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Long-term effects of very low-carbohydrate and high-carbohydrate weight-loss diets on psychological health in obese adults with type 2 diabetes: randomized controlled trial

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Abstract. Brinkworth GD, Luscombe-Marsh ND, Thompson CH, Noakes M, Buckley JD, Wittert G, Wilson CJ (Commonwealth Scientific and Industrial Research Organisation – Food and Nutrition, Adelaide; University of Adelaide, Adelaide; University of South Australia, Adelaide; Flinders University, Adelaide, SA, Australia). Long-term effects of very low-carbohydrate and high-carbohydrate weight-loss diets on psychological health in obese adults with type 2 diabetes: randomized controlled trial. (Orginal Article). *J Intern Med* 2016; doi: 10.1111/joim.12501.

Background/Objective. Very low-carbohydrate, high-fat (LC) diets are used for type 2 diabetes (T2DM) management, but their effects on psychological health remain largely unknown. This study examined the long-term effects of an LC diet on psychological health.

Methods. One hundred and fifteen obese adults [age: 58.5 ± 7.1 years; body mass index: 34.6 ± 4.3 kg m^{-2}; HbA_{1c}: 7.3 ± 1.1%] with T2DM were randomized to consume either an energy-restricted (~6 to 7 MJ), planned isocaloric LC or high-carbohydrate, low-fat (HC) diet, combined with a supervised exercise programme (3 days $week^{-1}$) for 1 year. Body weight, psychological mood state and well-being [Profile of Mood States (POMS), Beck Depression Inventory (BDI) and Spielberger State Anxiety Inventory (SAI)] and diabetes-specific emotional distress [Problem Areas in Diabetes (PAID) Questionnaire] and quality of life [QoL Diabetes-39 (D-39)] were assessed.

Results. Overall weight loss was 9.5 ± 0.5 kg (mean ± SE), with no difference between groups ($P = 0.91$ time × diet). Significant improvements occurred in BDI, POMS (total mood disturbance and the six subscales of anger-hostility, confusion-bewilderment, depression-dejection, fatigue-inertia, vigour-activity and tension-anxiety), PAID (total score) and the D-39 dimensions of diabetes control, anxiety and worry, sexual functioning and energy and mobility, $P < 0.05$ time. SAI and the D-39 dimension of social burden remained unchanged ($P \geq 0.08$ time). Diet composition had no effect on the responses for the outcomes assessed ($P \geq 0.22$ time × diet).

Conclusion. In obese adults with T2DM, both diets achieved substantial weight loss and comparable improvements in QoL, mood state and affect. These results suggest that either an LC or HC diet within a lifestyle modification programme that includes exercise training improves psychological well-being.

Keywords: diabetes, diet, macronutrient composition, psychological well-being, weight loss.

Introduction

Type 2 diabetes mellitus (T2DM) is a major global health problem, affecting more than 366 million adults worldwide, with the prevalence projected to double by 2030 [1]. Diet modification is a cornerstone of diabetes treatment, and the diabetes epidemic has seen an increase in the use of very low-carbohydrate, high-fat (LC) diets as a treatment option that may better support blood glucose control and cardiovascular disease risk management compared to traditional high-carbohydrate, low-fat (HC) diets [2–4]. However, few studies have examined the effects of these dietary

Trial Registration: http://www.anzctr.org.au/, ANZCTR No. ACTRN12612000369820.

patterns on mood and psychological well-being. Characterizing this impact has particular relevance for individuals with T2DM because they experience an increased risk and prevalence of depression [5, 6], which may worsen adherence to dietary and exercise regimes [5] and is associated with lower adherence to diabetes self-care [6].

We previously reported that individuals who were randomized to an energy-reduced HC diet versus an isocaloric LC diet in a group of overweight and obese adults without T2DM experienced greater improvements in psychological mood state during a 12-month period [7]. However, this finding requires confirmation, particularly in populations with increased risk of depression and poorer mental health such as those with T2DM. If evident in these populations, this altered mood response may have potential implications for the applicability of an LC diet for long-term diabetes management and warrants further investigation.

