



Impact of Depression and Anxiety on Change to Physical Activity Following a Pragmatic Diabetes Prevention Program Within Primary Care: Pooled Analysis From Two Randomized Controlled Trials

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OBJECTIVE

The impact of major affective disorders on the effectiveness of diabetes prevention programs at promoting health behaviors has not been established. We investigated whether depression modifies the effectiveness of two pragmatic diabetes prevention programs at promoting increased physical activity.

RESEARCH DESIGN AND METHODS

This study pooled data from two cluster randomized controlled trials (Walking Away from Type 2 Diabetes and Let's Prevent Type 2 Diabetes) that included individuals at high risk of type 2 diabetes who were recruited from primary care. The trials used very similar intervention methods to promote physical activity and had annual follow-up over a 36-month period. Depressive symptoms were measured by the Hospital Anxiety and Depression Scale, and physical activity was measured by a piezoelectric pedometer (Let's Prevent Type 2 Diabetes) or an accelerometer (Walking Away from Type 2 Diabetes) and expressed as steps per day.

RESULTS

This analysis included 1,163 individuals (571 control, 592 intervention) who had concurrent baseline and follow-up data for ambulatory activity, depression, and anxiety. The median depression score was 3 at baseline; 11% of individuals were classified as having mild to severe depression. Those with no depressive symptoms at baseline or during follow-up increased their ambulatory activity by 592 steps per day ($P < 0.001$); this effect decayed by 88 steps per day (95% CI 21, 155) for every additional depressive symptom score at baseline, and each increase in the depressive symptom score between baseline and follow-up further attenuated the intervention effect by 99 steps per day (95% CI 2, 196).

CONCLUSIONS

Both depressive symptom burden at baseline and change in this burden are associated with a graded reduction in the effectiveness of diabetes prevention programs at increasing physical activity in primary care.

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Major affective disorders, particularly depression, are thought to be both predictors and consequences of diabetes, and they are a leading cause of disability worldwide (1,2). The coexistence of depression with type 2 diabetes has been estimated to triple or quadruple health care costs when compared with those for diabetes alone (3,4). In addition, depression is associated with less therapeutic adherence, a less healthy lifestyle, higher complication rates, and an increased risk of death (5,6). The risk of depression might be elevated in those who are at high risk of diabetes (7,8). However, although the consequences of major affective disorders on diabetes management have been well researched, their effect on diabetes prevention is less clear.

Lifestyle programs have been shown to reduce the risk of developing diabetes by over 50% and have been translated into real-world primary care settings (9,10). As depression is known to reduce the level of self-care and healthy behaviors in individuals with type 2 diabetes (6,11), it may also reduce the effectiveness of diabetes prevention programs. Its impact on physical activity in particular requires investigation. Physical inactivity is an established predictor of the incidence of type 2 diabetes, cardiovascular disease, and depression (12,13), whereas interventions to increase physical activity have been shown to reduce symptoms of depression and improve cardiometabolic health (14–16). However, evidence shows that the association between physical activity and depression is bidirectional: depression is also associated with lower physical activity levels and less engagement with physical activity interventions (17,18). Despite this, limited research has tested the hypothesis that depression reduces the effectiveness of diabetes prevention programs at initiating and sustaining changes in physical activity. In the original Diabetes Prevention Program (DPP), depression at baseline was associated with self-reported physical activity at baseline (19); no association, however, was found between depression at baseline and physical activity at follow-up, suggesting the intervention was equally effective in those with and those without depressive symptoms. However, physical activity was assessed by self-report and the cohort was highly selected (19). Therefore, the effect of depression on objectively assessed changes in physical activity

requires further clarification within diabetes prevention programs designed for implementation within “real-world” settings.

The Let’s Prevent Type 2 Diabetes (hereafter referred to as Let’s Prevent) and Walking Away from Type 2 Diabetes (hereafter, Walking Away) trials were conducted within primary care and designed to investigate the effectiveness of lifestyle interventions at promoting behavior change and reducing the risk of type 2 diabetes (20–23). The interventions were delivered through group-based, theory-driven, structured education designed for implementation within real-world settings. Although Let’s Prevent and Walking Away differed in their focus on weight loss and dietary intake, they included very similar physical activity interventions based on personalized goal setting and pedometer use, and they adopted the same measure of depression and depressive symptoms. Both studies reported modest increases in ambulatory activity (steps per day) during long-term follow-up (20,22). Here we pool data from these studies with the primary aim of investigating whether the number and severity of depressive symptoms modify the effectiveness of the interventions at promoting ambulatory activity, which was objectively assessed. We hypothesize that a higher burden of depressive symptoms will reduce the effectiveness of the intervention at increasing the number of steps taken each day. Symptoms of anxiety are reported as a secondary outcome.

