

Long-term Effects of a Very Low-Carbohydrate Diet and a Low-Fat Diet on Mood and Cognitive Function

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Background: Very low-carbohydrate (LC) diets are often used to promote weight loss, but the long-term effects on psychological function remain unknown.

Methods: A total of 106 overweight and obese participants (mean [SE] age, 50.0 [0.8] years; mean [SE] body mass index [calculated as weight in kilograms divided by height in meters squared], 33.7 [0.4]) were randomly assigned either to an energy-restricted (approximately 1433-1672 kcal [to convert to kilojoules, multiply by 4.186]), planned isocaloric, very low-carbohydrate, high-fat (LC) diet or to a high-carbohydrate, low-fat (LF) diet for 1 year. Changes in body weight, psychological mood and well-being (Profile of Mood States, Beck Depression Inventory, and Spielberger State Anxiety Inventory scores), and cognitive functioning (working memory and speed of processing) were assessed.

Results: By 1 year, the overall mean (SE) weight loss was 13.7 (1.8) kg, with no significant difference between groups ($P = .26$). Over the course of the study, there

were significant time \times diet interactions for Spielberger State Anxiety Inventory, Beck Depression Inventory, and Profile of Mood States scores for total mood disturbance, anger-hostility, confusion-bewilderment, and depression-dejection ($P < .05$) as a result of greater improvements in these psychological mood states for the LF diet compared with the LC diet. Working memory improved by 1 year ($P < .001$ for time), but speed of processing remained largely unchanged, with no effect of diet composition on either cognitive domain.

Conclusions: Over 1 year, there was a favorable effect of an energy-restricted LF diet compared with an isocaloric LC diet on mood state and affect in overweight and obese individuals. Both diets had similar effects on working memory and speed of processing.

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WEIGHT LOSS AS A RESULT of dieting in obese individuals has been shown to reliably improve psychological state, including mood.¹⁻³ Despite the consistency of official recommendations advocating a high-carbohydrate, low-fat (LF), energy-restricted diet for obesity treatment,^{4,5} the obesity epidemic has led to widespread interest in alternative dietary patterns for weight management, including very low-carbohydrate (LC) “ketogenic” diets that are typically high in protein and fat (particularly saturated fat).⁶ While recent clinical studies have shown that LC diets can be an effective alternative dietary approach for weight loss,⁷⁻⁹ their long-term effects on psychological function, including mood and cognition, have been poorly studied.

Two small short-term studies of obese women who were following a low-energy (800-950 kcal/d [to convert to kilojoules, multiply by 4.186]) LF or LC diet for 4 to 6 weeks showed that diet composition did not affect mood state.^{10,11} Similarly, D’Anci et al¹² showed no differences in mood in overweight

and obese women who were following a mild hypocaloric LF or LC diet after 3 weeks, although the LC diet resulted in transiently lower scores on the confusion subscale of the Profile of Mood States (POMS) at 2 weeks. Recently, we reported that 8 weeks of consuming either a hypocaloric LC diet or an isoenergetic conventional LF diet resulted in similar improvements in mood state in overweight and obese men and women.¹³ These previous findings suggest that LC and LF diets have similar effects on mood, but these data must be considered somewhat preliminary because of the short duration of the studies. Over a longer period of 24 weeks, McClernon et al¹⁴ reported that mood improved after weight loss with either an LC or an LF diet, but the improvements were greater with the LC diet owing to larger reductions in the negative affect that was suggested to be related to the antidepressant effects of a ketogenic diet. However, their study was limited in that mood was not assessed using validated scales. Rather, they used a symptom checklist developed by practitioners specifically for evaluating and treating individuals using an LC diet for weight loss that may have biased the result toward a positive

effect of an LC diet as opposed to an LF diet. Also, the effects of an LC diet over the longer term remain unstudied, making it difficult to draw any definite conclusions regarding the long-term effects of an LC diet combined with moderate energy restriction on psychosocial health.

