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ORIGINAL ARTICLE

Effects of an energy-restricted low-carbohydrate, high unsaturated fat/low saturated fat diet versus a high-carbohydrate, low-fat diet in type 2 diabetes: A 2-year randomized clinical trial

Jeannie Tay PhD[1,2,6] | Campbell H. Thompson MD[2] | Natalie D. Luscombe-Marsh PhD[1] | Thomas P. Wycherley PhD[3] | Manny Noakes PhD[1] | Jonathan D. Buckley PhD[3] | Gary A. Wittert MD[2] | William S. Yancy Jr MD[4,5] | Grant D. Brinkworth PhD[1]

[1]Commonwealth Scientific and Industrial Research Organisation (CSIRO) – Health and Biosecurity, Adelaide, Australia

[2]Discipline of Medicine, University of Adelaide, Adelaide, Australia

[3]Alliance for Research in Exercise, Nutrition and Activity (ARENA), Sansom Institute for Health Research, University of South Australia, Adelaide, Australia

[4]Division of General Internal Medicine, Department of Medicine, Duke University Medical Center, Durham, North Carolina

[5]Center for Health Services Research in Primary Care, Veterans Affairs Medical Center, Durham, North Carolina

[6]Agency for Science, Technology and Research (A-STAR), Singapore

Correspondence
Grant Brinkworth, PhD, Commonwealth Scientific and Industrial Research Organisation- Health and Biosecurity, Riverside Corporate Park, 11 Julius Avenue, North Ryde, NSW, Australia, 2113.
Email: grant.brinkworth@csiro.au

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Aim: To examine whether a low-carbohydrate, high-unsaturated/low-saturated fat diet (LC) improves glycaemic control and cardiovascular disease (CVD) risk factors in overweight and obese patients with type 2 diabetes (T2D).

Methods: A total of 115 adults with T2D (mean [SD]; BMI, 34.6 [4.3] kg/m^2; age, 58 [7] years; HbA1c, 7.3 [1.1]%) were randomized to 1 of 2 planned energy-matched, hypocaloric diets combined with aerobic/resistance exercise (1 hour, 3 days/week) for 2 years: LC: 14% energy as carbohydrate, 28% as protein, 58% as fat (<10% saturated fat); or low-fat, high-carbohydrate, low-glycaemic index diet (HC): 53% as CHO, 17% as protein, 30% as fat (<10% saturated fat). HbA1c, glycaemic variability (GV), anti-glycaemic medication effect score (MES, calculated based on the potency and dosage of diabetes medication), weight, body composition, CVD and renal risk markers were assessed before and after intervention.

Results: A total of 61 (LC = 33, HC = 28) participants completed the study (trial registration: http://www.anzctr.org.au/, ANZCTR No. ACTRN12612000369820). Reductions in weight (estimated marginal mean [95% CI]; LC, −6.8 [−8.8,−4.7], HC, −6.6 [−8.8, −4.5] kg), body fat (LC, −4.3 [−6.2, −2.4], HC, −4.6 [−6.6, −2.7] kg), blood pressure (LC, −2.0 [−5.9, 1.8]/ −1.2 [−3.6, 1.2], HC, −3.2 [−7.3, 0.9]/ −2.0 [−4.5, 0.5] mmHg), HbA1c (LC, −0.6 [−0.9, −0.3], HC, −0.9 [−1.2, −0.5] %) and fasting glucose (LC, 0.3 [−0.4, 1.0], HC, −0.4 [−1.1, 0.4] mmol/L) were similar between groups ($P \geq 0.09$). Compared to HC, the LC achieved greater reductions in diabetes medication use (MES; LC, −0.5 [−0.6, −0.3], HC, −0.2 [−0.4, −0.02] units; $P = 0.03$), GV (Continuous Overall Net Glycemic Action calculated every 1 hour (LC, −0.4 [−0.6, −0.3], HC, −0.1 [−0.1, 0.2] mmol/L; $P = 0.001$), and 4 hours (LC, −0.9 [−1.3, −0.6], HC, −0.2 [−0.6, 0.1] mmol/L; $P = 0.02$)); triglycerides (LC, −0.1 [−0.3, 0.2], HC, 0.1 [−0.2, 0.3] mmol/L; $P = 0.001$), and maintained HDL-C levels (LC, 0.02 [−0.05, 0.1], HC, −0.1 [−0.1, 0.01] mmol/L; $P = 0.004$), but had similar changes in LDL-C (LC, 0.2 [−0.1, 0.5], HC, 0.1 [−0.2, 0.4] mmol/L; $P = 0.85$), brachial artery flow mediated dilatation (LC, −0.5 [−1.5, 0.5], HC, −0.4 [−1.4, 0.7] %; $P = 0.73$), eGFR and albuminuria.

Conclusions: Both diets achieved comparable weight loss and HbA1c reductions. The LC sustained greater reductions in diabetes medication requirements, and in improvements in diurnal blood glucose stability and blood lipid profile, with no adverse renal effects, suggesting greater optimization of T2D management.

KEYWORDS

dietary intervention, type 2 diabetes, weight control

1 | INTRODUCTION

The worldwide prevalence of type 2 diabetes (T2D) continues to surge despite therapeutic advances, highlighting the urgent need for more effective treatment strategies. Lifestyle management encompassing nutrition therapy and physical activity form the cornerstone of diabetes care. However, the most efficacious long-term nutrition therapy remains controversial. While leading health authorities now advocate an individualized dietary approach to diabetes management,[1,2] different diets may vary in their efficacy in improving glycaemic control and reducing the risk of cardiovascular disease (CVD).

Low-fat, high-unrefined carbohydrate diets have been the predominant public health weight-management recommendation for the past several decades and have typically been prescribed for the dietary management of T2D.[3,4] However, emerging evidence suggests that carbohydrate restriction and higher intakes of protein and unsaturated fats, independent of weight loss, improve glycaemic control and some CVD risk markers, potentially conferring greater benefits over high-carbohydrate diets[3–8]. Hyperglycaemia is a salient characteristic of T2D, and dietary carbohydrates, particularly those that are refined, are the greatest determinant of postprandial glycaemia.[8] Restricting the intake of carbohydrates to alleviate hyperglycaemia can lead to fewer glycaemic excursions and allow for reduction of medications. It is thus easily understood by, and acceptable to, patients.[9]

Despite the greater interest in, and use of, low-carbohydrate diets, their long-term effectiveness and sustainability in individuals with T2D have not been well studied. Current guidelines assert that there is insufficient evidence in isocaloric comparisons to recommend an ideal carbohydrate intake or to recommend such diets, over other diets, for individuals with diabetes.[1,10] Amongst the limited number of studies of low-carbohydrate diets in individuals with T2D beyond 1 year, 1 study prescribed a relatively high carbohydrate composition (~150-189 g/day, 40% energy) in the low-carbohydrate diet group and included only a small subgroup of 36 people with T2D.[11] Another study administered a low-intensity intervention with limited professional contact that resulted in reduced treatment adherence.[12] Neither study controlled for differences in energy intakes, assessed changes in diabetes medication use or glycemic variability (GV, emerging as an independent risk factor for diabetes complications[13]), nor considered physical activity. To address these limitations, we designed a randomized controlled trial (RCT) aimed at comparing the effectiveness of 2 isocaloric diets in individuals with T2D: a low-carbohydrate and low-saturated fat diet (LC) vs a conventional low-fat, higher-carbohydrate, low-glycemic index diet (HC).

We previously reported that, over 1 year, the LC produced greater improvements than the HC in glycaemic control (lower diabetes medication requirements and GV), and more favourable lipid profile changes (increased HDL-C and reduced triglycerides [TG]), in adults with T2D.[14] We reported these early results given their clinical importance to this high-risk study population.