To date, only two known studies have compared the long-term (12-month) effects of LC and HC diets on health-related and diabetes-specific quality of life (QoL) in T2DM [8, 9]. These studies showed that changes in the QoL measures did not differ between the diet groups, although greater improvements were observed with the LC diet for the health-related QoL domains of bodily pain, general health and the physical component [8]. However, these studies did not assess mood outcomes, including anxiety or depression, that have previously been shown to have differential long-term responses to LC and HC diets in individuals without diabetes.

The purpose of this study was to compare the effects of consuming either an energy-reduced LC diet or an energy-matched traditional HC diet over a 12-month period on mood state, including depression and anxiety and diabetes-related emotional stress, and QoL in a well-controlled randomized trial in obese adults with T2DM.

Methods

Study setting, participants and design

The study was conducted at the CSIRO Clinical Research Unit (Adelaide, Australia) between May 2012 and September 2013. The participants and study design were previously described in a study reporting separate outcomes (Fig. 1) [3]. In brief, 115 adults with T2DM (131 recruited, 16 withdrew prior to randomization), aged 35 to 68 years (mean ± standard deviation: 58.5 ± 7.1 years) and who were obese were block-matched for age, sex, body mass index (BMI), HbA_{1c} and diabetes medication using random varying block sizes before random computer-generated assignment to consume either an energy-restricted LC diet (n = 58) or an energy-matched traditional HC diet (n = 57) in a 1 : 1 ratio for 52 weeks. Randomization procedures (sequence generation and allocation concealment) were performed by research associates not involved in outcome assessments and intervention delivery. Exclusion criteria were a history of liver, cardiovascular, peripheral vascular, respiratory or gastrointestinal tract disease; current pregnancy or lactation; history of a malignancy; current depression (Beck Depression Inventory Score ≥29) [10]; history of or current eating disorder; or smoking. The study was approved by the Human Research Ethics Committees of the Commonwealth Scientific and Industrial Research Organisation, the University of South Australia, the University of Adelaide and Flinders University. All participants provided written informed consent prior to participation.

Interventions

Participants were provided with a prescriptive dietary plan of specific food quantities to achieve specified macronutrient profiles and energy levels as previously described [3]. Participants on the LC diet were prescribed a dietary plan aimed at providing 14% of total energy as carbohydrate (<50 g d^{-1}), 28% as protein and 58% as fat [35% monounsaturated fat (MUFA), 13% polyunsaturated fat (PUFA), <10% saturated fat). For participants on the HC diet, the prescribed dietary profile was 53% of total energy as carbohydrate, 17% as protein and <30% as total fat (15% MUFA, 9% PUFA and <10% saturated fat). Both diets were designed to be moderately energy restricted (2–4 MJ d^{-1}) with total energy intake and deficit planned to be energy matched. Participants met individually with a qualified dietitian on a fortnightly basis during the first 12 weeks of the study and monthly thereafter. Participants were provided with detailed individualized dietary advice, meal plans and recipe information pertaining to each diet. To facilitate dietary compliance, participants were given a selection of key foods (~30% of total energy) representative of each diet's macronutrient profile fortnightly for the first 12 weeks and then either key foods or a AUS$50 food voucher on an alternating basis at each monthly diet visit for the