Studies have also investigated the effects of carbohydrate consumption and carbohydrate-restricted diets on cognitive function.^{12,13,15-18} In young rats, treatment with a ketogenic LC diet resulted in severe cognitive impairment.¹⁵ Acute studies in humans have shown that glucose administration improves cognitive performance,^{16,17,19} with the hypothesis being that this effect is attributable to increased glucose metabolism in the brain, which then elevates acetylcholine levels and leads to increases in the amplitude of synaptic potentials.^{16,20} Concomitant increases in insulin levels as a result of elevations in glucose levels have also been implicated because hippocampal glucose metabolism is sensitive to insulin.^{21,22} Moreover, glucose-mediated secretion of gut hormones, some of which may affect brain metabolism and autonomic function, has been postulated.¹⁷ Glucose also influences the activity of neurotransmitters, including dopamine and serotonin,¹⁶ suggesting that glucose may influence cognitive function via indirect processes. In short-term interventional studies in humans, consumption of an LC diet can influence various aspects of cognition in either a positive or a negative manner.^{12,13,18} A small 4-week study in obese women demonstrated impaired cognitive function after consumption of a very low-energy (approximately 600 kcal) LC ketogenic diet compared with an isocaloric, higher-carbohydrate, lower-fat nonketogenic diet, with the impairment being most evident after 1 week.¹⁸ Similarly, a 3-week study in overweight and obese women showed poorer performance on a memory-based task but improved performance on a vigilance-attention task following an energy-restricted LC diet compared with a conventional LF diet.¹² Although the researchers suggested that dietary macronutrient composition did not differently affect preoccupation with food or distraction of physiologic signs of hunger that could not explain the differential changes in cognitive performance, possible mechanisms for the observed effects were not studied or discussed in these prior studies.^{12,18} In obese men and women, we also showed that following an energy-restricted LC diet for 8 weeks was associated with impairments in cognitive processing speed but not in working memory, relative to those following an isocaloric conventional LF diet.¹³ Collectively, this evidence suggests that long-term consumption of an LC diet may have implications for cognitive functioning, but so far, to our knowledge, no study has documented these effects beyond a few weeks. Herein, we extend the results of a previous investigation of the short-term effects¹³ of consuming either an energy-reduced LC diet or an isocaloric conventional LF diet on mood and cognitive function and report the long-term effects at 1 year.

METHODS

PARTICIPANTS AND DESIGN

The participants and study design have been previously described elsewhere in a study reporting on separate out-

comes.²³ Briefly, 118 participants (122 were recruited; 4 withdrew before randomization) aged 24 to 64 years (mean [SE] age, 50.0 [0.8] years) with abdominal obesity and at least 1 additional metabolic syndrome risk factor²⁴ were randomized to consume either an energy-restricted LC diet (n=57) or an isocaloric conventional LF diet (n=61) for 52 weeks. Exclusion criteria were a history of liver, cardiovascular, peripheral vascular, respiratory, or gastrointestinal disease; diabetes; pregnancy; or cancer. The study was approved by the Human Research Ethics Committees of the Commonwealth Scientific and Industrial Research Organisation and the University of South Australia, Adelaide. All participants provided written informed consent before participation.

The participants were provided with a prescriptive dietary plan of specific food quantities to achieve specified macronutrient profiles and energy levels. Participants on the LC diet were prescribed a dietary plan aimed at providing 4% of total energy as carbohydrate, 35% as protein, and 61% as fat (20% saturated fat), with the objective to restrict carbohydrate to less than 20 g/d for the first 8 weeks and with an option to increase to less than 40 g/d for the remainder of the study. For participants on the LF diet, the prescribed dietary profile was 46% of total energy as carbohydrate, 24% as protein, and 30% as total fat (<8% saturated fat), with the objective to restrict saturated fat intake to less than 10 g/d for the study duration and with the inclusion of an approved food exchange (equivalent to the energy content of 20 g of carbohydrate) between weeks 9 and 52. Both diets were designed to be moderately energy restricted (approximately 1433 kcal/d for women and 1672 kcal/d for men), with the total energy intake and energy deficit planned to be isocaloric. The participants met individually with a qualified dietitian fortnightly during the first 8 weeks of the study and then monthly thereafter; the dietitian provided detailed individualized dietary advice, meal plans, and recipe information pertaining to each diet. To facilitate dietary compliance, the participants were supplied with a selection of key foods (approximately 30% of total energy) that were representative of each diet's macronutrient profile fortnightly for the first 8 weeks, and then a A\$40 food voucher was provided at each monthly diet visit during the 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 as previously described.¹³

OUTCOME MEASURES

In the morning after an overnight fast, body weight (calibrated scales, model AMZ14; Mercury Digital Scales, Tokyo, Japan) and mood were measured at baseline and at weeks 8, 24, 40, and 52. Mood was assessed using 3 validated questionnaires: (1) the POMS,²⁵ which measures 6 separate aspects of mood, including tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment, and provides a global score of mood disturbance (total mood disturbance score [TMDS]) that is determined by subtracting the vigor-activity score from the sum of the 5 negative mood factors; (2) the Beck Depression Inventory (BDI)²⁶; and (3) the Spielberger State-Trait Anxiety Inventory (SAI).²⁷ These instruments were administered using time referencing to frame the responses to the following question: "How have you felt over the past week, including today?" Cognitive function was also assessed at baseline and at weeks 8 and 52 using 2 computer-based tests: digit span backward (DSB)²⁸ and inspection time,²⁹ which assess working memory and speed of processing, respectively, and have been described previously in detail.¹³ After the cognitive and/or mood assessments at weeks 0, 8, 24, and 52, a venous blood sample was obtained for the