We now report the longer-term (2-year) sustainability of these effects by comparing isocaloric LC and HC as part of a lifestyle intervention incorporating a structured exercise regime, with a comprehensive evaluation of glycaemic control, anthropometry and CVD risk markers in obese adults with T2D.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

The study design has been described previously.[15,16] This outpatient, single-centre, parallel-groups, RCT was conducted from May 2012 through September 2014 at the Commonwealth Scientific Industrial Research Organisation (CSIRO) Clinical Research Unit (Adelaide, Australia). Participants with established T2D under the care of a general practitioner and/or endocrinologist were recruited from the community, primarily through media advertisements, and included individuals aged 35 to 68 years with T2D (HbA1c ≥ 7.0% and/or using diabetes medication including insulin), and with a body mass index (BMI) of 26 to 45 kg/m^2. Major exclusion criteria were: type-1 diabetes; renal, hepatic, respiratory, gastrointestinal or cardiovascular disease; history of malignancy; any significant endocrinopathy (other than stable treated thyroid disease); pregnancy/lactation; history of or current eating disorder; or smoking. All study participants provided written informed consent. The CSIRO Human Research Ethics Committee approved the study.

Participants were block-matched for age, gender, BMI, HbA1c and diabetes medication using random varying block sizes and were allocated to the LC or HC (1:1) by random computer-generated assignment (Figure 1). The research associates who conducted these randomization procedures were not involved in outcome assessments and intervention delivery. The researchers involved in outcome assessment and data analysis were blinded to treatment assignment.

2.2 | Diet and physical activity interventions

The planned macronutrient compositions of the 2 diets were: LC, 14% carbohydrate (< 50 g/day), 28% protein and 58% total fat (35% monounsaturated fat and 13% polyunsaturated fat), with the inclusion of an additional 20-g carbohydrate allowance after week 24 for the remainder of the study; HC, 53% carbohydrate (processed carbohydrates and high glycaemic index foods were discouraged, with an emphasis on the selection of low glycaemic foods; overall glycaemic index of 46), 17% protein and <30% total fat (15% monounsaturated fat and 9% polyunsaturated fat), reflecting traditional dietary guidelines, with the inclusion of an approved food exchange (which met the macronutrient profile of the diet and was equivalent to the energy content of 20 g of carbohydrate) after week 24 for the remainder of the study so that the diets remained isocaloric. Saturated fat was limited in both diets (< 10% energy).

Participants met individually with a dietitian for diet instruction and support every 2 weeks for 12 weeks and monthly thereafter. During the first 12 weeks, participants were provided with key foods (~30% total energy) representative of their assigned diets to achieve the targeted macronutrient profiles (Table S1). These foods were listed in a semi-quantitative food record that participants completed daily. After 12 weeks, for the remainder of the study, participants

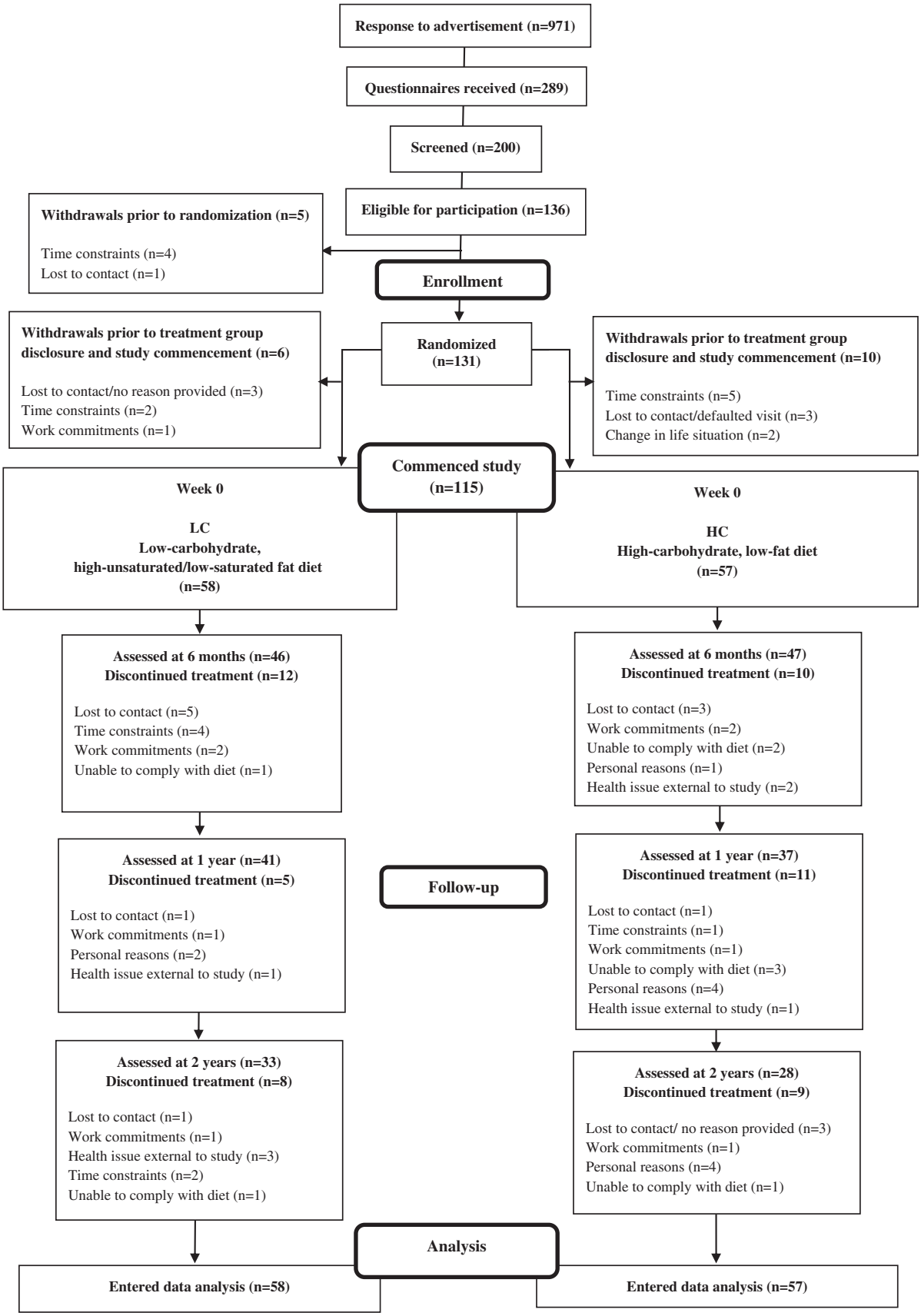

FIGURE 1 Study flow diagram

were provided with key food packs every second month and a 50 AUD voucher to subsidize purchase of key foods on every alternate second month. Participants prepared/purchased their own food/meals according to guidelines specific to their prescribed diets. Diet plans were individualized and energy-matched, with moderate (~30%) restriction to facilitate weight loss (500-1000 kcal/day deficit; 1357-

2143 kcal/day energy prescription).[17] Caloric prescriptions were maintained throughout the study to preserve planned isocaloric control between diets.

The same professionally supervised 60-minute exercise classes, incorporating moderate-intensity aerobic and resistance exercise on 3 non-consecutive days per week were prescribed for all participants. The dietitians and exercise professionals responsible for delivering the intervention were trained in behavioural strategies, including motivational interviewing and goal-setting techniques, that were applied during the intervention. This research design enabled the effects of the diets to be studied in the context of lifestyle intervention, whilst maintaining the ability to address the a priori research objective of comparing and isolating the differential effects of the HC and LC diets on the outcomes.

2.3 | Outcome measures

Body-weight and plasma ketones were measured monthly through the study. All other data were collected at baseline and at 24, 52 and 104 weeks. At each time point, fasting blood samples were collected from a forearm vein into tubes containing no additives for lipids, insulin, C-reactive protein (CRP) and creatinine; sodium fluoride/EDTA for glucose and ketones; and potassium/EDTA for HbA1c. Plasma or serum was isolated by centrifugation at 2000*g* for 10 minutes at 5°C (Beckman GS-6R centrifuge; Brea, California) and stored at −80°C until analysed. Urine samples to assess albumin were frozen at −80°C in polyethylene tubes until analysed.