RESEARCH DESIGN AND METHODS

This study reports data from the Walking Away and Let’s Prevent trials. Both studies were conducted concurrently within primary care in Leicestershire, U.K. The protocols and outcomes from each trial have been described in detail previously (20–23); both interventions used the same approach to promote physical activity. The trials obtained ethical approval from the National Health Service; written consent was obtained from each participant. Both trials are registered at www.ClinicalTrials.gov (Walking Away, reg. no. NCT00941954; Let’s Prevent, reg. no. NCT00677937).

Walking Away

A total of 808 adults were recruited from 10 family practices across urban and rural locations in Leicestershire, U.K., in 2010–

2011 (20,21). Individuals at high risk for nondiabetic hyperglycemia were identified by using the automated Leicester Risk Score, which applies a validated algorithm based on age, sex, BMI, ethnicity, prescribed antihypertensive medications, and family history of diabetes to data routinely collected within family practices (24). Those who scored above the 90th percentile in each practice were sent a letter from their family practice inviting them to attend a screening visit and take part in the study. Those taking steroids or who had received a diagnosis of type 2 diabetes, had a terminal illness, or were unable to take part in any walking activity were excluded. Practices were randomized to routine care (with the provision of a leaflet about lifestyle) or the Walking Away intervention, which consisted of a 3-h group-based, theory-driven, structured educational session that aimed to increase knowledge and perceptions of diabetes and diabetes risk factors and promote increased physical activity. Physical activity was largely promoted through walking by targeting self-efficacy, identifying barriers, and promoting self-regulatory skills through pedometer use. Individuals were encouraged to increase their ambulatory activity levels by up to 3,000 steps per day above their baseline level, depending on their preference and ability. Goal attainment was encouraged through the use of smaller proximal objectives, such as increasing activity by 500 steps per day every fortnight. Participants set an action plan detailing where, when, and how their first proximal goal would be reached, and they were encouraged to repeat this process for each new goal. A pedometer and steps-per-day diary were provided free. Two trained educators facilitated the program, delivering sessions in recruited family practices, local hospitals, and community settings such as church halls.

All participants in the intervention group were invited to attend two follow-up group-based sessions at 12 and 24 months; these were designed to reinforce the content of the initial session, review progress, support the maintenance of behavior change, and discuss reasons for relapse. Each follow-up refresher session lasted 2 h and was conducted by a single educator. Participants also received short telephone calls (~15 min) between annual sessions (at 6, 18, and 30 months).

Let's Prevent

A total of 880 adults were recruited from 44 family practices within the same geographical region in 2010–2011 (22,23); these adults were not also enrolled in Walking Away. As with Walking Away, individuals who scored within the 90th percentile of the automated Leicester Risk Score were invited to take part by a letter sent from their family practice. Those confirmed to have nondiabetic hyperglycemia without established diabetes or a terminal illness were included. Practices were randomized to routine care (leaflet) or Let's Prevent, a 6-h group-based, structured education program. Physical activity was promoted by using the intervention structure and content that were developed for Walking Away (see the WALKING AWAY description). In addition to the focus on physical activity through Walking Away, the Let's Prevent curriculum was extended to also promote weight regulation and a healthy diet. As with Walking Away, the Let's Prevent program was delivered by two trained educators within family practices, local hospitals, and community settings, and participants were invited to attend group-based follow-up sessions at 12 and 24 months.

Physical Activity

Walking Away

Participants wore an ActiGraph GT3X accelerometer on the right midaxillary line at the hip (attached via a waistband) for seven consecutive days during waking hours. Accelerometers were blinded to participants, meaning recorded data were not visible. We included those with at least 10 h of wear per day; 3 days of data were required for this study. Nonwear time was defined as a minimum of 60 min of continuous zero counts (20).

A physical activity data analysis tool (KineSoft version 3.3.76; Loughborough University, Loughborough, Leicestershire, U.K.) was used to derive output data, including steps per day.