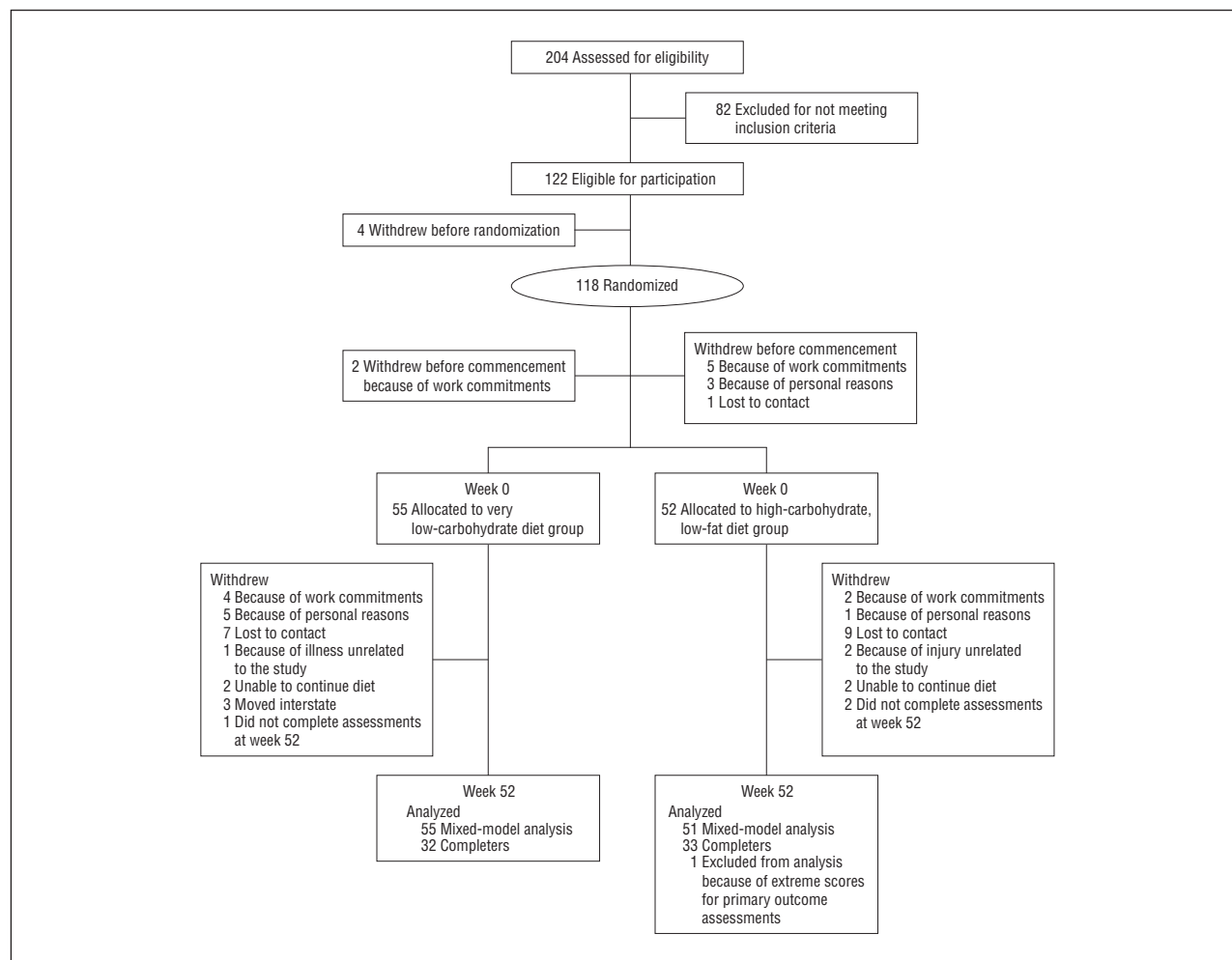


Figure 1. Flow of participants through the trial.

measurement of plasma glucose and serum insulin levels using a standard enzymatic kit (Roche Diagnostics, Basel, Switzerland) and an enzyme immunoassay kit (Mercodia ELISA; ALPCO Diagnostics, Uppsala, Sweden), respectively.