2.4 | Primary outcome

HbA1c (SA Pathology; Adelaide, Australia) was the primary outcome measure.

2.5 | Secondary outcomes

2.5.1 | Glycaemic variability and changes in diabetes medication

GV was assessed from 48-hour continuous blood glucose monitoring (CGM, iPro 2; Medtronic; North Ryde, Australia) and included $SD_{Glucose,}$ mean amplitude of glycaemic excursions (MAGE, average of blood glucose excursions exceeding 1 SD of the mean blood glucose value) and continuous overall net glycaemic action (CONGA-1 and CONGA-4, SD of differences between observations 1 or 4 hour (s) apart, respectively).[13,14]

An antiglycaemic Medication Effect Score (MES) based on medication potency and dosage was used to assess changes in utilization of antiglycaemic agents including insulin.[18] Higher MES corresponds to higher diabetes medication requirement.

2.5.2 | Anthropometric data

Height was measured using a stadiometer (SECA, Hamburg, Germany), body-weight using calibrated electronic scales (Mercury AMZ1, Tokyo, Japan) and waist circumference by tape measure positioned 3 cm above the iliac crest. Body composition (fat mass[FM] and fat-free mass [FFM]) was determined by whole-body dual-energy X-ray absorptiometry (DEXA; Lunar Prodigy; General Electric Corporation, Madison, Wisconsin).

2.5.3 | Cardiovascular and metabolic measures

Resting blood pressure was measured by automated sphygmomanometry (SureSigns VS3; Phillips, Andover, Massacusetts). Plasma glucose, serum total cholesterol, HDL-C, TG and CRP were measured on a Roche Hitachi 902 auto-analyser (Hitachi Science Systems Ltd, Ibaraki, Japan) using standard enzymatic kits (Roche Diagnostics, Indianapolis, Indiana). LDL-C levels were calculated using the Friedewald equation.[19] Non-HDL-C was calculated as the difference between total cholesterol and HDL-C.[20] Plasma insulin concentrations were determined using a commercial enzyme immunoassay kit (Mercodia AB, Uppsala, Sweden). HOMA index 2 assessed β cell function (HOMA2-%B) and insulin resistance (HOMA2-IR)[21]. Flow-mediated vasodilatation (FMD) of the brachial artery was evaluated according to recommended guidelines, as previously described.[22]

2.5.4 | Renal function markers

Serum creatinine was measured on a clinical analyser (Beckman AU480; Beckman Coulter Inc, Brea, California) using a standardized assay (Beckman kit #OSR6178). Glomerular filtration rate was estimated by the Chronic Kidney Disease Epidemiology Collaboration equation (eGFR-CKD-EPI).[23] Creatinine Clearance (CrCl) was estimated by the Cockcroft-Gault and the Salazar-Corcoran equation.[16] Albumin excretion rate (AER) and urinary albumin from 24-hour urine samples were measured at a certified commercial laboratory (SA Pathology, Adelaide, Australia).

2.5.5 | Diet and physical activity data

Dietary intake was assessed from a random sample of 7 consecutive days of daily weighed food records within every 14-day period, using Foodworks Professional Edition Version 7 (Xyris Software 2012, Highgate Hill, Australia) to obtain average quarterly nutrient intake over 104 weeks. The 24-hour urinary-urea/creatinine ratio (IMVS) was assessed as a marker of protein intake.[24] Plasma ketones (β-hydroxybutyrate) were assessed as a marker of reduced carbohydrate intake (RANBUT D-3 Hydroxybutyrate kit; Antrim, UK). Physical activity levels were assessed using data from 7 consecutive days of triaxial accelerometry (GT3X + model; ActiGraph, Pensacola, Florida), with pre-defined validity cutoffs[25] and including exercise session attendance.

2.6 | Statistical analyses

Primary analysis was by random-coefficient analysis, with data assumed to be missing at random. Linear mixed-effects models that included fixed effects for each time-point and diet-group assignment, and a diet group by time-point interaction were used to evaluate between-group differences in outcomes. The restricted maximum likelihood, linear mixed-effects model permits a variable number of observations for participants, and an unstructured covariance accounts for correlations between repeated measures over time. In accordance with an intention-to-treat principle, analyses included all available data from the 115 participants who commenced the study.

Baseline characteristics and exercise session attendance were compared by independent t-tests and χ^2 tests for continuous and categorical variables, respectively. Results are presented as estimated marginal means (95% confidence intervals, CI) by linear mixed-effects model analysis using SPSS 20.0 for Windows (SPSS Inc.; Chicago, Illinois) unless otherwise stated. Changes from baseline to Week 104 are reported. All statistical tests were two-tailed using a significance level of $P < 0.05$.

2.7 | Sample size and power

The study was designed to have 80% power to detect a previously reported 0.7% absolute difference in HbA1c (primary outcome) between diets,[5,18,26] based on an anticipated ~50% dropout rate, as typically observed in long-term diet and lifestyle interventions.[6,27,28]

3 | RESULTS

3.1 | Baseline characteristics

A total of 115 adults were randomized (LC, 57; HC, 58) (Figure 1). Baseline characteristics were well matched between groups (Tables 1 and 2). Most participants were using oral anti-glycaemic medications (LC, 48; HC,45); >75% were using metformin, 30% sulfonylureas and 10% exogenous insulin. Approximately two-thirds were using lipid-lowering medications and anti-hypertensives. Among the total, 53% of participants completed the study (LC, 33; HC, 28), with similar attrition and reasons for withdrawal between groups ($P = 0.40$) (Figure 1).

3.2 | Dietary intake, physical activity and adherence measures

The two groups reported similar caloric intakes ($P = 0.93$). Dietary intakes were consistent with the prescribed diets (Table 3). Compared to the HC, the LC group reported lower intakes of carbohydrate, and higher intakes of protein and fat. Plasma and urinary biomarker data also reflected higher protein and lower carbohydrate intake in the LC group. The LC group experienced an initial three-fold greater increase in plasma β-hydroxybutyrate levels compared to the HC group, with levels decreasing towards baseline over time (time x diet, $P = 0.02$) (Figure S1). The 24-hour urinary-urea data showed higher estimated protein intakes in the LC group (1.1-1.3 g/kg vs 1.0-1.1 g/kg, $P < 0.001$). Compared to the HC group, the LC group experienced greater increases in 24-hour urinary-urea/creatinine excretion ratio, which remained higher over the study period ($P = 0.001$) (Table 1). Accelerometry data indicated that physical activity levels were similar between groups ($P \geq 0.37$) (Table 1). Exercise session attendance was also similar between groups (LC, 56 ± 24%; HC, 58 ± 24%; $P = 0.80$).

3.3 | Weight and body composition

After 2 years, there were reductions in body-weight (Figure 2), total FM and waist circumference, with no differences between groups ($P \geq 0.09$ for all). Among completers, 69% maintained a weight loss of ≥5% (LC, 22; HC, 20; $P = 0.69$) and 34% achieved ≥10% weight reduction (LC, 12; HC, 9; $P = 0.73$).

3.4 | Glycaemic control: HbA1c, glycaemic variability, anti-glycaemic medication effect score (MES) and insulin sensitivity

HbA1c reductions were similar in both groups (−0.7 [−1.0, −0.5] %; $P = 0.52$) (Figure 3A). The LC group maintained greater reductions in diabetes medication requirements (antiglycaemic MES, LC, −0.5 [−0.6, −0.3], HC, −0.2 [−0.4, −0.02] units; $P = 0.03$) (Figure 3B). Over twice the number of LC participants had a ≥ 20% reduction in MES compared to HC participants (LC, 22; HC, 9).