Let's Prevent

Sealed NL-800 piezoelectric pedometers with a 7-day memory (NEW-LIFESTYLES) were used to measure steps per day. All participants were fitted with a pedometer (placed on their trunk with a clip along the right anterior axillary line) and instructed to wear it during waking hours for seven consecutive days and to keep a daily log of the times the instrument was attached

in the morning and taken off in the evening (22,23). At least three valid days of data were required; a valid day constituted at least 10 h of wear time as assessed by the pedometer log.

Minimum Clinically Important Change

A previous study suggested that an increase in 2,000 steps per day over 12 months is associated with an 8% reduction in the risk of cardiovascular mortality and morbidity in those with a high risk of type 2 diabetes (25), suggesting that an increase in ambulatory activity of 500 steps per day would be associated with around a 2% reduction in cardiovascular risk, which is near the lower limit of what could be considered clinically meaningful. Therefore, for illustrative purposes, we have taken 500 steps per day to be the minimum clinically meaningful difference in change in steps per day between the intervention and control groups.

Anxiety and Depression

The Hospital Anxiety and Depression Scale (HADS), in the form of a self-completed hard-copy questionnaire, was administered to participants in both trials at baseline and at 12, 24, and 36 months. HADS assesses anxiety and depression over 14 domains (7 for anxiety, 7 for depression), with four possible responses (scored 0–3) per domain (26). The summation of responses ranges from 0 to 21 for both the depression and anxiety scales; higher numbers are indicative of an increase in the number and severity of symptoms. HADS is widely used within primary care, community, and research settings, and it has been shown to be a valid measure for detecting clinical anxiety and depression (27,28). When using a threshold score of 8 to identify individuals with anxiety or depression disorders, sensitivity and specificity values between 0.7 and 0.9 have been reported (27). For the purposes of this study, the primary analysis was undertaken using depression and anxiety as continuous scores indicating the number and severity of symptoms. Data were also categorized into those with mild to severe anxiety or depression (a score ≥ 8) (27).

Participant Characteristics

This study also reports data on various characteristics collected following the methods reported in the original trials (20,22): age, sex, ethnicity, smoking status, BMI,

HbA_{1c}, and social deprivation (Index of Multiple Deprivation). Antidepressant medication use and previous cardiovascular disease (myocardial infarction, stroke, heart failure, angina) were captured through interview.

Data Pooling

Data generated from the Walking Away and Let's Prevent trials were pooled at the individual level for analysis. Walking Away (accelerometer) and Let's Prevent (pedometer) both used piezoelectric technology to measure physical activity, which has been shown to have a high level of accuracy in measuring steps taken (29); thus, these trials can be considered comparable in their assessments of steps per day (30). All other participant characteristics were measured using the same methods and standard operating procedures.

Statistical Analysis

Data were analyzed by using generalized estimating equations with an exchangeable matrix taking into account potential clustering within recruited family practices (general practices did not overlap between studies) and repeated follow-up measures over time. This approach ensures that all data captured for each individual contribute to the analysis, while taking into account that repeated measures have a within-person correlation (31). Change in steps per day was the dependent variable. Models were adjusted for measurement time point, treatment, sex, ethnicity, age, social deprivation, smoking status, cardiovascular disease, baseline antidepressant medication use, and baseline steps per day. We used treatment \times time interaction to assess whether the intervention effect varied by time (across 12, 24, and 36 months). To assess the modifying effect of the number and severity of depressive symptoms, we simultaneously added to the model baseline depressive symptom score and change in depressive symptom score and their interactions with treatment. We used the coefficient for baseline depressive symptom score \times treatment to derive the reduction in the intervention effect per unit depressive symptom score, which is referred to here as the decay in the intervention effect for every additional 1-unit-higher depressive symptom score. Similarly, we used the coefficient for change in depressive

symptom score \times treatment to derive the change in the intervention effect for each unit change in depressive symptom score from baseline to follow-up. We used the coefficient for treatment within the model to derive the intervention effect when baseline and change in depressive symptom scores were set to 0. We used the generated coefficients to model the continuous association of baseline and change in depressive symptom scores with the effectiveness of the intervention at promoting increased steps per day in those with a HADS score in the normal range (between 0 and 7). In addition, we report the intervention effect in those classified with mild to severe depression.

We used the same modeling to assess whether anxiety modified the intervention effect.