STATISTICAL ANALYSIS

Before hypothesis testing, data were examined for normality. Data obtained from the mood scales were skewed and normalized by log transformation before analysis. Comparisons of baseline data between experimental conditions and between study dropouts and completers were performed using independent *t* tests and χ^2 tests for continuous and categorical variables, respectively. The results indicated that there were no differences in baseline parameters between dropouts and completers. This result in conjunction with other considerations (including assessment of reasons for dropout) led us to believe that the assumption of the missing data being at random is reasonable. To evaluate the outcomes of this study, 2 separate analyses were performed. First, mixed-effects models with repeated measures over time within participants were used to compare mean changes over time between the 2 treatment groups. In the models, participant sex and age were included as factors, and change in weight was included as a covariate to adjust for differences in weight loss. 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 are not required across the entire study period; ie, there is efficient use of all available data collected from

the participants in the analysis.^{30,31} This analysis provides more precise modeling for longitudinal changes than last-observation-carried-forward methods that could result in bias in either direction.³² Second, a completer's analysis using repeated measures analysis of covariance (ANCOVA) was used to compare treatment effects in all patients who completed the outcome measures at all planned time points, with time as the within-subject factor and treatment and sex as between-subject factors. Age and changes in body weight were included in the model as covariates. When a statistically significant main effect was found, post hoc comparisons were performed to determine differences between the 2 treatments at week 52. Statistical analyses were performed with SPSS version 16.0 (SPSS Inc, Chicago, Illinois). All statistical tests were performed with $\alpha \leq 0.05$ (2-tailed).

RESULTS

Of the 118 participants who were randomized, 11 (2 on the LC diet and 9 on the LF diet) withdrew from the study before it began and were not included in the analysis; a further 38 withdrew throughout the intervention, and an additional 3 participants did not complete the mood and cognitive function assessments at the end of the study at week 52 (**Figure 1**). Another participant in the LF group had extreme scores for these primary outcomes (>4 SDs from the sample mean) and was identified as an outlier and subse-

quently excluded from the analysis. Overall, there was no difference between the groups in the number of volunteers who completed the study after randomization (LC group, 32 of 55 [58%]; LF group, 33 of 51 [65%]); $P = .84$). Of the volunteers who began the intervention, 19 (LC group, 13 of 55 [24%]; LF group, 6 of 52 [12%]; $P = .10$) were taking antidepressant medication. Throughout the intervention, 1 participant in the LC group took more antidepressant medication, and 2 participants took less. The results of the analysis did not change when the participants who were taking antidepressant medication were excluded.

On mixed-model analysis using data from all participants, both groups achieved substantial reductions in body weight over the course of the study, with no significant difference between the diets (mean [SE] change in weight: LC group, 96.0 [1.6] kg to 82.3 [2.1] kg; LF group, 97.6 [1.6] kg to 83.9 [1.9] kg; $P = .26$ for time \times diet interaction). There was an overall mean weight loss at 12 months of 13.7 (1.8) kg. Over the study period, both groups also had similar reductions in plasma glucose levels (mean [SE] change in plasma glucose levels [to convert glucose to milligrams per deciliter, divide by 0.0555]: LC group, 5.7 [0.9] mmol/L to 5.4 [0.09] mmol/L; LF group, 5.7 [0.8] mmol/L to 5.3 [0.08] mmol/L; $P = .41$ for time \times diet interaction) and serum insulin levels (mean [SE] change in serum insulin levels [to convert insulin to picomoles per liter, multiply by 6.945]: LC group, 9.0 [0.8] μ IU/mL to 5.4 [0.8] μ IU/mL; LF group, 10.5 [0.7] μ IU/mL to 6.5 [0.7] μ IU/mL; $P = .38$ for time \times diet interaction). A completer's analysis using ANCOVA gave similar results for these outcomes (difference in weight loss, $P = .20$; difference in glucose levels, $P = .79$; and difference in insulin levels, $P = .75$).

MOOD MEASURES

At baseline, there was no significant difference between groups on the BDI, SAI, or POMS subscale scores or on the TMDS score that was within 1 SD of the normal range for healthy adult populations.^{25,27,33} The data for mood scores during the intervention based on the estimated marginal means from the mixed models are presented in **Figure 2**. As previously reported,¹³ both groups had an initial reduction in scores on the BDI, SAI, and POMS (including the TMDS and the 6 subscales: tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment) that was of similar magnitude by week 8. However, over the longer term, the overall course of change on the SAI, TMDS, and anger-hostility, confusion-bewilderment, and depression-dejection subscales of the POMS differed between the 2 treatment groups ($P < .05$ for time \times diet interaction) because the average scores for these parameters decreased initially in both diet groups and then tended to remain low in the LF group but rebounded toward baseline levels over time in the LC group (Figure 2). Post hoc analysis showed that at week 52 the scores on the POMS subscales of anger-hostility ($P = .006$), confusion-bewilderment ($P = .02$), and depression-dejection ($P = .05$) and the TMDS score ($P = .001$) were significantly lower in the LF group than in the LC group. On the SAI, the differences were also evident between the diet groups at week 52 ($P = .06$). A similar pattern of change was evident on the BDI, although the difference between the diet groups did

not reach statistical significance ($P = .11$ for time \times diet interaction). The overall trajectory (ie, all time points) of changes in the scores on the remaining POMS subscales—tension-anxiety, fatigue-inertia, and vigor-activity—showed no effect of diet.