Greater reductions in GV (MAGE, $SD_{Glucose}$, Glucose range, MODD, $AUC_{Total\ glucose\ per\ min}$, CONGA-1 and CONGA-4) occurred in the LC group compared to the HC group ($P = 0.001$-0.24) (Table 2, Figure 3). Differences persisted over 2 years and were statistically significant for CONGA-1 (LC, −0.4 [−0.6, −0.3], HC, 0.1 [−0.1, 0.2] mmol/L; $P = 0.001$) and CONGA-4 (LC, −0.9 [−1.3, −0.6], HC, −0.2 [−0.6, 0.1] mmol/L; $P = 0.02$) (Figure 3C,D). Fasting blood glucose and insulin markers (insulin, HOMA2-IR and HOMA2-%B) decreased, with no difference between groups (Table 2, $P \geq 0.13$).

3.5 | CVD risk factors: blood pressure, lipids, endothelial function and CRP

TAG decreased to a greater degree and HDL-C levels were maintained with the LC compared to the HC ($P \leq 0.004$) (Table 2). Changes in non-HDL-C, total cholesterol, LDL-C, blood pressure and CRP did not differ between groups ($P \geq 0.44$). Endothelial function (FMD) did not change in either group ($P = 0.73$). Concerning lipid-lowering medications, 5 participants reduced dosage (LC, 3; HC, 2) and 3 participants increased dosage (LC, 1; HC, 2). Concerning anti-hypertensive medications, 15 participants (LC, 10; HC, 5) reduced dosage and 5 participants (LC, 3; HC, 2) increased dosage.

3.6 | Renal markers

eGFR levels remained in the normal to mildly depressed range in both groups. Comparable increases in SCr and reductions in eGFR and CrCl occurred in both groups (Table 2, $P \geq 0.07$). In 7 participants (LC, 4; HC, 3) albuminuria was moderately increased (AER 30-300 mg/24 h) at baseline and was normalized and maintained in 4 participants (LC, 2; HC, 2). Albuminuria persisted in 2 participants (LC, 1; HC, 1) and 1 LC participant withdrew at Week 4 before study completion. All other participants who were normoalbuminuric at baseline remained so after 2 years.

3.7 | Adverse events

There were no adverse event-related treatment discontinuations. A total of 21 participants (LC, 11; HC, 10) reported musculoskeletal ailments associated with exercise training. These participants continued the exercise program following recovery, although one participant from the HC group, who reported exacerbation of pre-existing fibromyalgia secondary to resistance training (Week 64), withdrew from

TABLE 1 Baseline participant characteristics and estimated marginal mean changes (95% CI) in body-weight and composition, dietary biomarkers and physical activity after 2 years on a low-carbohydrate, high-unsaturated/low-saturated fat diet (LC) or an isocaloric high-carbohydrate, low-fat diet (HC) [a]

Variable	LC		HC		Mean difference in change between groups	*P* Value[b]
	Baseline	Change	Baseline	Change		
Participant characteristics						
Male/Female [n (%)]	37 (64) / 21 (36)	-	29 (51) / 28 (49)	-	-	-
Age (years)	58 (56 to 60)	-	58 (56 to 60)	-	-	-
Diabetes Duration (years)	6 (4 to 7)	-	8 (6 to 10)	-	-	-
Body-weight and composition						
Body-weight (kg)	101.7 (97.8 to 105.7)	−6.8 (−8.8 to −4.7)	101.6 (97.6 to 105.6)	−6.6 (−8.8 to −4.5)	−0.1 (−3.1 to 2.8)	0.26
BMI (kg/ $m^{2)}$	34.2 (33.1 to 35.3)	−2.1 (−2.8 to −1.5)	35.1 (34.0 to 36.2)	−2.3 (−3.0 to −1.6)	0.1 (−0.8 to 1.1)	0.33
Waist Circumference (cm)	112.4 (109.7 to 115.2)	−7.9 (−10.0 to −5.7)	112.5 (109.8 to 115.3)	−7.2 (−9.5 to −5.0)	−0.6 (−3.7 to 2.5)	0.54
Total FFM (kg)	62.0 (59.1 to 64.8)	−2.2 (−2.8 to −1.6)	60.1 (57.2 to 62.9)	−2.0 (−2.7 to −1.4)	−0.2 (−1.0 to 0.7)	0.71
Total FM (kg)	39.8 (37.1 to 42.4)	−4.3 (−6.2 to −2.4)	41.5 (38.8 to 44.2)	−4.6 (−6.6 to −2.7)	0.3 (−2.4 to 3.0)	0.09
FM:FFM ratio	0.7 (0.6 to 0.7)	−0.1 (−0.1 to −0.02)	0.7 (0.7 to 0.8)	−0.1 (−0.1 to −0.02)	0.01 (−0.04 to 0.1)	0.25
Dietary biomarkers						
24 h Urinary Urea/ Creatinine ratio[c]	39.9 (37.6 to 42.2)	4.2 (1.2 to 7.2)	38.7 (36.4 to 41.0)	0.8 (−2.5 to 4.0)	3.4 (−1.0 to 7.9)	0.001
Physical activity[d]						
Mean activity count (counts/min)	188.9 (171.6 to 206.3)	−12.3 (−34.2 to 9.7)	182.7 (165.2 to 200.2)	−2.5 (−25.3 to 20.2)	−9.8 (−41.4 to 21.8)	0.37
MVPA (min/day)	46.4 (41.4 to 51.5)	1.1 (−5.0 to 7.1)	44.0 (38.9 to 49.0)	0.6 (−5.7 to 7.0)	0.4 (−8.4 to 9.2)	0.62
MVPA (% of total wear time)	3.5 (3.2 to 3.9)	−0.3 (−0.8 to 0.2)	3.4 (3.0 to 3.7)	−0.7 (−1.2 to −0.2)	0.4 (−0.3 to 1.1)	0.62

Abbreviations: LC, low-carbohydrate, high-unsaturated/low-saturated fat diet; HC, high-carbohydrate, low-fat diet; BMI, body mass index; FM, fat mass; FFM, fat-free mass; MVPA, moderate to vigorous intensity physical activity. The following variables were square root transformed to attain normality before analyses: FFM; accelerometry data and urinary-urea/creatinine excretion ratio. Untransformed values are presented to facilitate interpretation. Baseline participant characteristics data are presented as mean (95% confidence interval). All other data are presented as estimated marginal means (95% confidence intervals) by linear mixed-effects model analysis, unless otherwise stated.

[a] Total analysed, n = 115 (LC, 58; HC, 57) for all data unless otherwise stated.

[b] *P* value refers to between-group differences over time (time x diet interaction) by linear mixed-effects model analysis. All baseline values were not significantly different between diet groups ($P > 0.05$) by chi-square tests (categorical variables) and independent samples t-test (continuous variables).

[c] Total analysed, n = 114 (LC, 57; HC, 57) for 24-hour urinary urea/creatinine ratio data; no urine analysis was available at baseline for 1 participant in the LC group.

[d] Total analysed, n = 115 for accelerometry data; data from 2 participants (LC, 1; HC, 1) at 24 weeks, from 6 participants (LC, 4; HC, 2) at 52 weeks and from 1 participant in the LC group at 104 weeks that did not meet validity criteria were excluded from these analyses.

