepressant effect is mostly driven by the SSRI users. To determine whether the association between depression symptoms or antidepressant use and weight regain might be different in moderate and substantial initial weight losers, we performed a sensitivity analysis to look for a significant interaction between the weight loss categorical variable (3–7 vs. ≥7% weight loss) and the four depression measures. Because no significant interaction was found, we did not conduct further subgroup analyses.

CONCLUSIONS—Fifty-seven percent of successful weight losers (≥3% from baseline after 1 year of the DPP) regained their initially lost weight after an average of 5.1 years; 43% of successful weight losers were able to maintain some amount of weight loss. These findings are not surprising, given the results of other studies that substantiate the difficulties of sustaining initial weight loss over the long term (23). Participants in the active DPP treatment arms (lifestyle and metformin) were somewhat more successful in maintaining weight loss than placebo group participants (with differences becoming evident early in the follow-up period), yet many active group participants also regained weight. The weight regain similarities between the metformin and lifestyle groups in this analysis parallel those seen in the entire DPPOS cohort and in part reflect the fact that some lifestyle components were offered to metformin group participants, and the lifestyle group intervention became somewhat less intense after the completion of the initial DPP study (24).

In unadjusted models, both depression symptoms and antidepressant use
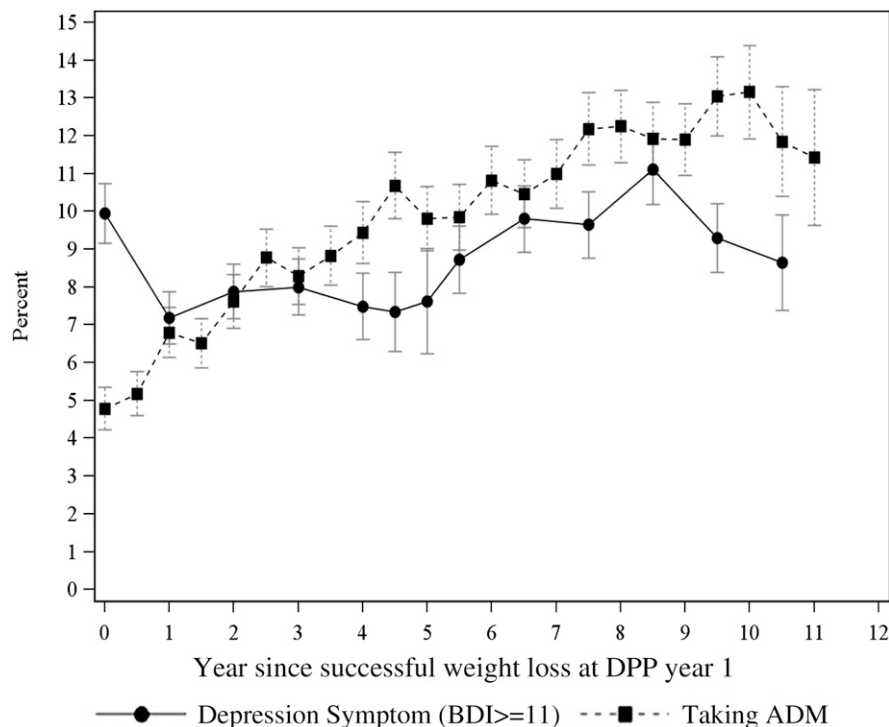
Figure 2—*Depression symptoms and antidepressant medication use over time among participants who achieved at least 3% weight loss.*

at either the previous DPP visit or their cumulative measures were associated with weight regain. After adjustment for multiple factors potentially related to weight gain, antidepressant use, but not depression symptoms, remained associated with a risk of weight regain in these participants. The risk of weight regain was 72% higher for participants using antidepressants at the visit 6 months prior compared with non–antidepressant users. This association remained when the analysis was restricted to SSRI antidepressant users.

SSRIs were the most frequently used (78%) antidepressants among DPP participants (25). Even though SSRIs are traditionally thought to be associated with less weight gain than are many older antidepressants, recent examinations (26) have suggested the tendency for some SSRI users to gain weight over time—a finding consistent with other DPP analyses (7). It is therefore possible that the weight regain seen in our participants is due to antidepressant side effects. The small number of participants using non-SSRI antidepressants precluded a comparison of risk of weight regain by antidepressant class.

There are several possible explanations for the failure of depression symptoms in predicting weight gain in our cohort. While weight gain is a feature of some forms of depression, it is not as prevalent as weight loss (27). Other investigators have found that the prevalence of obesity is related to depression severity (1,2). Individuals with more severe depression were excluded from DPP—only 2.7% had moderate or greater levels of depression at the time of initial enrollment (18)—and most of the participants with BDI score ≥ 11 during the period of observation had only mild symptoms. Therefore, it is possible that more severe, but not milder, depression symptoms would be related to weight regain, but we did not have enough power to detect this association. This would not discount the association between antidepressant medication use and weight regain, however.

Depression symptoms were assessed annually during our period of observation, while antidepressant medication use was assessed every 6 months. Thus, it is possible that, similar to the initial DPP cohort, depression symptoms in our participants were of short duration and may have resolved by the time of follow-up assessment (25). The frequent attention DPP participants received throughout the study may have helped lead to symptom resolution in some participants with milder depression symptoms. It is also possible that antidepressants were effective in treating the mild depression symptoms in our population, leading to symptom resolution while antidepressant use continued. While the DPP and DPPOS were not designed to ascertain this, a recent analysis (26) noting marginal differences between antidepressants and placebo for participants with mild depression symptoms lessens this possibility. We therefore cannot differentiate between spontaneous, antidepressant-aided, and psychosocial support–assisted resolution of depression symptoms in our cohort. All of these possibilities would lead to a failure to detect an association between depression symptoms as a predictor of weight regain.

Our analysis was also limited by the small number of participants (7.4%) reporting both depression symptoms and antidepressant use. The lower-than-expected prevalence of depression in our sample may be the result of DPP study selection criteria (individuals taking higher than the normal starting antidepressant dose were excluded) and recruitment bias (depressed individuals may have been less likely to volunteer for a long intensive study). The vast majority of participants in our cohort had mild depression symptoms that did not likely meet the threshold for major depressive disorder, which may explain why many participants with depression symptoms did not report taking antidepressants. We therefore could not test for differences between participants with both depression symptoms and antidepressant use compared with participants with only depression symptoms or only antidepressant use. Furthermore, the mild nature of depression symptoms in our cohort may limit the generalizability of our findings to other populations of individuals at risk for diabetes with more severe depression.

In our study of successful initial weight losers, after adjustment for multiple relevant covariates, antidepressant use at the previous (6 month) DPPOS visit was predictive of weight regain on follow-up. This suggests that overweight individuals with impaired glucose intolerance who successfully lose weight and who are recent antidepressant medication users may be at higher risk for regaining weight than non–antidepressant users with impaired glucose tolerance. Maintaining initially successful weight loss strategies over time can be difficult (23). These at-risk individuals may benefit from ongoing support via regularly structured coaching and reinforcement to help them maintain their successful weight loss strategies and refine them for new or unexpected challenges to maintaining behavior change. Early detection of weight regain could lead to intensification of weight loss strategies or the addition of new strategies to minimize regained weight. Future studies could design and elucidate practical, effective strategies for real-world settings to help these at-risk individuals maintain successful weight loss.

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