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A randomised trial comparing low-fat diets differing in carbohydrate and protein ratio, combined with regular moderate intensity exercise, on glycaemic control, cardiometabolic risk factors, food cravings, cognitive function and psychological wellbeing in adults with type 2 diabetes: study protocol

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Abstract

Background

Hypocaloric low-fat diets, high in protein with moderate carbohydrate (HP) can enhance weight loss, improve glycaemic control and improve cardiometabolic health risk factors in type 2 diabetes mellitus (T2DM). However, it is unclear whether the metabolic benefits observed during weight loss are sustained during energy-balance and weight maintenance. Furthermore, there is a lack of evidence regarding the effect of HP diets on food cravings, cognitive function and psychological wellbeing in T2DM, despite carbohydrate food cravings, cognitive impairment and depression being associated with hyperglycaemia.

Methods / Design

Overweight / obese adults with T2DM were randomised to consume either a HP diet (n=32, ~32% protein, 33% carbohydrate, 30% fat) or a higher-carbohydrate diet (HC, n=29, ~22% protein, 51% carbohydrate, 22% fat) for 24 weeks with 30 minutes of moderate intensity exercise five days/week for the study duration. There were 2 phases: a 12 week weight loss phase followed by a 12 week weight maintenance phase. Primary outcome was glycaemic control (glycosylated haemoglobin; HbA1c). Secondary outcomes were cardiometabolic risk factors (body composition, fasting blood pressure, blood lipids, glucose, insulin and C-reactive protein), food cravings, cognitive function (memory; psychomotor and executive function) and psychological well-being. Outcomes were measured at baseline and the end of each 12-week intervention phase. Data will be analysed as intention-to-treat using linear mixed effects models.

Conclusion:

This study will examine the effects of two dietary interventions on health outcomes in T2DM during weight loss and notably following weight maintenance where there is a paucity of evidence.

Keywords: diabetes, glycemic, cardiometabolic, cognitive, psychological, protocol

Introduction

Weight control, diet and exercise are the cornerstones of T2DM management. Strategies that enhance weight loss and facilitate weight loss maintenance are needed to improve glycaemic control and reduce diabetes-related complications. High-protein (HP) diets may promote greater weight loss and reductions in HbA1c and blood pressure (BP) in the short term compared to high-carbohydrate (HC) diets [1]. But whilst several studies have investigated the effects of a HP diet in a state of weight loss, there is limited data examining the effects of HP diets on glycaemic control and cardiometabolic health in patients with T2DM during weight maintenance. Moreover, few studies have included concurrent moderate intensity exercise which is an important standard of care adjunct to diabetes management. Additionally, with the suggested benefits of HP diets for promoting weight loss, very few studies have investigated the effects of diets on food cravings in T2DM despite binge eating behaviour being identified in this population [2] and poor glycaemic control being associated with increased carbohydrate food cravings [3].

Furthermore, previous studies have indicated that individuals with T2DM have a greater rate and risk of cognitive decline compared with controls without T2DM and a higher risk of dementia [4]. The cognitive domains affected are processing speed; attention; verbal and visual memory; psychomotor performance/coordination and executive function [5-8]. The pathogenesis of cognitive decline in T2DM is not fully understood but hyperglycaemia and hyperinsulinaemia are considered pivotal in the aetiology of cognitive impairment as they can lead to macrovascular disease and microvascular changes in the brain [9]. Despite improvements in HbA1c observed following consumption of a HP diet, no studies to date have evaluated the effects of a HP diet on cognitive function in T2DM. It is plausible that diet strategies that promote better glycaemic control, reduce insulin resistance, and reduce cardiovascular risk factors may also prevent or limit cognitive decline in T2DM.

Almost 66% of individuals with T2DM experience diabetes-related psychological problems [10] and are at greater risk for developing depression [11]. A study of overweight/obese adults with T2DM found weight loss, independent of physical activity, improved diabetes-related emotional distress and quality of life (QOL) scores [12]. Furthermore, in a study of obese women with polycystic ovary syndrome, an energy-restricted HP diet showed greater improvements in self-esteem and depression scores, compared to a HC diet despite no significant differences in weight loss between the groups [13]. Studies investigating associations between dietary intake and psychological wellbeing, such as depression, during weight maintenance (without active weight loss) in a T2DM population are lacking.

The primary aim of this study was to compare the effects of isocaloric HP and HC diets, each combined with regular moderate intensity exercise, on HbA1c in overweight and obese adults with T2DM following active weight loss and after 12 weeks weight loss maintenance. Secondary outcomes included: cardiometabolic risk factors (body composition, BP, lipids, fasting glucose and insulin and C-reactive protein), food cravings, cognitive function (memory; psychomotor and executive function) and psychological well-being (diabetes-related stress, QOL, physical and mental health and sleep quality).