TABLE 2 Estimated marginal mean changes (95% CI) in glycaemic control, diabetes medication, cardiovascular disease risk and renal markers after 2 years on a low-carbohydrate, high-unsaturated/low-saturated fat diet (LC) or an isocaloric high-carbohydrate, low-fat diet (HC) [a]

Variable	LC		HC		Mean difference in change between groups	*P* Value [b]
	Baseline	Change	Baseline	Change		
Glycemic control						
Fasting glucose (mmol/ L)	7.8 (7.3 to 8.4)	0.3 (−0.4, 1.0)	8.4 (7.8 to 9.0)	−0.4 (−1.1 to 0.4)	0.7 (−0.3 to 1.7)	0.13
Mean glucose (mmol/ L)	8.4 (7.9 to 8.9)	−0.7 (−1.4 to −0.02)	8.7 (8.2 to 9.1)	−0.6 (−1.4 to 0.1)	−0.1 (−1.1 to 0.9)	0.18
$AUC_{Total\ glucose\ per\ min}$ (mmol/ L)	8.4 (7.9 to 8.9)	−0.7 (−1.4, −0.02)	8.6 (8.1 to 9.1)	−0.6 (−1.3 to 0.1)	−0.1 (−1.1 to 0.9)	0.18
Minimum glucose (mmol/ L)	4.8 (4.5 to 5.2)	0.1 (−0.5 to 0.6)	4.8 (4.5 to 5.2)	−0.3 (−0.8 to 0.3)	0.3 (−0.4 to 1.1)	0.69
Maximum glucose (mmol/ L)	14.0 (13.1 to 14.9)	−2.0 (−3.1 to −0.8)	14.3 (13.4 to 15.2)	−0.6 (−1.8 to 0.5)	−1.3 (−2.9 to 0.3)	0.23
Glucose range (mmol/ L)	9.1 (8.3 to 10.0)	−2.1 (−3.1 to −1.2)	9.5 (8.7 to 10.3)	−0.6 (−1.6 to 0.4)	−1.6 (−2.9 to −0.2)	0.24
MODD (mmol/ L) [c]	1.9 (1.6 to 2.1)	−0.4 (−0.7 to −0.1)	2.1 (1.8 to 2.3)	−0.3 (−0.6 to −0.004)	−0.1 (−0.5 to 0.3)	0.16
CVD risk markers						
SBP (mmHg)	130.4 (126.9 to 133.8)	−2.0 (−5.9 to 1.8)	132.6 (129.1 to 136.0)	−3.2 (−7.3 to 0.9)	1.1 (−4.5 to 6.8)	0.76
DBP (mmHg)	79.9 (77.4 to 82.4)	−1.2 (−3.6 to 1.2)	80.8 (78.2 to 83.3)	−2.0 (−4.5 to 0.5)	0.8 (−2.7 to 4.2)	0.44
Total Cholesterol (mmol/ L)	4.5 (4.2 to 4.7)	0.2 (−0.1 to 0.6)	4.3 (4.0 to 4.6)	0.1 (−0.3 to 0.4)	0.2 (−0.3 to 0.7)	0.85
LDL-C (mmol/ L)	2.5 (2.3 to 2.8)	0.2 (−0.1 to 0.5)	2.4 (2.2 to 2.6)	0.1 (−0.2 to 0.4)	0.1 (−0.3 to 0.5)	0.85
HDL-C (mmol/ L)	1.2 (1.1 to 1.3)	0.02 (−0.05, 0.1)	1.3 (1.2 to 1.3)	−0.1 (−0.1 to 0.01)	0.1 (−0.02 to 0.2)	0.004
TG (mmol/ L)	1.6 (1.5 to 1.8)	−0.1 (−0.3 to 0.2)	1.4 (1.3 to 1.6)	0.1 (−0.2 to 0.3)	−0.2 (−0.5 to 0.2)	0.001
Non-HDL-C (mmol/L) [d]	3.3 (3.0 to 3.5)	0.2 (−0.2 to 0.5)	3.0 (2.8 to 3.3)	0.1 (−0.2 to 0.5)	0.04 (−0.4 to 0.5)	0.51
FMD (%) [e]	5.6 (4.8 to 6.5)	−0.5 (−1.5 to 0.5)	5.4 (4.5 to 6.2)	−0.4 (−1.4, 0.7)	−0.1 (−1.5 to 1.3)	0.73
Fasting insulin (mU/L) [f]	15.9 (13.8 to 18.1)	−2.6 (−4.6 to −0.7)	15.9 (13.7 to 18.1)	−1.8 (−3.9 to 0.2)	−0.8 (−3.6 to 2.0)	0.72
HOMA2-IR [f]	1.9 (1.7 to 2.2)	−0.3 (−0.5 to −0.1)	2.0 (1.7 to 2.2)	−0.2 (−0.5 to 0.03)	−0.1 (−0.4 to 0.3)	0.88
HOMA2-%B [f]	64.7 (55.8 to 73.5)	−5.6 (−11.5 to 0.2)	60.8 (51.7 to 69.9)	−5.8 (−12.0 to 0.3)	0.2 (−8.3 to 8.7)	0.28
CRP (mg/ L) [g]	2.8 (2.2 to 3.4)	−0.6 (−1.1 to −0.03)	2.8 (2.2 to 3.5)	−0.8 (−1.4 to −0.2)	0.2 (−0.6 to 1.0)	0.74
Diabetes medications						
Antiglycaemic MES	1.3 (1.0 to 1.5)	−0.5 (−0.6 to −0.3)	1.1 (0.9 to 1.4)	−0.2 (−0.4 to −0.02)	−0.2 (−0.5 to 0.04)	0.03
MES reduction ≥20% [n (%)] [h]		22 (38%)		9 (16%)		0.04
MES reduction ≥50% [n (%)] [h]		12 (21%)		8 (14%)		1.0
Renal markers						
Serum creatinine (μmol/L)	69 (65 to 72)	3 (1 to 5)	71 (67 to 75)	3 (0.3 to 5)	0.1 (−3 to 3)	0.19
Urinary albumin (mg/ L)[i]	3.3 (1.1 to 5.4)	−0.9 (−2.8 to 1.1)	2.4 (0.3 to 4.5)	−0.04 (−2.1 to 2.0)	−0.8 (−3.7 to 2.0)	0.14
AER (mg/ 24 h)[i]	6 (2 to 11)	3(−6 to 11)	5 (1 to 9)	0.3 (−9 to 9)	2 (−10 to 15)	0.38

(*Continues*)

TABLE 2 (Continued)

Variable	LC		HC		Mean difference in change between groups	*P* Value [b]
	Baseline	Change	Baseline	Change		
eGFR- CKD-EPI (ml/min/1.73m^2)[j,m]	96 (93 to 99)	−4 (−6 to −2)	91 (88 to 95)	−3 (−5 to −1)	−1 (−4 to 2)	0.32
CrCl-Cockcroft-Gault (ml/min)[k,n]	82 (77 to 87)	−8 (−10 to −5)	77 (72 to 82)	−8 (−11 to −5)	0.4 (−3 to 4)	0.33
CrCl-Salazar-Corcoran (ml/min)[l,o]	127 (119 to 134)	−12 (−16 to −8)	120 (112 to 127)	−13(−17 to −9)	1 (−5 to 7)	0.07

Abbreviations: LC, low-carbohydrate, high-unsaturated/low-saturated fat diet; HC, high-carbohydrate, low-fat diet; $AUC_{Total\ glucose\ per\ min}$, total area under the curve for blood glucose standardized by valid wear time; MODD, mean of daily differences between paired blood glucose values during successive 24-hour periods; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; Non-HDL-C, non-high-density lipoprotein cholesterol; FMD, flow-mediated dilatation; HOMA2-IR, homeostasis model of assessment index 2- insulin resistance; HOMA2-%B, homeostasis model of assessment index 2- β cell function; CRP, C-reactive protein; AER, albumin excretion rate; eGFR, estimated glomerular filtration rate; CKD-EPI, chronic kidney disease epidemiology collaboration; CrCl, creatinine clearance. To convert mmol/ L to mg/ dL, multiply by 18 (for glucose), by 38.7 (for cholesterol) and by 88.6 (for triglycerides). To convert μmol/ L to mg/ dL, multiply by 0.0113 (for serum creatinine). The following variables were transformed to attain normality before analyses: HbA1c, $AUC_{Total\ glucose\ per\ min,}$ mean and fasting glucose, AER and urinary albumin (reciprocal transformation); insulin, HOMA2-IR and HOMA2-%B (square root transformation); TG, FMD, minimum and maximum glucose, $SD_{Glucose}$, glucose range, MAGE, CONGA-1, CONGA-4, MODD, CRP and MES, (logarithmic transformation). Untransformed values are presented to facilitate interpretation. All data are presented as estimated marginal means (95% confidence intervals) by linear mixed-effects model analysis, unless otherwise stated.