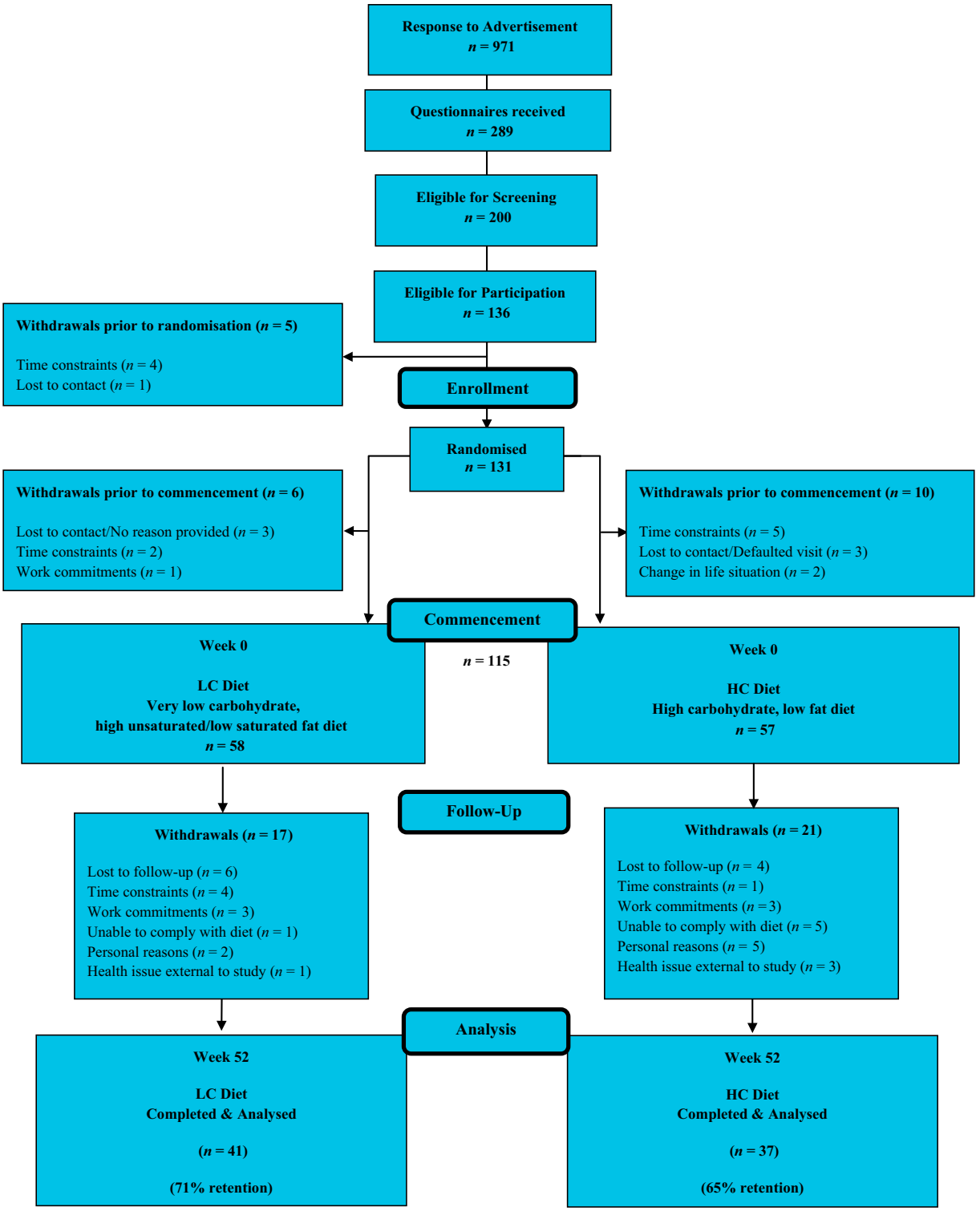

Fig. 1 *Study flow diagram.*

remainder of the study. Both dietary patterns were also structured to include specific food quantities and weights to ensure that the correct macronutrient and energy requirements were achieved. All participants also undertook a multicomponent exercise programme that was delivered and supervised by exercise professionals, consisting of 60 min of combined aerobic and resistance exercise performed at a moderate intensity on three nonconsecutive days per week.

Outcome measures

In the morning after an overnight fast, body weight (calibrated scales; Mercury AMZ1; Tokyo, Japan) and mood were measured at baseline and monthly intervals throughout the 52-week intervention. Mood was assessed using three validated questionnaires: the profile of mood states (POMS) [11], which measures six separate aspects of mood, tension-anxiety, depression-dejection, anger-hostility, vigour-activity, fatigue-inertia and confusion-bewilderment, and also provides a global score of mood disturbance [total mood disturbance score (TMDS)], which is determined by subtracting the vigour-activity score from the sum of the five negative mood factors; the Beck Depression Inventory (BDI) [10]; and the Spielberger State Anxiety Inventory (SAI) [12]. These instruments were administered using time referencing to frame the responses to the question 'How have you felt over the past week including today?'