Materials and Methods

Study design

This was a 24 week, two-arm parallel-group randomised dietary intervention study comparing two isocaloric low-fat diets differing in protein and carbohydrate ratio over two phases: a 12-week energy-restricted (~30% caloric reduction) weight loss phase followed by a 12-week energy-balance weight maintenance phase. There were 3 assessment time points: baseline (Week 0), end of active weight loss phase (Week 12) and end of weight maintenance phase (Week 24). Anthropometric, cardiometabolic health, body composition and cognitive function assessments and the administration of psychological wellbeing questionnaires were conducted at the research facility of the Alliance for Research in

Nutrition, Exercise and Activity (ARENA), Sansom Institute for Health Research, University of South Australia, Adelaide, Australia. The dietary intervention was delivered and monitored at the Commonwealth Scientific and Industrial Research Organisation (CSIRO) - Food and Nutrition, Adelaide, Australia. The study was approved by the University of South Australia Human Research Ethics Committee, the CSIRO Human Research Ethics Committee and registered with the Australia and New Zealand Clinical Trials Register (ACTRN12613000008729). Prior to commencing the study, the procedures were explained in detail to participants and they were asked to confirm they had approval from their medical practitioner before written informed consent was obtained.

Recruitment and screening

Participants were recruited in Adelaide, Australia through advertisements via newspapers, television, medical centres, outpatient departments, diabetes organisations and the university website. Interested people contacted ARENA by telephone or email and were provided with an information sheet and a diet and lifestyle questionnaire (DLQ) requesting information on current disease management, medical conditions, medications, weight, smoking status, dietary requirements and ability to exercise.

Based on information provided in the DLQ, participants who appeared eligible attended a screening appointment to assess their body mass and height (to calculate BMI), blood pressure (BP) and HbA1c. For those older than 40 years, the DemTect questionnaire [14] was administered to detect any mild cognitive impairment and participants were required to score ≥ 13 (indicative of age-appropriate cognitive abilities) for inclusion. The eligibility criteria are described in Table 1.

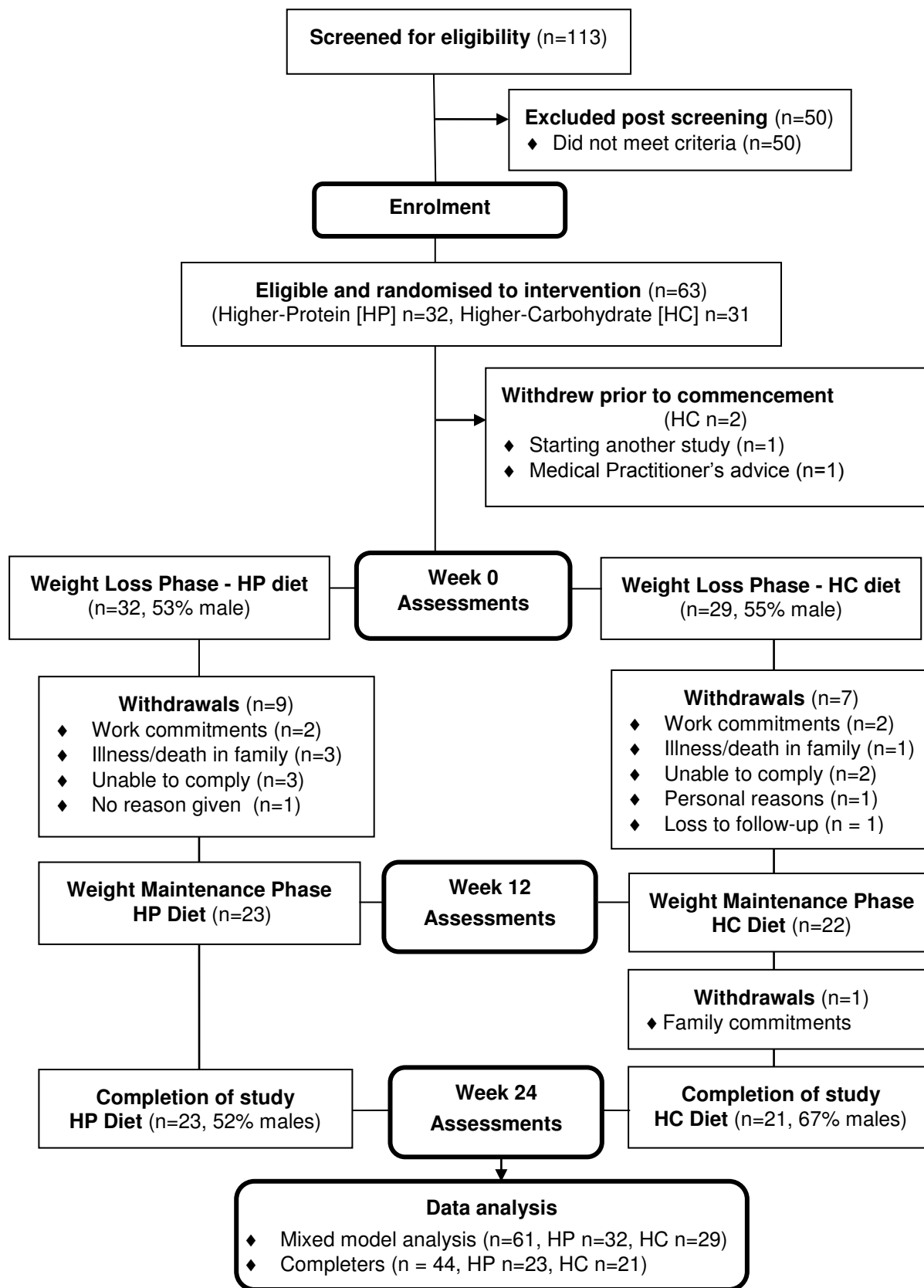
Table 1 Eligibility criteria for the study