[a] Total analysed, n = 115 (LC, 58; HC, 57) for all data unless otherwise stated.

[b] *P* value refers to between-group differences over time (time × diet interaction) by linear mixed-effects model analysis.

[c] Total analysed, n = 113 (LC, 57; HC, 56) that met the criteria for 48-hour valid continuous glucose monitoring (CGM) data collection to calculate comparisons between 2 successive days.

[d] Non-HDL-C was calculated as the difference between total cholesterol and HDL cholesterol concentration.

[e] Total analysed, n = 115 for FMD data; outlying data from 1 LC participant at baseline (LC, 1) and 1 HC participant at 24 weeks (HC, 1) were excluded from analyses.

[f] Total analysed, n = 108 (LC, 56; HC, 52) for insulin and HOMA2 data; 7 participants using insulin medication at baseline and at 24, 52 and 104 weeks or who withdrew before these time points were excluded from analyses.

[g] Total analysed, n = 112 (LC, 56; HC, 56) for CRP data; 3 participants with CRP >10 mg/L at baseline and at 24, 52 and 104 weeks or who withdrew before these time points were excluded from these analyses.

[h] *P* value for number of participants who showed ≥20% and ≥50% reduction in diabetes medication effect score (MES) analysed by χ^2 test.

[i] Total analysed, n = 113 (LC, 56; HC,57) for Urinary Albumin and AER data; no urinary albumin analyses were available at baseline for 2 participants in the LC group.

[j] eGFR-CKD-EPI (ml/min/1.73m^2) = $141 \times \min(SCr\ (mg/dL)\ /\kappa, 1)^{\alpha} \times \max(SCr(mg/dL)/\kappa, 1)^{-1.209} \times 0.993^{Age}$ [×1.018 if female] [×1.159 if black]. where κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, SCr is serum creatinine, min indicates the minimum of SCr/κ or 1 and max indicates the maximum of SCr/κ or 1.

[k] CrCl-Cockcroft-Gault (ml/min) = [140 − age(yrs)] × FFM(kg)/ (Scr (mg/dL) × 72) [×0.85 if female], where FFM is fat-free mass.

[l] CrCl-Salazar-Corcoran (ml/min) = [137 − age(yrs)] × {[0.285 × weight(kg)] + [12.1 × height(m)^2]/[51 × Scr(mg/dL)] for males; [146-age(yrs)] × {[0.287 × weight(kg)] + [9.74 × height(m)^2]}/[60 × Scr(mg/dL)] for females.

[m] Reference Levey et al.,[23].

[n] Reference Gault et al.[29].

[o] Reference Salazar and Corcoran[30].

TABLE 3 Energy intake and macronutrient composition of the 2 diets over 2 years

Nutrient	Diet group	1–3 months	4–6 months	7–9 months	10–12 months	13–15 months	16–18 months	19–21 months	22–24 months
Total energy (kcal)	**LC**	1558 (1504 to 1612)	1596 (1533 to 1658)	1696 (1613 to 1778)	1683 (1592 to 1775)	1767 (1667 to 1866)	1734 (1631 to 1836)	1711 (1610 to 1811)	1707 (1604 to 1811)
	HC	1550 (1496 to 1604)	1628 (1567 to 1690)	1671 (1591 to 1752)	1708 (1616 to 1800)	1684 (1582 to 1784)	1714 (1611 to 1818)	1747 (1645 to 1848)	1757 (1651 to 1863)
Carbohydrate (g) [a]	**LC**	55 (50 to 60)	60 (54 to 66)	71 (63 to 79)	74 (65 to 82)	79 (69 to 89)	77 (68 to 87)	80 (70 to 90)	83 (73 to 94)
	HC	202 (197 to 207)	209 (203 to 215)	214 (206 to 222)	216 (208 to 224)	213 (203 to 223)	213 (203 to 222)	215 (205 to 225)	216 (206 to 227)
Carbohydrate (% energy) [a]	**LC**	14 (13 to 14)	15 (14 to 15)	16 (15 to 17)	17 (16 to 18)	17 (16 to 18)	17 (16 to 18)	18 (17 to 19)	19 (17 to 20)
	HC	51 (50 to 51)	50 (49 to 51)	50 (49 to 51)	49 (48 to 50)	48 (47 to 49)	48 (47 to 49)	48 (47 to 49)	48 (46 to 49)
Protein (g) [a]	**LC**	104 (100 to 107)	103 (100 to 107)	105 (101 to 110)	106 (101 to 110)	108 (103 to 113)	106 (101 to 112)	106 (101 to 111)	105 (100 to 111)
	HC	73 (69 to 76)	75 (72 to 78)	75 (71 to 78)	77 (72 to 82)	76 (71 to 82)	78 (72 to 83)	78 (73 to 83)	79 (73 to 84)
Protein (% energy) [a]	**LC**	27 (27 to 27)	26 (26 to 27)	25 (25 to 26)	26 (25 to 26)	25 (24 to 26)	25 (24 to 25)	25 (25 to 26)	25 (25 to 26)
	HC	19 (19 to 19)	19 (18 to 19)	18 (18 to 19)	18 (18 to 19)	19 (18 to 19)	19 (18 to 19)	18 (18 to 19)	18 (18 to 19)
Total fat (g) [a]	**LC**	96 (92 to 99)	98 (94 to 101)	102 (97 to 107)	100 (94 to 105)	105 (99 to 111)	103 (96 to 109)	99 (93 to 105)	98 (91 to 104)
	HC	42 (38 to 45)	45 (41 to 49)	48 43 to 53)	50 (45 to 56)	49 (43 to 55)	52 (46 to 58)	54 (48 to 61)	55 (48 to 62)
Total fat (% energy) [a]	**LC**	54 (53 to 55)	54 (53 to 55)	53 (52 to 54)	52 (51 to 53)	52 (51 to 53)	52 (51 to 53)	51 (50 to 52)	50 (49 to 52)
	HC	24 (23 to 25)	24 (24 to 25)	25 (24 to 26)	26 (25 to 27)	26 (25 to 27)	27 (25 to 28)	27 (26 to 29)	27 (26 to 29)
Saturated fat (g) [a]	**LC**	17 (17 to 18)	18 (17 to 20)	21 (19 to 22)	21 (19 to 22)	22 (20 to 24)	23 (21 to 24)	23 (21 to 24)	22 (20 to 24)
	HC	13 (12 to 13)	14 (13 to 15)	16 (14 to 17)	16 (15 to 18)	16 (14 to 18)	17 (15 to 19)	18 (16 to 19)	18 (16 to 20)
Saturated fat (% energy) [a]	**LC**	10 (9 to 10)	10 (10 to 11)	11 (10 to 11)	11 (10 to 11)	11 (10 to 12)	11 (11 to 12)	12 (11 to 12)	11 (11 to 12)
	HC	7 (7 to 8)	8 (7 to 8)	8 (8 to 9)	8 (8 to 9)	8 (8 to 9)	9 (8 to 9)	9 (8 to 9)	9 (8 to 10)
Monounsaturated fat (% energy) [a]	**LC**	29 (28 to 29)	28 (28 to 29)	27 (27 to 28)	27 (26 to 27)	26 (26 to 27)	26 (26 to 27)	26 (25 to 26)	25 (24 to 26)
	HC	10 (9 to 10)	10 (10 to 11)	10 (10 to 11)	11 (10 to 11)	11 (10 to 11)	11 (10 to 12)	11 (11 to 12)	11 (10 to 12)
Polyunsaturated fat (% energy) [a]	**LC**	12 (12 to 13)	12 (12 to 12)	12 (11 to 12)	11 (11 to 12)	11 (11 to 12)	11 (11 to 12)	11 (10 to 11)	11 (10 to 11)