The completer's analysis (ie, only those participants who completed the study) using ANCOVA gave a similar pattern of results on the mixed-model analysis for all mood measures presented in Figure 2. Across the course of the study, there were significant time \times diet interactions for the SAI ($P = .02$), BDI ($P = .04$), TMDS ($P = .004$) and POMS scales: confusion-bewilderment ($P = .04$), anger-hostility ($P = .04$), depression-dejection ($P = .04$) such that scores improved in the LF group compared with the LC group. Again, the pattern of change for the remaining POMS subscales of tension-anxiety, fatigue-inertia, and vigor-activity did not differ between groups ($P \geq .16$ for time \times diet interaction).

COGNITIVE FUNCTIONING MEASURES

Values for the cognitive functioning tests are reported in the **Table**. At baseline, there was no significant difference between groups for working memory or speed of processing. Overall, the mixed-model analysis showed significant improvements in working memory over time ($P < .001$ for time effect) as a result of the long-term maintenance of improvements that occurred during the initial 8 weeks of the study; no differential effect of diet treatment was observed ($P = .88$ for time \times diet interaction). For speed of processing, although there was a significant main effect of time ($P = .011$) that arose because of an initial reduction in task performance time after 8 weeks, rebound was evident after 12 months in both groups, and across the entire study period, there was no statistically significant difference between groups ($P = .49$ for time \times diet interaction) (Table). The completer's analysis using ANCOVA gave similar results for these outcomes. At week 52, there was a significant inverse correlation between the change in working memory and the change in fasting plasma insulin levels ($r = 0.34$; $P = .007$).

COMMENT

In this large, randomized, controlled study, we compared the long-term effects of a moderate energy-restricted LC diet with those of a conventional isocaloric LF diet on mood and cognitive function in overweight and obese individuals. We previously reported marked improvements in mood with both diets over the shorter term of 8 weeks.¹³ In the present study, for the majority of the mood measures, including the SAI, BDI, and TMDS and the POMS subscales of anger, depression, and confusion, a significant effect of diet composition was observed showing that scores improved over the longer term and then remained stable for participants who were on the LF diet (ie, a positive effect of the diet on mood was maintained), but in the LC group, despite an initial improvement, scores returned toward baseline levels over time (ie, mood returned toward more negative baseline levels).

The sustained improvements in mood in the LF group compared with the LC group are consistent with results from epidemiological studies showing that diets high in