Sensitivity Analysis

To assess whether differences in the rates of those attending the primary (initial) intervention session or the annual follow-up maintenance sessions could confound interactions for the depressive or anxiety symptom scores, we assessed whether baseline depressive and anxiety symptom scores were associated with intervention attendance. We also repeated the analysis when restricting the intervention sample to those who 1) attended the initial intervention session or 2) attended the initial intervention session and at least one follow-up maintenance session.

Data were analyzed in SPSS software version 24. $P < 0.05$ was considered significant for main effects and interactions. Data are reported as the mean (95% CI) unless stated otherwise.

RESULTS

This study included 1,163 individuals who had concurrent steps-per-day and depressive symptom data at both baseline and follow-up, of whom 571 were allocated to the control group and 592 were allocated to the intervention group. Supplementary Fig. 1 shows the flow of participant inclusion, and Supplementary Table 1 compares the characteristics of those included and those excluded. On average, those included were 65 years of age and had a high BMI (31.4 kg/m²); 35% were female.

The numbers of steps per day taken by participants within each study at each time point are shown in Table 1. Within the pooled cohort at baseline, the control group took a mean (SD) of 6,556 (3,129)

steps per day and the intervention group took 6,530 (3,004) steps per day. Across follow-up time points, those in the intervention groups had more ambulatory activity than the combined control groups (intervention effect, 363 steps per day [95% CI 155, 571]; $P = 0.001$). We identified no interaction with time ($P = 0.097$).

The median depressive symptom score at baseline was 3 (interquartile range 1, 5); 121 individuals (10%) had a score of 0, while 125 (11%) were categorized with mild to severe depression. Depressive symptom scores at baseline and follow-up within each study are presented in Supplementary Table 2. Depressive symptom score at baseline ($P = 0.010$ for interaction) and change during follow-up ($P = 0.046$ for interaction) both modified the intervention effect for change in steps per day. Every additional depressive symptom score at baseline was associated with a decay in the intervention effect of 88 steps per day (95% CI 21, 155), and each increase in depressive symptom score between baseline and follow-up was associated with a further decay in the intervention effect of 99 steps per day (95% CI 2, 196).

Figure 1 shows the modeled reduction in the intervention effect for every additional 1-unit-higher depressive symptom score within the normal range and how this varies if the score decreased or increased by 2 units from baseline to follow-up. For example, those with a depressive symptom score of 0 at baseline and follow-up would, on average, increase their ambulatory activity by 592 steps per day as a result of taking part in the intervention. For an individual with a depressive symptom score of 3, corresponding to the median level within the population, the mean intervention effect reduced to 328 steps per day; however, this intervention effect could be increased to 526 steps per day if depressive symptoms were reduced by 2 units between baseline and follow-up. When the baseline depressive symptom score was 7, representing the upper limit of normal, no intervention effect occurred. These modeled results were supported by an analysis examining the observed intervention effect in the subsample categorized with mild to severe depression at baseline, which confirmed that no difference existed in the change in ambulatory activity

(intervention effect, 39 steps per day [95% CI -538 , 616]; $P = 0.895$) between the control and intervention groups (Fig. 2).

The median anxiety symptom score at baseline was 5 (interquartile range 2, 7); 106 individuals (9%) had a score of 0, while 260 (22%) were categorized with mild to severe anxiety. Anxiety symptom scores at baseline and follow-up within each study are presented in Supplementary Table 3. Neither baseline ($P = 0.240$ for interaction) nor change ($P = 0.759$ for interaction) in anxiety symptom score modified the intervention effect (data displayed in Supplementary Fig. 2).

In total, 83 individuals (14%) randomized to the intervention group did not attend the primary interventions, whereas 178 (32%) did not attend the maintenance session at 12 months and 241 (44%) did not attend at 24 months. Neither depressive ($P = 0.229$ for the initial session; $P = 0.709$ for the 12-month session; $P = 0.095$ for the 24-month session) nor anxiety ($P = 0.122$, $P = 0.259$, $P = 0.094$, respectively) symptom score at baseline was associated with intervention attendance. Furthermore, the pattern of results for the depressive symptom score was maintained when we restricted the intervention group to those who attended the initial intervention session or those who attended the initial intervention session and at least one follow-up session (Supplementary Fig. 3).