(*Continues*)

TABLE 3 (Continued)

Nutrient	Diet group	1–3 months	4–6 months	7–9 months	10–12 months	13–15 months	16–18 months	19–21 months	22–24 months
	HC	4 (4 to 4)	4 (4 to 4)	4 (4 to 5)	4 (4 to 5)	4 (4 to 5)	4 (4 to 5)	4 (4 to 5)	4 (4 to 5)
Total cholesterol (mg) [a]	LC	238 (230 to 247)	250 (238 to 262)	259 (244 to 274)	266 (250 to 281)	289 (269 to 308)	296 (278 to 313)	288 (267 to 309)	285 (265 to 304)
	HC	127 (118 to 135)	146 (135 to 158)	147 (132 to 162)	147 (131 to 163)	150 (130 to 170)	161 (143 to 178)	168 (147 to 190)	163 (143 to 183)
Dietary fibre (g) [a]	LC	24 (24 to 25)	25 (24 to 26)	25 (24 to 27)	26 (24 to 27)	26 (24 to 28)	25 (23 to 27)	25 (23 to 26)	25 (23 to 27)
	HC	31 (30 to 32)	31 (30 to 32)	31 (29 to 32)	31 (30 to 33)	31 (29 to 33)	31 (29 to 33)	31 (29 to 33)	31 (29 to 33)

Abbreviations: LC, low-carbohydrate, high-unsaturated/low-saturated fat diet; HC, high-carbohydrate, low-fat diet. Data are presented as estimated marginal means (95% confidence intervals) by linear mixed-effects model analysis. Total analysed, n = 114 (LC, 57; HC, 57); 1 LC participant with no diet data collected was excluded from these analyses. The following variables were logarithmically transformed to attain normality before analyses: total energy, total fat, carbohydrate, protein, saturated fat and cholesterol. Untransformed values are presented to facilitate interpretation.

[a] $P < 0.001$ for between group differences (diet effect) by linear mixed-effects model analysis.

FIGURE 2 Estimated marginal mean change in body-weight after 2 years on a low-carbohydrate, high-unsaturated fat/low-saturated fat diet (LC) or a high-carbohydrate, low-fat diet (HC). Error bars represent 95% CIs. Differences between groups were not significant by linear mixed-effects model analysis ($P = 0.26$)

the study for personal reasons before symptoms had resolved (Week 68). Table S2 records other adverse events.

4 | DISCUSSION

After 2 years, planned energy-matched LC and HC, prescribed in combination with regular exercise, for adults with obesity and T2D achieved clinically relevant weight loss and improvements in glycaemic control and CVD risk factors. Compared to the HC, the LC maintained more favourable lipoprotein profile changes and sustained greater reductions in diabetes medication requirements and diurnal GV.

While both diets sustained clinically meaningful and equivalent reductions in weight and HbA1c, the LC achieved these improvements with more than two-fold greater reductions in diabetes medication requirements. Considering that the population presently examined had relatively low levels of baseline diabetes medication, the mean 0.5-unit MES reduction in the LC group reflected a complete cessation of diabetes medication (metformin 500 mg twice/day) in 1 LC participant, or a change in medications from gliclazide MR 60 mg once/day to metformin 500 mg once/day in another. However, the mean 0.2-unit MES reduction in the HC group reflected a reduction of 2.5 mg glibenclamide once daily in an HC participant or 10 units biphasic insulin aspart in another participant weighing 115 kg. Therefore, the greater reduction in diabetes medication in the LC group could translate to at least 1 less tablet per day. It is anticipated that reductions in individuals using higher levels of diabetes medication would be significantly even greater[18]. Multiple-drug therapy may be required to achieve T2D treatment goals[52,54], but cost considerations, including indirect healthcare system costs associated with drug administration, formulary restrictions and potential side effects including hypoglycaemia and weight gain, serve as barriers to medication adherence.[10] Consequently, the benefits of an LC to achieve glycaemic goals with lower medication could be considered clinically significant.

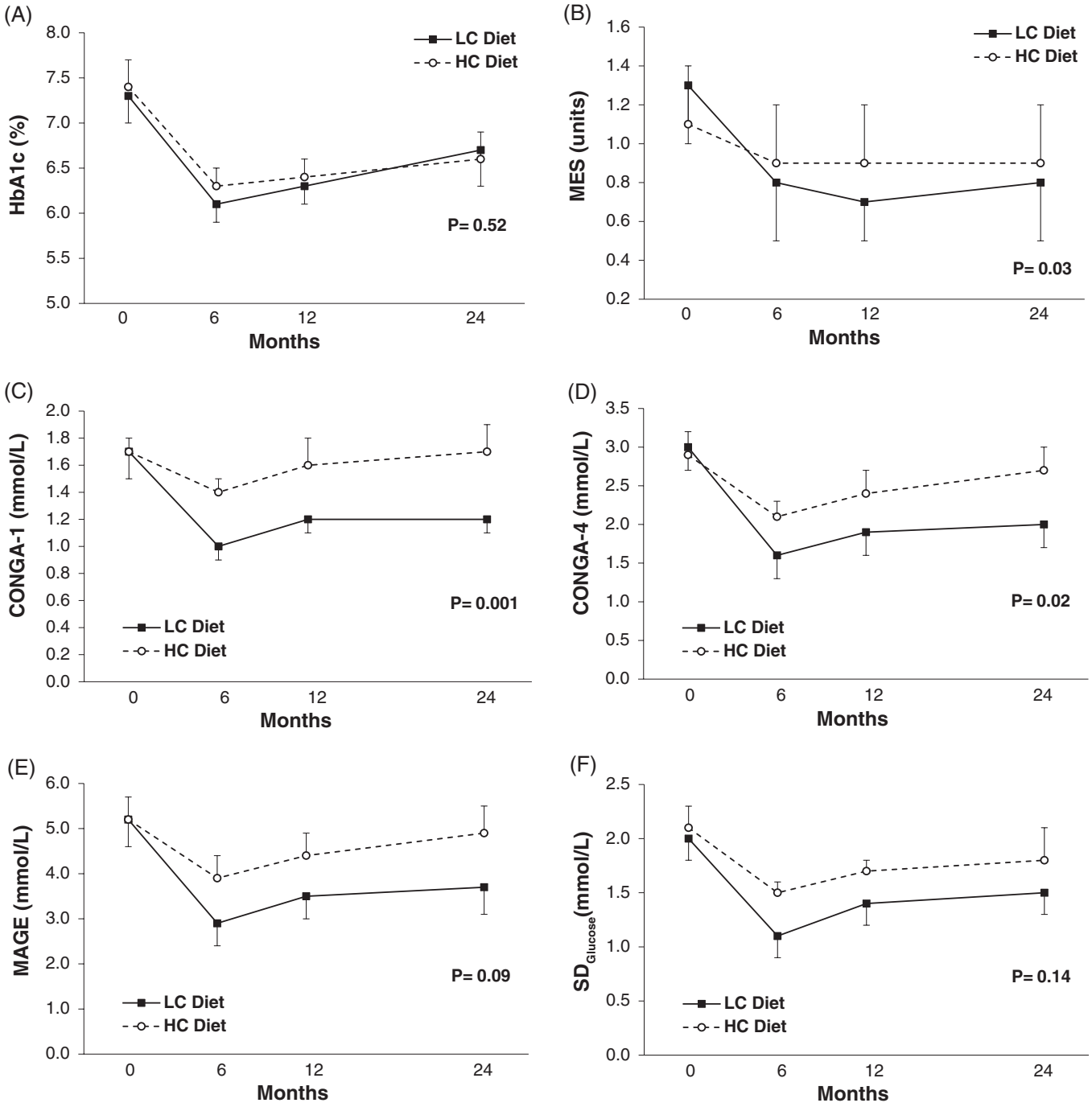

FIGURE 3 Estimated marginal mean changes in HbA1c (A), MES (B) and glycaemic variability indices, CONGA-1 (C), CONGA-4 (D), MAGE (E) and SD $_{Glucose}$ (F), after 2 years on a low-carbohydrate, high-unsaturated/low-saturated fat diet (LC) or a high-carbohydrate, low-fat diet (HC). Error bars represent 95% CIs. *P* values are for differences between groups by linear mixed-effects model analyses. CONGA- 1, Continuous overall net glycaemic action of observations 1 hour apart; CONGA- 4, Continuous overall net glycaemic action of observations 4 hours apart; MAGE, Mean amplitude of glycemic excursions; MES, Medication Effect Score; SD $_{Glucose,}$ SD of blood glucose