Inclusion criteria
<ul style="list-style-type: none">• Diagnosed with T2DM• Aged 18-70 years• HbA1c between 6.5-10.5% at screening• BMI greater than 25 kg/m²• Weight ≤ 135kg (maximum capacity for dual X-ray absorptiometry [DEXA])• Non-smoker for more than 6 months• Proficient in written and spoken English (to perform the cognitive tests)• Age-appropriate cognitive abilities (determined using the DemTect questionnaire)
Exclusion criteria
<ul style="list-style-type: none">• Liver, kidney, gastrointestinal or cardiovascular disease• Respiratory disease (apart from stable asthma)• Retinopathy• Malignancy (within last 6 months)• Proteinuria• Uncontrolled hypertension (>170/100)• Taking medication for a neurological or psychiatric condition (except stable antidepressants > 3 months)• Neurological or psychiatric condition• History of head or brain injury• Musculoskeletal injury or peripheral vascular disease sufficient to impede exercise• Undertaking a weight loss program or taking appetite suppressants• Pregnant or lactating• Unable to participate in the trial for 6 months• Participated in another study within last 30 days

Enrolment into study and diet allocation

Eligible participants were notified in writing and invited to attend a group information session. At this time, participants were instructed to confirm with their medical practitioner that it was safe for them to partake in the study. As each individual participant was enrolled into the study they were allocated to either a higher-protein (HP) diet or a higher-carbohydrate (HC) diet by an investigator, who had no participant contact, using the process of minimization [15]. Stratification was based on age; gender and BMI as they were considered to be important prognostic factors to the outcomes investigated in this study. A total of 63 participants were enrolled into the study (HP $n=32$, HC $n=31$). Figure 1 showing the flowchart for participants through the study.

Figure 1: Flow diagram for study participants



Study Intervention

Dietary intervention

The diets were isocaloric with the planned macronutrient content for the HP diet being ~32% of total energy as protein, 33% carbohydrate, 30% total fat (<10% of total fat intake as saturated fat) and the HC diet was ~22% protein 51% carbohydrate, 22% total fat (<10% saturated fat). The HC diet is similar to the recommended macronutrient intakes outlined in the Australian healthy eating guidelines [16]. Both dietary patterns incorporated a variety of foods within all five food groups as depicted in Table 2. As expected, the total fat intake in the HP diet is higher than the HC diet as a result of larger meat portions and the inclusion of reduced-fat cheese and almonds. However, both diets meet the recommendations for dietary intakes of total and saturated fats ($\leq 30\%$ and $\leq 10\%$ of energy intake respectively) [16]. Alcohol intake was restricted to two standard drinks per week with a standard drink defined as containing 10g alcohol. Our dietary patterns were planned to include all food groups (albeit with limitations to variety and portion sizes) in order to compare diets that are practical (i.e. can be achieved and adhered to in free-living individuals) with results that will be of clinical interest.

Table 2. Daily food quantities and nutrient analysis based on a 6000kJ/day higher-protein or higher-carbohydrate diet

Higher-Protein diet	Higher-Carbohydrate diet
30g High fibre breakfast cereal*	30g High fibre breakfast cereal*
350 mL Milk (reduced fat)	350 mL Milk (reduced fat)
40g Cheese (reduced fat)*	
105g Bread (mixed grain)*	140g Bread (mixed grain)*
300g Fruit (fresh)	450g Fruit (fresh)
½ cup Vegetables (salad)	½ cup Vegetables (salad)
2 cups Vegetables (non-starchy)	2 cups vegetables (non-starchy)
	150g starchy vegetables (cooked) or ½ cup rice (cooked) or 1 cup pasta (cooked)

50g Luncheon meat (e.g. ham, tuna, chicken, egg)	25g Luncheon meat (e.g. ham, tuna, chicken, egg)
200g Meat (raw weight, lean)*, #	100g Meat (raw weight, lean)*, #
200g Legumes (optional, replace meat)	100g Legumes (replace meat)
20g Almonds (raw, unsalted)*	
15g Oil/margarine	20g Oil/margarine
Alcohol (≤ 2 standard drinks/week, optional)	Alcohol (≤ 2 standard drinks/week, optional)

Nutritional Analysis as % Energy (g/day)^:

Protein 31% (109g)	Protein 22% (74g)
Carbohydrate 33% (121g)	Carbohydrate 52% (179g)
Fat 30% (42g)	Fat 20% (31g)
- 10% Saturated Fat (16g)	Saturated Fat 5% (8g)
Fibre (30g)	Fibre (35g)

* Foods provided # Fresh, Lean Australian Pork 4 x week

^ Analysis using FoodWorks® Professional Edition, version 7, 2012; Xyris Software, Highgate Hill, Australia