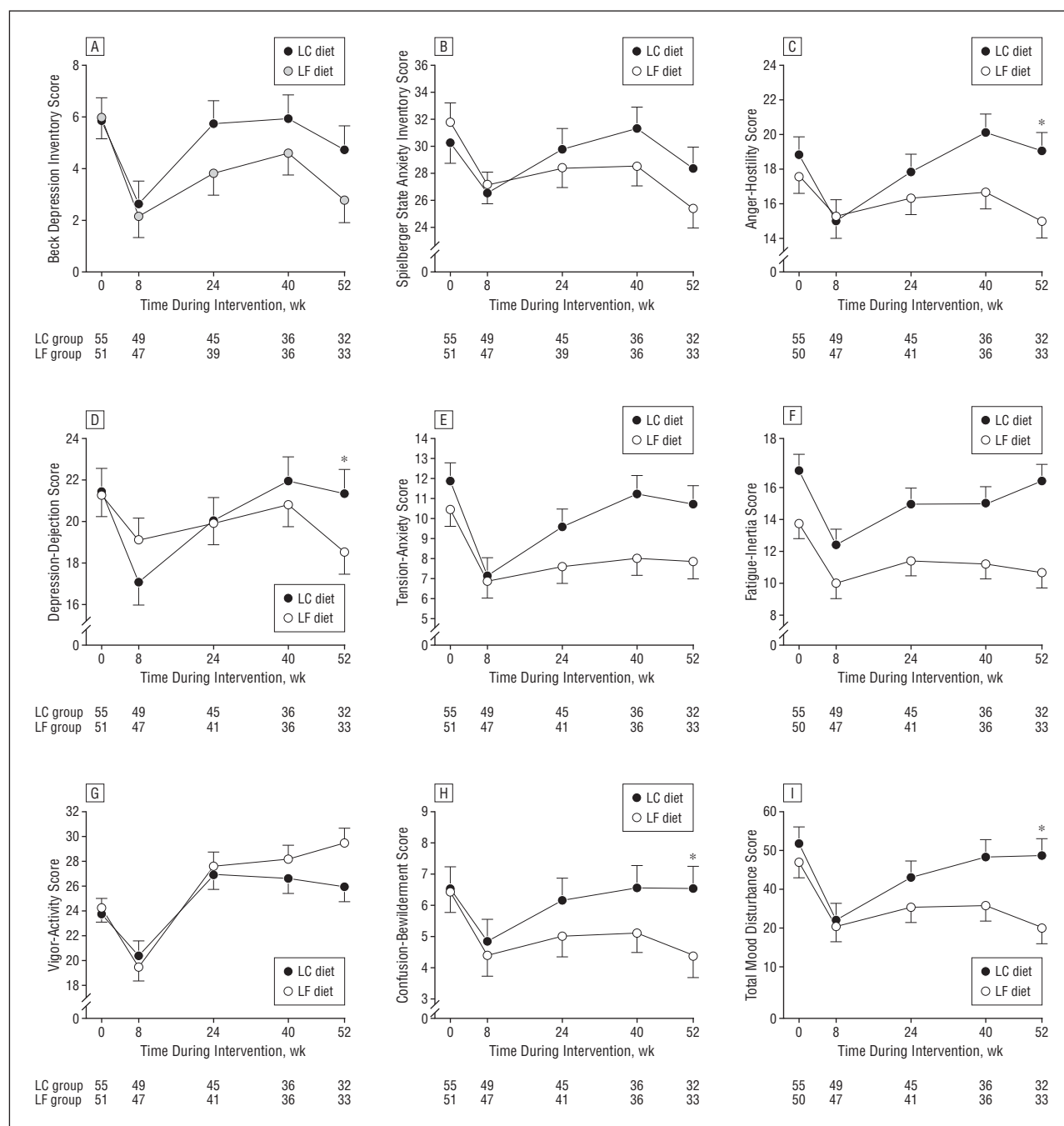


Figure 2. Estimated marginal means (SEs) of mood scores before and after 8, 24, 40, and 52 weeks of energy restriction with a low-carbohydrate, high-fat (LC) diet or a high carbohydrate, low-fat (LF) diet. Beck Depression Inventory score (A), Spielberger State-Trait Anxiety Inventory score (B), and the Profile of Mood States subscales: anger-hostility (C), depression-dejection (D), tension-anxiety (E), fatigue-inertia (F), vigor-activity (G), confusion-bewilderment (H), and total mood disturbance score (I). The asterisk indicates that the score is significantly higher compared with the LF diet ($P < .05$).

carbohydrate and low in fat and protein are associated with lower levels of anxiety and depression and have beneficial effects on psychological well-being.³⁴⁻³⁶ However, a previous intervention study by McClernon et al¹⁴ did show reductions in negative affect following an ad libitum LC diet compared with an energy-reduced LF diet over 24 weeks. The reason for this discrepancy in findings is not entirely clear, but it is important to note that unlike our study, which used validated mood and mental health assessment instruments, the study by McClernon and colleagues derived a measure of negative affect from a non-

validated symptom checklist developed by practitioners for use in evaluating and treating patients undergoing an LC diet for weight loss. This checklist may have biased the responses toward positive effects of an LC diet compared with an LF diet. Moreover, we compared the effects of LC and LF diets under isocaloric conditions, whereas the previous study by McClernon et al¹⁴ used different dietary approaches to deliver the LC and LF diets without specifically controlling for energy intake, which led to markedly greater weight loss with the LC diet (-12.9 kg vs -6.7 kg). Although attempts were made by McClernon and coau-

Table. Mixed-Effects Model of the Effects of an Energy-Restricted, Low-Carbohydrate, High-Fat (LC) Diet and a High-Carbohydrate, Low-Fat (LF) Diet Over 12 Months on Working Memory (Digit Span Backward) and Inspection Time

	Estimated Marginal Mean (SE) ^a		
	Week 0	Week 8	Week 52
Working memory			
LC diet	4.2 (0.3)	4.9 (0.3) ^b	4.8 (0.3) ^b
LF diet	3.9 (0.2)	4.7 (0.2) ^b	4.8 (0.3) ^b
Inspection time, ms			
LC diet	63.3 (2.5)	59.1 (2.5) ^b	63.1 (2.6)
LF diet	66.7 (2.3)	56.6 (2.3) ^b	63.5 (2.5)

^aParticipant numbers were as follows: 55 in the LC group and 51 in the LF group during week 0; 49 in the LC group and 47 in the LF group during week 8; and 32 in the LC group and 32 in the LF group during week 52. For working memory and inspection time, higher and lower numbers, respectively, indicate better performance for each task.