Large prospective RCTs suggest optimization of glucose control to achieve near-normoglycaemia is a key treatment goal in T2D, to reduce the risk or slow progression of diabetes-related complications, especially microvascular diseases.[10,31–35] However, some of these studies showed intensive glucose control with medications that actually increased the risk of hypoglycaemia, weight gain and even mortality.[31,36] This finding argues that emphasizing lifestyle strategies, including dietary modifications and increased physical activity, rather than pharmacology may be healthier. Observational data suggest that neuropathic symptoms may improve with circumventing extreme blood glucose fluctuations.[37] The LC produced greater reductions in GV, with statistical significance for CONGA-1 and CONGA-4, measures of short-term glycaemic excursions. GV and HbA1c may reflect different aspects of blood glucose regulation and accumulating evidence suggests that GV is an independent risk factor for diabetes complications.[13] HbA1c provides limited characterization of GV and is not significantly altered by transient hyperglycaemia or hypoglycaemic excursions, and short-term glucose fluctuations may determine

up to 89% of the diabetes complications risk not explained by HbA1c.[38] This is the first 2-year RCT to report on a diet strategy that achieved greater GV improvements in T2D. The ability of the LC to achieve more physiologically stable blood glucose profiles that were sustained over the long-term, post-active weight-loss, extends the benefits of LC for improving glycaemic control in T2D.

T2D increases CVD risk and multifactorial risk reduction involves blood pressure and lipid management. Both groups had comparable reductions in blood pressure. Additionally, the LC sustained greater reductions in TAG and maintained HDL-C levels. The combination of high TAG and low HDL-C is the most prevalent pattern of dyslipidaemia and an important contributor to accelerated atherosclerosis in diabetes.[39] Evidence for the pharmacological treatment of these lipid fractions is considerably weaker than that for statin therapy.[10] This underscores the potential benefits of LC as a lifestyle strategy for reducing CVD risk in T2D. In patients with T2D, a 15% decrease in the risk of coronary artery disease has been associated with a 0.1 mmoL/L increment in HDL-C.[40] Therefore, the maintenance of HDL-C levels with the LC and the 0.12 mmoL/L differential change observed between the diet groups would probably translate to a reduction in CVD risk. In fact, the fatty acid composition of the LC prescribed in this study, which was high in unsaturated fat and low in saturated fat, was similar to a Mediterranean diet which was associated with a 29% reduction in major CVD events compared to a HC in the PREDIMED trial.[41] Changes in LDL-C and non-HDL-C (a comprehensive measure of cholesterol content in atherogenic lipoproteins including IDL, VLDL, Lp(a) and LDL-C, and a marker of residual CVD risk beyond LDL-C)[20] did not differ between groups. FMD is considered an important prognostic predictor for future cardiac events and did not change significantly in either group.[42]

Concerning the long-term safety effects, clinical markers of renal function, including eGFR, CrCl and albuminuria, a surrogate marker for diabetic nephropathy, did not differ between groups after 2 years. This supports the clinical applicability of LCs as a strategy to manage weight, diabetes and comorbidities such as hypertension and dyslipidaemia despite their higher protein content, which some experts have warned may worsen renal function.

The lifestyle interventions undertaken in this study achieved ≥5% weight loss in more than two-thirds of participants after 2 years, a clinically significant magnitude of weight loss.[43] This is comparable to that achieved by pharmacotherapy[44] and by the intensive lifestyle intervention undertaken in Look AHEAD.[45] Conversely, smaller weight losses (−3 to −5 kg) have been observed in other trials of similar duration.[11,12] This could be attributed to differences among the studies in intervention intensity. In the present study and in Look AHEAD, participants were followed up individually, at least monthly, whereas contact in the studies with a lower magnitude of weight loss was limited to group sessions every 6 to 24 weeks. This highlights the importance of ongoing professional support to achieve successful long-term adherence to diet and weight loss maintenance. Exercise also was formally prescribed as part of the present intervention and that of Look AHEAD, and findings from the National Weight Control Registry[46] further highlight the importance of regular physical activity in successful long-term lifestyle interventions for weight management.

The moderately high attrition that occurred may limit interpretation of the results. However, the similar dropout rates observed between groups, which is consistent with previous studies,[5–7,12,27,28,47–49] suggests that both diets were similarly accepted and highlights the persisting need to improve maintenance of lifestyle modifications. Furthermore, treatment fidelity was maintained over the 2-year study duration. While the increase in carbohydrate allowance to 70 g/day in the LC group after 24 weeks, and the isocaloric increase in calorie intake allowance in the HC group could explain in part, the partial weight regain over time, dietary assessments, supported by changes in biomarkers and secondary metabolic outcomes, indicated an adequate level of adherence to diet and differentiation between the LC and HC. The isocaloric prescription of diets was an important strength of the study that enabled comparisons of the long-term efficacy and metabolic health effects between the diets, without the confounding effect of differences in energy intake and weight loss. Participants were followed beyond initial weight loss into weight stabilization and even weight regain, providing further insight into the long-term effectiveness of both diets. Whilst achievement of high compliance was a strength of the study, the intensity of the intervention delivered, with high levels of professional support and subsidized food provisions, may limit generalization for wide-scale community adoption. Future initiatives need to integrate these research outcomes into cost-effective community-based delivery models.

As participants were predominantly Caucasians, future studies should investigate the utility of LC in individuals of diverse ethnicities. In Asians, the rising risk of T2D has been attributed to inadequate compensatory β-cell response to increasing insulin resistance.[50] In African Americans, dietary glycaemic load has been shown to interact with insulin sensitivity to predict greater increases in adiposity.[51] By reducing the glycaemic load to insulin-resistant tissues to achieve durable glycaemic control and weight management,[53] the LC may be particularly beneficial to populations that bear a disproportionate burden of T2D.

In summary, after 2 years, the planned isocaloric HC and LC, limited in saturated fat and administered as a lifestyle intervention programme, achieved comparable reductions in HbA1c, body-weight and blood pressure in adults with obesity and T2D. Additionally, the LC maintained greater improvements in lipid profile, diurnal blood glucose stability and reductions in requirements for diabetes medication. Whilst there may not be a one-size-fits-all dietary approach for obesity and T2D management, these data suggest that diets differ in their efficacy in improving glycaemic control and reducing CVD risk. These results provide support for the long-term safety, clinical efficacy and potential therapeutic role of the LC in long-term T2D management.

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Conflict of interest

The authors do not declare any conflict of interest relevant to this manuscript.

Author contributions

A/Prof Grant Brinkworth is the guarantor of this work and, as such, had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors participated in the study concept and design. All authors participated in analysis and interpretation of data. J. T. and G. D. B. drafted the manuscript. C. H. T., N. L. M., M. N., J. D. B., G. A. W. and W. S. Y. critically revised the manuscript for intellectual content. All authors read and approved the final manuscript. G. D. B., M. N., J. D. B., N. L. M. and C. H. T. obtained funding. Study supervision was provided by G. D. B., C. H. T., N. L. M., M. N. and J. D. B.

ORCID

Jeannie Tay http://orcid.org/0000-0002-5830-4280
Grant D. Brinkworth http://orcid.org/0000-0001-9017-8395

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