At the baseline visit, participants commenced their allocated diet under the supervision of a qualified dietitian. Individual estimated energy requirements (EER) were calculated using the Schofield Equations based on sex, age and initial body weight [17]. A moderate energy restriction of ~ 30% of the EER was prescribed (equating to ~ 6000 – 7000kJ/day) to facilitate weight loss for the first 12 weeks with the aim of a 5% reduction of initial body weight. Participants attended dietetic appointments every two weeks where they were weighed and energy intake was adjusted, if necessary, to assist with weight loss while still maintaining the assigned macronutrient profile. Immediately following the weight loss phase (Week 12), energy intake was titrated up (using ~ 500 kJ/day increments) over a two to four week period to achieve weight maintenance for a further 12 weeks whilst retaining the prescribed macronutrient profile.

Throughout the study, participants were required to weigh or measure their food intake and complete a daily semi-quantitative food record which was collected by the dietitian every two weeks. To facilitate dietary compliance, participants were provided with study foods corresponding to their assigned dietary pattern: fresh lean pork (steaks, fillets or strips),

wholegrain breakfast cereal, mixed grain bread, fat-reduced cheese (HP only) and unsalted almonds (HP only). Participants received comprehensive dietary advice about their allocated diet, carbohydrate choices (low – moderate GI), spreading carbohydrate intake across the day as well as meal planning, recipe ideas and how to weigh/measure and record their dietary intake (digital scales were provided). Dietary intake will be assessed based on the analysis of seven consecutive days from every two-weekly food record and will be averaged to attain a score for the weight loss and weight maintenance phases. Analysis will be performed using a computerised database (FoodWorks® Professional Edition, version 7, 2012; Xyris Software, Highgate Hill, Australia).

Prior to commencing the study, participants completed the Cancer Council Victoria's Dietary Questionnaire for Epidemiological Studies Version 2 [18] which is a validated questionnaire for adults [19] that evaluates the frequency and portion sizes for a comprehensive list of Australian foods and provides an overview of habitual general food, macronutrient (% and g/day) and micronutrient intakes over the past 12 months.

Physical activity intervention

All participants were prescribed to undertake self-monitored moderate intensity, aerobic exercise for a minimum of 30 minutes five times a week (150 minutes/week) for the duration of the study. Moderate intensity was considered as a rate of perceived exertion (RPE) equating to a 'somewhat hard' level which reflects RPE13 on the Borg 6-20 Scale [20]. This method was chosen as it has been shown to improve fitness and considered 'pleasant' in a previous study [21]. To demonstrate the intensity of RPE13, participants walked or jogged on a treadmill at a 0° gradient at each clinic visit. Treadmill speed was increased until the participant perceived the pace as 'somewhat hard', corresponding to RPE13. The treadmill's speed was hidden from the participants' view. Participants continued to exercise at this intensity for 3 minutes, with RPE reassessed at the end of each minute. The speed at which RPE 13 was achieved was recorded and participants were instructed to perform their

prescribed exercise at this intensity. The exercise test was repeated at Weeks 12 and 24 to remind participants to continue to exercise at a pace that was 'somewhat hard' (RPE13), particularly as fitness levels increased. Participants self-selected the type of exercise performed and free memberships to the University of South Australia's gymnasiums (2 locations) and organised walking groups were available on a voluntary basis. Participants completed daily physical activity logs by recording the date, type of exercise and duration of exercise which was used to monitor compliance at the end of each study phase with the treadmill exercise to assess changes in fitness levels.

Clinic visits

Each clinic visit (Week 0, Week 12 and Week 24) was conducted in the morning, took approximately 3.5 hours and followed the same protocol. The participant attended the clinic after an overnight fast (water as required) and without taking their morning medications which were administered with breakfast. Weight, height (baseline only), waist circumference, BP and body composition were measured and medications (prescribed and over-the-counter) were documented. Changes to medication type and doses were recorded throughout the study. A venous blood sample was collected and cognitive function tests were conducted in a quiet environment. A series of psychological wellbeing questionnaires were then completed by the participant during a breakfast break of approximately 20 minutes where foods aligning with their assigned dietary intervention were offered. Following this, the participant completed the treadmill exercise before attending the CSIRO clinic to consult with the dietitian. Record sheets to document fasting BGL, physical activity and medication changes were provided and collected fortnightly at the dietetic visits.

Clinical assessments

Anthropometry

All anthropometric assessments were conducted with participants barefoot, wearing minimal clothing. Height was measured twice (baseline only) using a portable stadiometer (Seca

220;Vogel & Halke, Hamburg, Germany) to the nearest 0.1cm. Body mass was measured twice using calibrated electronic scales (Tanita Ultimate Scale 2000; Tokyo, Japan) and BMI was calculated using the formula: mass (kg)/height (m)². Waist circumference was measured, using a metal measuring tape (Lufkin Executive Thin line 2m metal measuring tape), at the narrowest point of the abdomen or, if there was no obvious narrowing, at the midpoint between the lower costal (10th rib) border and the iliac crest. Two measurements were taken unless they differed by more than 2% whereby a third measurement was obtained. The mean of the measurements was used for analysis. The investigator was trained in ISAK International Standards for Anthropometric Assessment [22].