CONCLUSIONS

In a pooled analysis of two randomized controlled diabetes prevention trials with physical activity interventions based on promoting walking, the presence and severity of depressive symptoms was associated with reduced effectiveness at promoting increased steps per day in a dose-response manner, even within normal ranges (e.g., when the severity of depressive symptoms is below those considered as mild to severe depression). Those without any depressive symptoms at baseline or follow-up increased their ambulatory activity by 592 steps per day over a 3-year period; however, this intervention effect decayed by 88 steps per day for every additional 1-unit-higher depressive symptom score at baseline and by a further 99 steps per day for every 1-unit increase in the score between baseline and follow-up. The secondary

Table 1—Ambulatory activity (steps per day) within the Let’s Prevent and Walking Away trials at baseline and each annual follow-up

	Let’s Prevent				Walking Away			
	Control		Intervention		Control		Intervention	
	Participants (n)	Physical activity (steps per day)	Participants (n)	Physical activity (steps per day)	Participants (n)	Physical activity (steps per day)	Participants (n)	Physical activity (steps per day)
Baseline	292	6,432 (3,089)	290	6,290 (2,793)	279	6,686 (3,171)	302	6,760 (3,180)
12 months	268	6,122 (3,099)	253	6,552 (2,806)	260	6,313 (3,271)	284	6,821 (3,200)
24 months	228	6,159 (3,073)	235	6,706 (2,793)	251	5,942 (2,769)	270	6,246 (3,029)
36 months	201	5,600 (3,035)	192	5,985 (2,891)	237	5,963 (2,875)	238	6,307 (3,166)

Data are presented as mean (SD) unless otherwise indicated.

analysis found that anxiety did not modify the intervention, suggesting that the findings are specific to depression. To our knowledge, this is the first study to assess the impact of depression and anxiety symptom burden on change in physical activity (objectively assessed) following referral to a pragmatic diabetes prevention program within primary care.

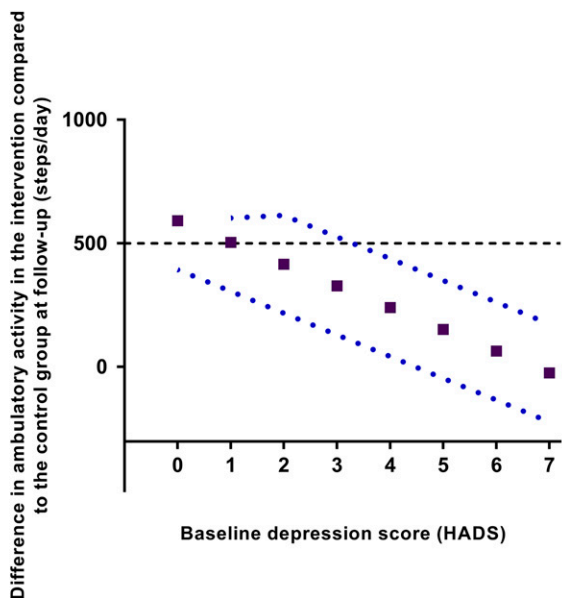
The median symptom scores for depression and anxiety observed among the cohorts within this study are consistent

with normative HADS data from primary care in England and are set against a background of an increasing prevalence of common mental health disorders more generally (32,33). This study therefore suggests that median depressive symptom scores observed within primary care are associated with a reduction in the effectiveness of promoting physical activity to levels below those that could be considered clinically meaningful (<500 steps per day) within a diabetes prevention

program. However, because changes in the depressive symptom score were also associated with the intervention effect, the majority would achieve a clinically meaningful increase in physical activity if depressive symptoms were reduced by at least two, which is potentially achievable through simple cognitive-behavioral interventions (34–36).

The results of this study contrast with those reported for the DPP, which did not find that baseline depression modified the effectiveness of the intervention at promoting increased physical activity (19,37). However, physical activity was assessed by self-report, which is accompanied by substantial measurement error (19,37). Depression was, however, found to predict objectively measured weight regain in the DPP (38), supporting the impact of depression on lasting behavior change. Our results are consistent with the wider physical activity literature, which has shown that depression or symptoms of depression are associated with a lower likelihood of achieving physical activity goals or engaging with physical activity interventions in older adults or following a coronary event (17,18). Given the many benefits of physical activity to both cardiometabolic and mental health (12–16), the potential for depressive symptoms to diminish intervention effectiveness is likely to be reinforced, whereby depression reduces the potential for promoting meaningful changes in physical activity, which in turn leads to a relative worsening of both cardiometabolic and mental health. This is also consistent with the bidirectional association reported between type 2 diabetes and depression (39).