^bP = .01 for time, significantly different compared with week 0.

thors to control for weight loss in the statistical models because of the association between weight loss and psychological well-being,^{1,37,38} the possibility cannot be dismissed that the greater weight loss with the LC diet accounted for the greater reductions in negative affect. McClernon et al¹⁴ also noted that in addition to dieting, individuals in the LC group received nutritional supplements while those in the LF group did not, raising the possibility that the group differences in symptoms observed could be attributed to a placebo effect of the nutritional supplements rather than to the LC diet per se.

Consistent with previous studies that have shown improvements in mood and emotional outcomes after weight loss,^{1,37,38} and after participation in supervised weight-loss programs with social support,^{1,39,40} improvements in mood were observed in the participants in the LF group in our study. However, despite similar and substantial weight losses in the LC group, after improvements were realized over the short term, the mood state of the participants had returned to baseline levels at the end of 1 year. This outcome suggests that some aspects of the LC diet may have had detrimental effects on mood that, over the term of 1 year, negated any positive effects of weight loss. For mood scores that realized statistically significant differences, medium effect sizes (0.5-0.7) were also determined for the difference in the changes between the diets, which have been identified as clinically relevant.^{41,42} Although a complete explanation for this effect cannot be determined from the current data, there are several plausible reasons. The present study was conducted as a controlled clinical trial in which participants were randomly assigned to the LC or LF diet rather than self-selecting a diet based on their food preference and eating habits. In Western society, established eating patterns and the most common traditional dietary recommendations favor a high-carbohydrate dietary pattern,^{4,5} with bread, pasta, rice, and fruit consumed in large quantities. Therefore, the LC diet being so far removed from normal dietary habits may have created a significant challenge for participants, leading to the possibility of food preoccupation, social eating impairment, and dysphoria. Although, in the short term, participants may have been able

to meet the challenges presented by this dietary pattern, over the longer term, it may have increased participant isolation, leading to the negative impact on mood state that may provide a possible explanation for the effects that were observed. However, these social effects cannot be extrapolated from the current data, and future studies addressing this hypothesis are warranted.

The possibility that the prescriptive nature of the dietary regimens had a negative impact on affect should also be considered. Although a major strength of the current study was the use of highly prescriptive plans by which the dietary patterns were structured to include specific food quantities combined with regular dietary advice and counseling to ensure correct macronutrient and energy requirements, this highly prescriptive method may have alienated some participants. However, the stringent structured approach did not appear to have a negative effect on mood in the LF diet; therefore, the observed response would suggest an interactive effect with diet, with the LC diet magnifying any psychological discomfort associated with the structure of the regimen. Further research should test this hypothesis. In current practice, LC diets are typically followed ad libitum, without specific prescription of energy intake, promoting unlimited intake of protein and fat, with the only food restriction being to limit the intake of carbohydrate.^{43,44} Whether the detrimental effects of the LC diet on mood that were observed in our study would exist if delivered ad libitum without intensive dietary control over the long term remains unknown; data reported by McClernon et al¹⁴ suggest that this may not be the case.

Mood among long-term consumers of LC diets may also be negatively affected by changes in serotogenic expression and neurotrophic factors. While a high-carbohydrate intake can increase serotonin synthesis, fat and protein intakes reduce serotonin concentrations in the brain.⁴⁵⁻⁴⁷ There is an abundance of evidence demonstrating a link between serotogenic functions of the brain and aspects of psychological functioning, particularly depression and anxiety.^{48,49} Mood has also been shown to be dependent on and directly proportional to brain-derived neurotrophic levels,⁵⁰ with high-fat diets reducing brain-derived neurotrophic levels,⁵¹ possibly as a result of alterations in the levels of corticosterone.^{52,53} Further studies evaluating the psychophysiological effects of LC diets on serotonin and neurotrophic factors are required.

Despite these results, it is important to note that mood state scores on average for both groups at baseline and throughout the study remained within the normal range for healthy adults.^{25,27,33} Consequently, the present findings are limited to healthy, obese, young to middle-aged adults with normal mood state and cannot be generalized to clinical populations. In addition to mood, cognitive function has also been shown to be acutely affected by meal composition,⁵⁴ with the short-term (≤8 weeks) consumption of an LC diet potentially producing negative effects on cognitive functioning.^{12,13,18} In a previous article, we reported that, after 8 weeks, obese participants on an LC diet had less improvement in speed of processing (inspection time task) but similar improvements in working memory compared with obese participants on a conventional LF diet.¹³ In the current study, the trajectory of change in speed of processing and working memory across time did not

vary between participants assigned to the 2 diets over the long term. This finding is consistent with previous studies showing that short-term decrements in cognitive performance were not sustained in persons on an LC diet.^{12,18} Together, the study results suggest that any decrements in cognitive performance following introduction to an LC diet are transient and short-lived.