Diabetes-related QoL and distress were also assessed at weeks 0, 24 and 52. QoL was assessed by the self-administered Diabetes-39 Questionnaire that assesses five distinct dimensions of diabetes-related QoL: anxiety/worry (four items), social burden (five items), diabetes control (12 items), sexual functioning (three items) and energy and mobility (15 items) [13]. Reponses for each item were on a Likert scale that ranged from 1 (not affected at all) to 7 (extremely affected). Raw scores obtained from each dimension were transformed onto a 0–100 scale, with higher scores indicative of greater impact on QoL. Diabetes-related emotional distress was measured by the Problem Areas in Diabetes (PAID) Questionnaire, a 20-item self-report instrument [14], which has been widely adopted as a measure of psychological adjustment specific to diabetes [15, 16]. Items are rated on a 5-point Likert scale (0 = not at all to 5 = completely) that assesses a range of different elements of diabetes-related psychological distress, such as anger, frustration and fear, from no problem to a serious problem. Higher scores indicate higher distress (score range = 0–100). High internal consistency ($\alpha = 0.92$) has been reported, and construct validity has been demonstrated [17].

Table 1 *Diabetes-39 Questionnaire dimensions and the problem areas in diabetes questionnaire score at baseline and after 24 and 52 weeks of either an energy-restricted very low-carbohydrate, high-fat diet or an energy-matched high-carbohydrate, low-fat diet*

Questionnaire Scale	Diet	Week 0	Week 24	Week 52
Diabetes-39				
Diabetes control	LC	19.3 ± 2.2	17.1 ± 2.3	18.5 ± 2.8
	HC	20.3 ± 2.2	14.1 ± 2.3	15.8 ± 2.8
Anxiety and Worry	LC	31.8 ± 2.9	25.9 ± 3.0	31.5 ± 3.8
	HC	25.9 ± 2.9	17.3 ± 3.0	22.1 ± 3.9
Social Burden	LC	9.3 ± 1.7	9.4 ± 2.2	10.8 ± 2.3
	HC	7.7 ± 1.7	8.0 ± 2.1	8.1 ± 2.3
Sexual Functioning	LC	24.3 ± 4.0	18.0 ± 3.6	19.6 ± 3.5
	HC	22.8 ± 4.1	12.7 ± 3.7	11.9 ± 3.5
Energy and Mobility	LC	18.1 ± 2.1	14.2 ± 2.1	19.3 ± 2.3
	HC	17.5 ± 2.1	11.7 ± 2.1	12.5 ± 2.3
PAID	LC	22.7 ± 2.0	12.1 ± 1.5	15.4 ± 1.8
	HC	22.3 ± 2.1	11.9 ± 1.4	12.3 ± 1.9

Data are estimated marginal means (SEs). LC, very low-carbohydrate, high-fat diet; HC, high-carbohydrate, low-fat diet; PAID, Problem Areas in Diabetes. No significant difference in responses between diet groups ($P \geq 0.28$).

Although diet assignment was discernible by participants and diet interventionists, blinding was maintained for researchers involved in outcome assessment and data analysis until study completion.