Resting blood pressure

Resting Systolic and Diastolic blood pressure was recorded using the Cardiovascular Profiler™ (HDI Cardiovascular Profiler CR2000) after participants had been seated for 5-10 minutes with legs uncrossed, feet flat on the floor and arm resting comfortably on a table. The same arm was used for all assessment visits with the appropriately sized cuff. Four consecutive readings were recorded at ~ 2 minute intervals with the mean of the last three measurements used for analysis.

Body composition

A whole body scan, using DEXA (Lunar Prodigy Model, General Electric, Madison WI USA), was performed with participants wearing a light cotton gown and all external metal objects removed. Scans at Week 12 and Week 24 were conducted in the same position and under the same baseline scan conditions. Total body fat mass (%), total body lean mass (%), kg) and abdominal fat mass (kg) were obtained using enCORE™ 2010 software (GE Healthcare enCORE version 13.31).

Biochemical analyses

Fasting blood samples for HbA1c, glucose, insulin, C-reactive protein, triglycerides, total cholesterol, high-density lipoproteins and low-density lipoproteins (LDL-C) were obtained through venepuncture using the Vacuette® blood collection system. Samples (except ApoE4) were kept on ice and taken to an accredited commercial pathology laboratory (SA Pathology, Adelaide, Australia) within 2 hours of collection for analysis. Plasma LDL-C was calculated using the Friedewald equation provided that triglyceride levels were < 4.2mmol/L [23]. A blood sample for Apolipoprotein E-4 allele (APOE_ε4, indicator of increased risk for Alzheimer Disease) was taken using the same method described above. The sample was centrifuged (4°C, 4000rpm, 10 minutes) before the plasma was aliquoted and frozen at -20°C then stored at -80°C. APOE_ε4 analysis was performed using the TaqMan® SNP Genotyping Assay kit (Applied Biosystems, Warrington, UK) as described by Koch et al (2002) [24].

Insulin Resistance

Insulin resistance was calculated using The Homeostasis Model Assessment (HOMA2) Calculator v2.2.3 [25]. This method to determine an insulin resistance score (HOMA2-IR) has been validated in T2DM with no differences shown between gender, age, BMI or diabetes status[26]. A higher HOMA2-IR score indicates greater insulin resistance. Participants on insulin therapy or with fasting insulin levels > 57 mU/L were excluded from these calculations.

Medication Effect Score (MES)

As BGL are affected by changes in weight, insulin resistance, carbohydrate intake and exercise, antihyperglycaemic medication is usually titrated to stem rising hyperglycaemia or prevent hypoglycaemia thus potentially influencing HbA1c results. To compare changes in antihyperglycaemic medication regimes between the 2 groups, a MES was calculated at the end of each phase. This study chose a technique described in a dietary intervention study with a T2DM population [27] as it captures potency, dose changes as well as discontinued

medications compared to other methods which only consider the total number of diabetes medications taken [28]. The percentage of the maximum daily dose for each class of medication was calculated and multiplied by the medication's corresponding adjustment factor. The MES is the sum of each of these calculations. The maximum daily dose was obtained from the Monthly Index of Medical Specialties (MIMS) Australia [29] with insulin considered to be 1unit/kg/day of baseline weight [27]. The adjustment factor is the mean decrease in HbA1c expected with monotherapy with the following values used: Biguanides 1.5, Sulphonylureas 1.5, DPP-4 inhibitors 0.65, GLP-1 agonists 0.75 and insulin 2.5 [30]. For medications that are a combination of classes, each class was calculated separately and summed. A higher MES indicates greater antihyperglycaemic medication use.

Cognitive function battery

The cognitive battery selected has been used in previous dietary intervention studies for adults with both T2DM and impaired glucose tolerance [31,32]. It consisted of a series of six tests to examine a range of cognitive abilities: Visual Verbal Learning Test (VVLT) is the visual analogue of the Rey Auditory Verbal Learning task [33] and assesses immediate and delayed memory, and interference effects [34]; Visual Spatial Learning Test (VSLT) which assesses non-verbal, visuospatial memory and learning [35]; Corsi Block Tapping Test which assesses spatial working memory [36-38]; Grooved Pegboard [39] and computerised Psychomotor Test [31] which assess psychomotor performance, manual dexterity and fine motor skills and the Tower of Hanoi which assesses executive function (problem solving and planning ability) [40]. Table 3 describes the tests and the dependent variables obtained for each. With the exception of the Grooved Pegboard and the Visual Spatial Learning Test, which were administered manually by the investigator, tests were performed on a Toshiba laptop computer (model R830) using E-Prime software V2 (Psychology Software Tools, Sharpsburg, PA, USA). Three parallel equivalent versions of each test (except the Grooved Pegboard) were used to allow for repeat testing and the order of version was counterbalanced for each participant and visit.