Because it is well recognized that glucose is the brain's primary fuel⁵⁵ and that hypoglycemia impairs cognitive function,^{56,57} it could have been hypothesized that the LC diet may have negatively affected cognitive performance relative to the LF diet. However, despite a restricted carbohydrate intake, the LC diet did not induce a hypoglycemic state, which is likely attributable to increased gluconeogenesis to maintain blood glucose levels, and after the intervention, participants in both groups had similar fasting plasma glucose levels that were within the normal range. Although it is not possible to measure local changes in brain glucose levels because the level of glucose in the blood reflects the level of glucose in the brain,⁵⁸ maintenance of normal glucose levels may explain the lack of any difference in cognitive performance between the diets.

In the present study, the improvement in working memory, as assessed by DSB, that occurred after 8 weeks was sustained over 12 months in both diet groups. In contrast, previous studies have indicated that caloric restriction that leads to substantial weight loss has a minimal impact on cognitive performance, including working memory as assessed by DSB, in overweight and obese individuals.⁵⁹⁻⁶² In the present study, because of the lack of a nondieting control group, improvements in working memory reflecting practice effects in both groups cannot be entirely dismissed. In contrast to the present findings, a recent study by Witte et al⁶² that did include a nondieting control group showed no change in a digit span task in overweight individuals after 3 months of energy restriction, suggesting that the improvements in DSB in the present study may not be explained by learning effects. However, the possibility cannot be dismissed that the differences in study duration (3 months vs 12 months) and the dietary regimens and delivery methods that were used also could have contributed to the discrepancies in the findings. Alternatively, Witte and colleagues demonstrated substantial improvements in episodic memory performance as assessed by a word-recall task after energy restriction, which was correlated with decreases in fasting plasma levels of insulin. We also observed a significant inverse correlation between the change in DSB (a measure of working memory) scores and the change in fasting plasma insulin levels; ie, the DSB scores increased with decreases in the plasma insulin levels. This association leads to the hypothesis that if episodic memory had been assessed in the present study, even greater improvements may have occurred compared with the study by Witte et al.⁶² These data also provide additional support to the postulated suggestion of improved memory after caloric restriction via improved insulin signaling in the brain.⁶² Further research is needed to examine the cause of the improvement in memory performance with dieting.

The current study focused on the assessment of 2 critical components of cognitive functioning: working memory and speed of processing. Although these 2 domains are fundamental components of cognition and measures that have demonstrated sensitivity to dietary change,⁶³ they

do not constitute a comprehensive battery for the assessment of cognition. For example, it is possible that aspects of cognition such as attention, short-term memory, long-term memory, and executive function might be influenced more by changes in the macronutrient content of a weight-loss diet. This potential limitation affects the confidence with which conclusions can be drawn regarding the long-term effects of LC and LF diets on cognitive function. Therefore, further studies should be undertaken to assess a greater range of cognitive domains. Moreover, the current results highlight the importance of future research that recognizes the role of practice in changing cognitive performance. Studies concerned with measuring intervention effects should undertake practice sessions until asymptotic levels of performance are achieved before randomization. Notwithstanding the increase in participant burden, it is important for future studies to perform repeated testing on a more frequent basis than was performed in our study to better characterize the time course of effects.

In conclusion, we found that despite similar weight loss after energy-restricted LC and LF diets for 12 months and rapid improvements in mood during the first 8 weeks with both diets, over the long term many of the benefits regressed in the LC diet group such that participants on the LF diet achieved better outcomes. However, there was no evidence that the dietary macronutrient composition of LC and LF diets affected cognitive functioning over the long term, as changes in cognitive function were similar for both diets. Further studies are required to evaluate the effects of these diets on a wider range of cognitive domains.

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Author Contributions: Dr Brinkworth 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. *Study concept and design:* Brinkworth, Noakes, Clifton, and Wilson. *Acquisition of data:* Brinkworth. *Analysis and interpretation of data:* Brinkworth, Buckley, Noakes, Clifton, and Wilson. *Drafting of the manuscript:* Brinkworth and Buckley. *Critical revision of the manuscript for important intellectual content:* Brinkworth, Buckley, Noakes, Clifton, and Wilson. *Statistical analysis:* Brinkworth and Clifton. *Obtained funding:* Brinkworth, Buckley, and Noakes. *Administrative, technical, and material support:* Brinkworth, Buckley, Noakes, and Wilson. *Study supervision:* Brinkworth.

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