Statistical analysis

Prior to hypothesis testing, data were examined for normality. Data obtained from skewed variables and outcome subscales were normalized prior to analysis: BDI, SAI and POMS anger-hostility and depression-dejection by inverse transformation and POMS confusion-bewilderment, tension-anxiety, fatigue, total mood disturbance, Diabetes-39 subscales and PAID by log transformation. Baseline data for participants who dropped out of the study were compared with data for participants who completed the study, using Student's independent *t*-tests and chi-squared tests for continuous and categorical variables, respectively. No differences in baseline parameters were found between participants who dropped out and those who completed the study. This finding in conjunction with other considerations (including assessment of reasons for dropout) led us to believe that assuming the missing data were random was reasonable. Study outcomes were analysed as intention-to-treat using mixed-effects models with repeated measures over time within participants to compare mean changes over time between the two treatment groups. The model included all available data from each time-point measurement from the 115 participants who began the study, with fixed effects being the main effect at each time-point and diet group assignment and the diet group by time-point interaction. The primary advantages of a mixed-model analysis are that participants are treated as random effects in the repeated-measures model and that complete data across the entire study period are not required. That is, all available data collected from a participant in the analysis are used efficiently [18, 19]. This approach provides more precise modelling for longitudinal changes than last-observation-carried-forward methods that could result in bias in either direction [20]. Where a statistically significant main effect was found, *post hoc* comparisons were made to determine the differences between means. Sex was also included as a factor in the analyses, but no significant effect of sex was observed for any of the outcomes. The sample size of the study was determined based on the previously reported primary outcome of HbA_{1c} [3]. The study was designed to have sufficient power (80%, $\alpha = 0.05$) to detect an 1% absolute difference in HbA_{1c} between the LC and HC diets that had previously been observed [21, 22]. This level of change in HbA_{1c} is considered clinically relevant [23]. For the psychological health outcomes being reported here, there was also sufficient power (80%, $\alpha = 0.05$) to detect a differential change between the diet groups across the domains assessed, including BDI, POMS depression-dejection, POMS TMDS and PAID with a medium effect size (Cohen's $d = 0.5$). This level of change is clinically relevant [24, 25], and it is comparable to differences in the change in psychological mood state previously observed between LC and HC diets over 12 months [7]. Statistical analyses were performed using IBM SPSS statistics 20.0 for Windows (Chicago, IL, USA). All statistical tests were performed with α level ≤ 0.05 (two-tailed).

Results

Of the 131 participants randomized, 16 (six in the LC group and 10 in the HC group) withdrew from the study prior to beginning the intervention and were not included in the analysis; a further 38 (17 and 21 in the LC and HC groups, respectively) withdrew during the intervention [3]. Overall, the groups did not differ in terms of the number of participants who completed the study after randomization [LC, 41/58 (71%); HC, 37/57 (65%); $P = 0.51$].

During the study, both groups achieved substantial reductions in body weight, with no significant difference between the diets (LC, 101.8 ± 2.0 kg to 92.6 ± 2.0 kg, HC 101.1 ± 2.0 kg to 91.0 ± 2.0 kg; $P = 0.83$ time $\times$ diet interaction). The overall mean weight loss percentage at 12 months was 9%.

Data for mood scores during the intervention based on the estimated marginal means from the mixed models are presented in Figure 2. Over time, both groups experienced reductions in the BDI and the POMS (including the TMDS and the five subscales: tension-anxiety, depression-dejection, anger-hostility, fatigue-inertia and confusion-bewilderment) scores and an increase in the POMS vigour-activity subscale ($P < 0.05$ for time), with a magnitude of change between week 0 and 52 of 14% to 43% across these outcome measures. SAI remained unchanged throughout the intervention ($P = 0.54$ for time). No differences were found in the time-course responses between the dietary groups for