Table 3. A description of the cognitive battery tests and Outcome variables

Test	Description	Outcome variable
Visual Verbal Learning Test (VVLTL)	16 words (list A) appear in a random sequence at the rate of 1 word/ 2 s on the screen. Participants had 60s to verbally recall the words. This task was repeated 3 times (A1, A2, and A3) before a different 16-word list was presented (list B) and participants had 60s to recall list B (B1). Immediately after recalling B1, participants had 60 s to recall list A (A4) without further presentation.	Immediate recall score = mean score (A1 to A3) Proactive Interference = A1 minus B1 Retroactive Interference = A3 minus A4
Visual Spatial Learning Test (VSLT)	A board of 24 squares (6x4) was placed in front of the participant with 15 tiles of various designs arranged in a 5 x 3 pattern above the board. Unseen by the participant, 7 tiles were arranged on the board in a specific pattern. The participant was given 10 s to sight the board and remember the designs and placement of the tiles. Again unseen by the participant, the tiles were reincorporated back with the others and the participant was given 2 min to recreate the pattern. This was repeated for 3 trials using the same pattern (trials 1, 2 and 3).	Total immediate recall score = mean (number of correct designs + positions + design and position) for trials 1-3
Corsi Block Tapping Test	White blocks arranged on the screen changed colour from white to red and then back to white again (1 block per second) in a specific sequence and involving 2-9 blocks. Once a sequence finished, the participant responded by clicking on the blocks, as quickly as possible, in the same order presented to them.	Number of sequences correctly recalled, accuracy, reaction time and errors made.
Grooved Peg Board	The peg board was placed in front of the participant and consists of an integrated well containing metal grooved pegs and a pegboard of 25 (5 x 5 rows) randomly positioned slots. Starting with their dominant hand, participants picked up one peg at a time and rotated it to fit into a slot starting from top to bottom and side to side. Time taken to insert all 25 pegs was recorded. The process is repeated with the non-dominant hand.	Time (s) taken to complete the task for each hand
Psychomotor Test	Using a computer mouse, participants were asked to click on a small red square (target) as it appears at various locations on the screen as quickly and as accurately as possible. A new target appeared at random immediately after each mouse click irrespective of accuracy. The cursor returned to the centre of the screen after each attempt.	Number of accurate hits (max 88) and reaction time for correct responses (ms)
Tower of Hanoi	At the top of the computer screen were 3 rods with 4 discs of different sizes and colours in a particular formation (target). At the bottom of the screen were 3 rods with the same 4 discs but in a different arrangement (starting formation). Aim was to rearrange the starting formation to match the target in the least number of moves possible. There is only 1 correct sequence of moves and the participant is told how many moves are required. If an error was made, the task resets. There were 5 levels consisting of 4, 5, 6, 7 or 8 moves and each level was repeated twice for a total of 10 tasks.	Number of errors made and completion time (s)
Delayed VVLTL	Approximately 30 min after the completion of the last trial, participants were given 60 s to verbally recall the words from list A without further presentation (A5).	Delayed recall = number correct words (A5)
Delayed VSLT	Approximately 30 min after the completion of trial 3, participants had 2 min to recreate the pattern without further presentation (trial 4).	As per VSLT

Food craving questionnaires

Food Craving Inventory (FCI)

The original validated 28 item version of the FCI [41] was modified to represent Australian foods by substituting cornbread for pie or pasty, relocating biscuits to the sweets subscale and removing cookies. This version consisted of a list of 27 food items and participants were instructed to indicate how often, in the last month, they have experienced food cravings for each item on a Likert scale where 1 = never, 2 = rarely, 3 = sometimes, 4 = often and 5 = always/almost every day. There are 4 sub-scales which categorised foods of similar composition: high fats; carbohydrate /starches; sweets and fast food fats. To calculate each sub-scale score, the values given for the corresponding items are summed and the mean is recorded. The total score is the mean of the 4 subscales. Cronbach's alpha coefficients will be calculated for the total and sub-scale scores to ensure the scale's internal consistency has not been adversely affected by the changes. A higher score indicates greater food cravings.

General Food Craving Questionnaire – Trait (G-FCQ-T)

The G-FCQ-T is a reliable and validated questionnaire consisting of 21 common statements that people make about their general desire for food [42]. Participants considered each statement and how often it would apply to them in a 'general' context. Answers utilise a Likert scale: 1 = never/not applicable; 2 = rarely; 3 = sometimes; 4 = often; 5 = usually and 6 = always. Each statement relates to one of the four sub-scales: loss of control (statements: 1,2,10,12,18 and 19); preoccupation with food (statements: 3,4,5,13,14 and 16); positive outcome expectancy (statements: 6,7,9,11,20) and emotional cravings (statements: 8,15,17 and 21). Each sub-scale has a score equating to the sum of the scale values given to the corresponding statements. The G-FCQ-T total score is the sum of each of the subscale scores. A higher score indicates greater food cravings.