This study has important strengths and limitations. Strengths include the population with a high risk of type 2 diabetes recruited from primary care and the



- Shows how the intervention effect decays for a given depressive symptom score at baseline.
- Shows how the intervention effect changes if the depressive symptom score were to increase (upper line) or decrease (lower line) by 2 units from baseline to follow-up (bounded by a depressive symptom score of 0 at the upper end).
- Threshold at which the intervention effect could be considered clinically meaningful (steps/day)

Figure 1—Influence of depression score at baseline and change in depression score in modifying the effectiveness of the intervention at increasing steps per day. Data are adjusted for follow-up time period and various patient characteristics, including sex, ethnicity, age, social deprivation, smoking status, previous cardiovascular disease, antidepressant medication use at baseline, and steps per day at baseline.

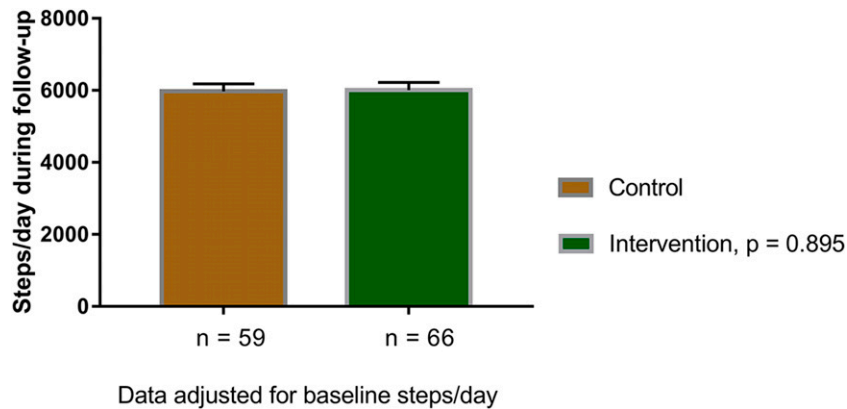


Figure 2—Ambulatory activity levels (steps per day) at follow-up in those categorized with mild to severe depression.

pragmatic nature of the interventions, making both the population and the intervention reflective of real-world prevention. In addition, the objective assessment of steps per day and the inclusion of studies that were conducted with the same standard operating procedures and physical activity intervention are strengths. Finally, the randomized design of the studies included in this analysis strengthens the conclusions, especially for the intervention effect on physical activity. Limitations include the number of individuals without concurrent baseline and follow-up data (31%), which may introduce bias and limit generalizability. HADS is not an instrument for use in diagnosing depression or anxiety, and our results should therefore be interpreted as relating to the general burden of depressive and anxiety symptoms rather than the presence of a major affective disorder. Although the majority of participants (86%) attended the initial intervention program, only 56% also attended both follow-up maintenance sessions. However, the modifying effect of depressive symptom scores was maintained within a per-protocol analysis, and the intervention attendance reflects that reported for implemented diabetes prevention services (40). In addition, as the interventions included in this study were not aimed at reducing depression, we cannot assume causation with regard to the modifying effect of depression. Further research is required to confirm whether introducing strategies to reduce depression will improve the effectiveness of interventions within diabetes prevention programs.

In conclusion, this study suggests that the presence of depressive symptoms is

associated with a reduction in the effectiveness of diabetes prevention programs at promoting physical activity within primary care. Therefore, diabetes prevention programs should consider broadening their content to include a focus on depression as a core aim. Simple tools—like HADS, used in this study—are available to help identify those who would benefit most from such an approach. However, considering the average levels of depressive symptoms observed in this cohort, a general focus on depression within diabetes prevention may benefit the majority of those referred. Given that the intervention studies used in this analysis were not aimed at reducing depression, the hypotheses generated by this research need to be evaluated in future diabetes prevention trials or ongoing services.

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(PH38), Type 2 diabetes: prevention in people at high risk. An adapted version of the Let's Prevent Type 2 Diabetes intervention is in the framework for the National Health Service Diabetes Prevention Programme, led by Ingeus (main contractor) and the Leicester Diabetes Centre, University Hospitals of Leicester (subcontractor). **Author Contributions.** T.Y. analyzed the data and wrote the manuscript. T.Y., L.J.G., K.K., and M.J.D. conceived and designed the studies. T.Y., L.J.G., J.H., C.L.E., K.K., and M.J.D. analyzed and interpreted data, critically revised the manuscript, and approved the final version of the manuscript. J.H. and C.L.E. acquired data. T.Y. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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