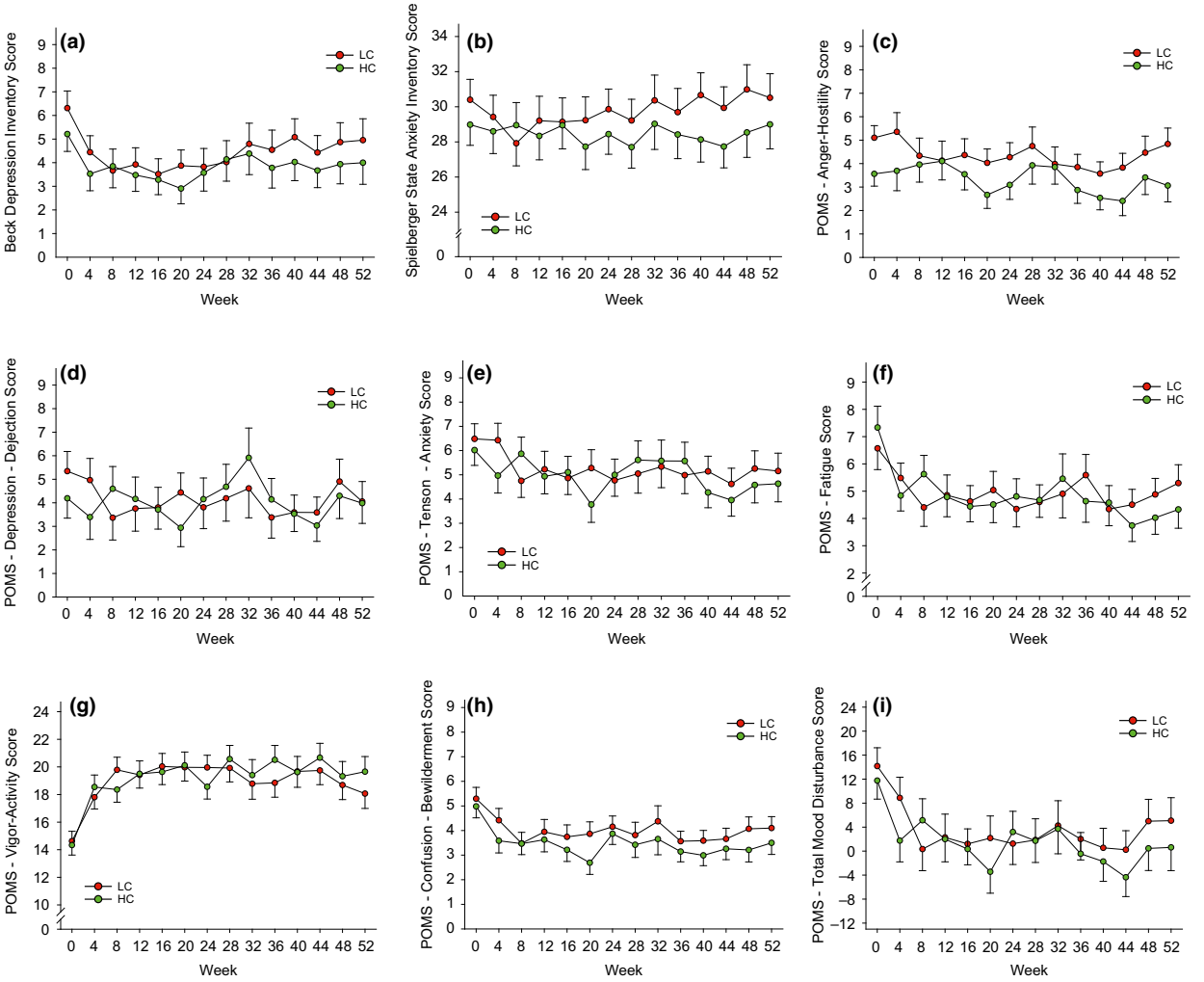

Fig. 2 *Estimated marginal means (SEs) of mood changes before and after 52 weeks of energy restriction with a very low-carbohydrate, high-fat (LC) for a high-carbohydrate, low-fat (HC) diet. Beck Depression Inventory Score (a), Spielberger State-Trait Anxiety Inventory Score (b) and the Profile of Mood States (POMS) subscales: anger-hostility (c), depression-dejection (d), tension-anxiety (e), fatigue-inertia (f), vigour-activity (g), confusion-bewilderment (h), total mood disturbance (i). No significant difference between diet groups responses across the mood outcome scales (P ≥ 0.22).*

any of the mood outcomes assessed ($P \geq 0.22$ time × diet).

Overall, across the course of the study, significant improvements (represented by score reductions) occurred in the PAID total score and all of the Diabetes-39 dimensions ($P \leq 0.02$), except for social burden ($P = 0.82$), with no differences in the response between the diet groups ($P \geq 0.28$), Table 1.

Of the participants who commenced the intervention, 17 [LC, 12/58 (21%); LF, 5/57 (9%); $P = 0.11$] were taking antidepressant medication. Removal of these participants from the analysis did not alter the outcomes for any of the variables assessed.

Detailed descriptions of the dietary intake analysis method and outcomes have been previously reported [3]. In summary, both groups achieved good compliance to the prescribed dietary intakes over the duration of the study: carbohydrate: LC, 54.0 to 74.0 g d^{-1} (13.4–16.6% energy), HC, 202.0 to 217.6 g d^{-1} (50.5–49.0%); protein: LC, 103.1 to 106.1 g d^{-1} (27.0–25.6%), HC, 72.1 to 78.5 g d^{-1}

(18.9–18.4%); total fat: LC, 95.9 to 101.5 g d^{-1} (54.4–52.5%), HC, 42.4 to 51.8 g d^{-1} (24.1–26.1%); saturated fat: LC, 17.2 to 21.2 g d^{-1} (9.8–11.0%), HC, 12.6 to 16.8 g d^{-1} (7.2–8.5%); monounsaturated fat: LC (30.7–28.8%), HC (11.4–12.0%); polyunsaturated fat: LC (12.4–11.1%), HC (4.1–4.2%).