General Food Craving Questionnaire – State (G-FCQ-S)

The G-FCQ-S is a reliable and validated questionnaire consisting of 15 statements assessing the current desire for general foods at that moment in time [42]. Participants consider how each statement relates to them and indicate their response on a Likert scale: 1 = strongly agree, 2 = disagree; 3 = neutral, 4 = agree and 5 = strongly agree. Each statement relates to one of the 5 sub-scales: an intense desire to eat (statements: 1,2,3); anticipation of positive reinforcement that may result from eating (statements: 4,5,6); anticipation of relief from negative states and feelings as a result from eating (statements: 7,8,9); obsessive preoccupation with food or lack of control over eating (statements: 10,11,12) and Craving as a psychological state (statements: 13,14,15). Each sub-scale has a score equating to the sum of the scale values given to the corresponding statements. The G-FCQ-S total score is the sum of each of the subscale scores. A higher score indicates greater food cravings.

Self-administered psychological wellbeing questionnaires

Diabetes-39 Quality of Life Questionnaire (D-39)

The D-39 is a reliable and validated 39 item questionnaire designed to assess the quality of life for individuals with diabetes [43]. It covers five domains of health: energy and mobility (15 items), diabetes control (12 items), anxiety and worry (4 items), social burden (5 items), sexual functioning (3 items) plus 2 questions indicating an overall rating of quality of life and the participants perception of the severity of their diabetes [44]. This study used a horizontal line divided into 7 boxes numbered from 1 (not affected at all) through to 7 (extremely affected) which is an adaption described in a previous study where participants placed a cross in the box which best describes how their quality of life has been affected over the past month by each question [43]. Subscale scores equate to the sum of the value given to the pertaining items which is then converted to a transformed score (0-100) using the following formula: $((\text{gross classification} - \text{minimum value}) / (\text{maximum value} - \text{minimum value})) \times 100$

[43]. A higher score indicates poorer health except for the 'Overall Quality of Life' score where a higher score indicates better quality of life.

Problems Areas in Diabetes (PAID)

PAID is a reliable and validated questionnaire [45] which measures diabetes-specific emotional distress related to living with and managing diabetes including guilt, fear, anger, depressed mood and worry [46]. Participants answer 20 questions using a Likert scale with 5 options: 0 = not a problem, 1 = minor problem, 2 = moderate problem, 3 = somewhat serious problem and 4 = serious problem. The total score (between 0-100) is the sum of the responses for each question multiplied by 1.25. A score ≥ 40 identifies participants at risk for greater diabetes related distress [47].

Perceived Stress Scale (PSS-10)

The PSS-10 is a shorter version of the validated PSS questionnaire [48]. It consists of 10 items which measure a person's perceived distress and perceived coping ability [49]. It relates to feelings and thoughts during the last month and is a useful tool to examine the role of stress levels in regards to diseases and behaviour disorders [48]. For each question, participants indicated how often, over the past month, they felt or thought a certain way by circling a number on a Likert scale: 0 = never, 1=almost never, 2=sometimes, 3=fairly often and 4=very often. To calculate the total score, the scores for the 4 positive items (items 4, 5, 7 and 8) are reversed and then all scores are summed. Total scores range from 0 – 40 and a higher score indicates greater stress.

SF-36 v2 Health Survey™ (SF-36)

The SF-36 v2 Health Survey™ is a reliable and validated questionnaire [50]. It consists of 36 questions which assesses self-reported functional health and wellbeing [51]. The questions measure different aspects of physical and mental health and are grouped into 8 scales: physical functioning; role-physical; bodily pain; general health; vitality; social

functioning; role—emotional and mental health. Participants answer using a Likert scale with 3 or 5 alternatives which are specific to each question. The sum of the values given for the pertaining questions provide the score for each scale and a Physical Component Summary and a Mental Component Summary are calculated from those scores [51].

Leeds Sleep Evaluation Questionnaire (LSEQ)