Discussion

This large, randomized controlled study showed that both energy-restricted LC and HC diets resulted in comparable changes in mood, psychological profile and QoL responses in overweight and obese adults with T2DM. This contrasts with our previous trial in which greater improvements in mood were observed over the long term (52 weeks) with consumption of a HC diet compared with a LC diet. The discrepancy in the findings between these studies and the lack of any differential long-term effects in mood and psychological well-being response between the LC and HC diets in the present study could be related to several differences in experimental design.

Compared to individuals without diabetes, individuals with diabetes have higher levels of metabolic disturbance, which lead to a higher incidence of health complications and more distress associated with their well-being [26]. It is therefore possible that individuals in the current study experienced higher global levels of positive affect due to participating in the supervised lifestyle modification programme and/or from achieving substantial weight loss and metabolic improvements [3], and these factors may have masked any differential effects between the prescribed macronutrient compositions. Guldbrand *et al.* [8] also reported no differential long-term responses to the mental health component of the health-related QoL questionnaire in obese adults with T2DM who were randomly advised to follow either an LC or HC diet. Moreover, other data from the present trial that were previously reported demonstrated that improvements in glycaemic control and metabolic risk factors were greater with the LC diet than with the HC diet [3]. This was evident by a threefold greater reduction in diabetes-related medication requirements and improved diurnal blood glucose stability combined with more favourable changes in the blood lipid profile with the LC diet compared to the HC diet. These greater metabolic health improvements achieved with the LC diet may have magnified the mood-enhancing effects and positive affect experienced, counteracting any long-term negative mood responses induced by the LC diet that were previously observed.

In contrast to our previous study, which provided no specific physical activity recommendations or prescription [7], the present study included an intensive, planned and supervised exercise programme. The benefits of physical exercise for improving psychological well-being are well established [27]. Results of a recent systematic review indicate that the improvements in emotional well-being and QoL observed in the present study are consistent with some, but not all studies examining the effects of exercise training on psychological outcomes in individuals with T2DM [28]. It is therefore possible that the exercise-induced mood-enhancing effects that were not acquired in the previous study may have counteracted any negative mood effects associated with the LC diet. However, due to the lack of a nonexercising group, it remains unclear whether these additional mood benefits could be entirely attributed to the exercise *per se* or to some other factor. The possibility that these effects could also be attributed, at least in part, to the increased levels of professional attention and social support that participants received at the exercise sessions cannot be dismissed.

Discrepancies between the results of the previous and current studies may also be due to differences in the specific nutrient profiles of the LC diets that were used. The LC diet prescribed in the present study was low in saturated fat (<10% total energy) and high in unsaturated fat (MUFA 35% and PUFA 13% of total energy). In contrast, whilst the LC diet in the previous study had comparable total fat levels (58% total energy), the saturated fat content was higher (21% total energy) and the unsaturated fat content was lower (MUFA 25% and PUFA 8% of total energy). A recent large prospective cohort study of 12 059 individuals over 6 years showed an inverse dose–response relationship for total PUFA and MUFA intake and the risk of depression [29]. Furthermore, Kien *et al.* [30] showed that substituting dietary monounsaturated fat for saturated fat was associated with improved mood as assessed by POMS. Collectively, this evidence suggests that the greater intakes of monounsaturated fat and lower intakes of saturated fat with the LC diet in the present study may have negated the negative long-term mood responses previously reported.

Alternatively, differences in the level of dietary carbohydrate intake and restriction between the studies may also be an important factor. In our previous study that showed greater mood improvements with a HC diet compared to a LC diet, the prescribed and reported carbohydrate levels with the LC diet were between 20 and 40 g d^{-1} (5% to 10% of total energy). These levels were lower compared with those in the LC diet used in the present study (54–74 g d^{-1}; 13% to 17% total energy) or the study by Gaulbrand *et al.* [8] (90–103 g d^{-1}). It remains possible that the modest, yet less severe carbohydrate restrictions with the LC diet in the present study reduced the challenges associated with maintaining compliance to a LC dietary pattern and any consequent negative mood responses. Carbohydrate intake has also been shown to increase serotonin synthesis [31, 32], and it is well established that serotonin plays a role in offsetting mood disorders such as anxiety and depression [33, 34]. It is therefore possible that the small, but higher level of carbohydrate intake of the LC diet in the present study compared to the previous study may have increased the level of serotonin synthesis during the study, thereby reducing any negative mood affects related to reduced serotonin synthesis arising from carbohydrate restriction. Collectively, these studies suggest that a threshold level of carbohydrate intake that promotes mood alterations may exist. However, this level cannot be determined from the present study, and further studies should evaluate the dose–response relationship between the level of carbohydrate restriction and the onset of negative mood responses.

Irrespective of the lack of any differences between the diet groups, global improvements across the mood measures were observed. The LookAHEAD study reported comparable changes in body weight (8.6%) and reductions in depressive symptoms measured by BDI (−1.4 units) in overweight and obese individuals with T2DM after 1 year of an intensive lifestyle intervention [35]. Higher depressive symptoms are associated with poorer diet and medication adherence, functional impairment, higher primary healthcare costs [36], diabetes-related vascular complications [37] and increased risk of mortality [38]. These results suggest that weight loss resulting from lifestyle modification may be an important treatment strategy for reducing the risk of developing depressive symptoms and for managing depression-related noncompliance health behaviours and complications in this population.

In further support, the observed improvements in emotional well-being measured by decreases in PAID have been associated with significantly better diabetes self-care and coping skills [39, 40] and reductions in short- and long-term complications [14]. These outcomes may lead to higher morale and better psychological adjustment to diabetes and consequently contribute to better long-term glycaemic control [41].

The improvements in the QoL domain of sexual function observed in both groups are consistent with previous studies that have demonstrated that lifestyle intervention-based weight loss improves a variety of sexual function measures in obese individuals, including persons with T2DM [42–45]. The exact mechanisms of this response cannot be determined from the present data, but they may be related to improvements in endothelial function and/or psychological factors related to body image [42]. Sexual dysfunction is highly prevalent in men and women with T2DM [46, 47], being reported to be twice as high as in individuals without diabetes [48]. Collectively, this evidence highlights the important benefits of long-term weight loss achieved with lifestyle modification beyond the number of well-established metabolic health benefits that may provide further motivation to obese adults with T2DM to improve adherence with lifestyle modification.

A limitation of the present study was that it was conducted in a T2DM population without depression, reflected by the baseline mood scores that are typical for healthy adults [10–12]. Depression affects approximately 20% of individuals with diabetes [49, 50], and further studies that examine the effects of these dietary patterns in patients with diabetes and clinical depression are required to understand the wider generalizability of the current findings. Similar to this point, the QoL questionnaire is limited by ceiling and flooring effects for the degree in which a score can be improved or reduced. Therefore, because the baseline QoL scores were at the lower end of the scale, indicating a higher QoL, this may have reduced the magnitude of change observed with the interventions examined.

In summary, both energy-reduced LC and HC diets administered as part of a holistic lifestyle modification programme incorporating exercise training achieved similar improvements in mood state, QoL and diabetes self-management beliefs in overweight and obese adults with T2DM. This outcome

suggests that both dietary patterns can be used as a strategy for diabetes and weight management without negatively affecting psychological well-being. However, further studies are required to evaluate these effects in diabetes populations with pre-existing depressive symptoms.

Conflict of Interest Disclosures

No conflicts of interest to declare.

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Role of the Sponsors

The sponsor had no role in the design or conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript; and decision to submit the manuscript.

Author Contributions

GDB had full access to all study data and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors involved in study concept and design and analysis and interpretation of data; critically revised the manuscript for intellectual content; read and approved the final manuscript; and obtained funding. GDB involved in drafting of the manuscript. GDB, NLM, CHT, MN and JDB involved in study supervision.

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