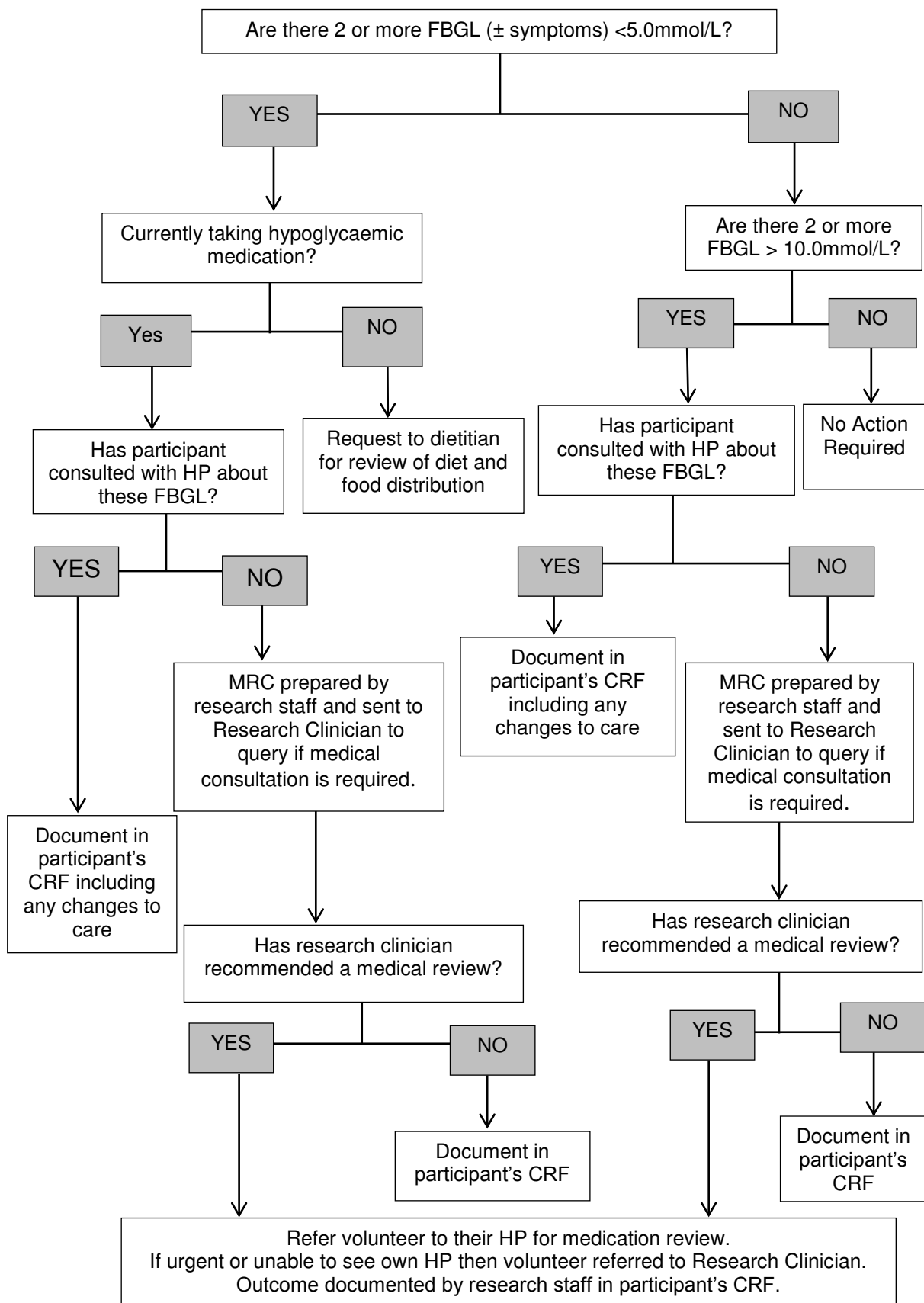
The original LSEQ is a reliable and validated questionnaire widely used in clinical research to measure sleep and early morning behaviour [52]. This current study used a shortened version of the LSEQ which consisted of 8 questions to evaluate the original 4 domains: getting to sleep (2 items), quality of sleep (2 items), awakening from sleep (2 items) and behaviour following wakefulness (2 items). The same 8 questions were asked twice: initially pertaining to a 'typical night's sleep' and then as 'last night's sleep'. Participants indicated their answer by putting a vertical mark through the relevant point of a 100mm horizontal visual analogue scale between two extremes e.g. 'very easy' to 'very difficult' when describing ease of getting to sleep. A total score for each domain was determined by calculating the mean of the responses for the 2 items pertaining to them. A higher score indicates a lower sleep quality. Cronbach's alpha coefficients will be calculated for each domain to ensure the scale's internal consistency has not been adversely affected by the modification made.

Medical management plan

Due to diet, exercise and weight changes, it was expected some participants would experience changes in fasting BGL outside acceptable limits, particularly those on insulin and oral hypoglycaemic agents. Participants were required to document their daily fasting BGL, including any symptoms experienced, and note any changes to prescribed or over-the-counter medications. These records were reviewed at each 2-weekly diet visit by the research team using the Medical Management Plan flowchart (figure 2) which was developed together with the study's clinician to identify and respond to participants who may

be at risk of hypo/hyperglycaemia before symptoms were experienced. The responsibility for making changes to a participant's medication was with their own health practitioner and the role of the clinician was to advise when a medical consultation was required and to confer with the participant only in the event that they were unable to see their health practitioner within a suitable timeframe. As weight loss and increased physical activity can also reduce antihypertensive medication requirements, a medical management request to the study clinician was sent if a participant's BP reading, at any clinic visit, was 90/60mmHg or less and they were taking BP medication. Alternatively, if a BP reading was 180/110mmHg or higher the participant was asked to consult their health practitioner.

Figure 2. Flow -chart for managing fasting blood glucose level (FBGL) records



MRC: Medical Review Case CRF: Case File Record HP: Health Practitioner

Sample size

This study was powered on the primary outcome of change in HbA1c. Based on data from a previous intervention measuring HbA1c in a T2DM population [53], it was estimated 48 participants would provide 80% power to detect a significant ($P < 0.05$) 0.75% (absolute) difference between diets for change in HbA1c based on a standard deviation of 0.9%. A total of 61 participants were recruited to allow for a ~ 20% withdrawal rate.

Statistical analysis

Non-normally distributed variables will be logarithmically transformed before analysis.

Where normality is not achieved, non-parametric methods for analysis will be used.

Baseline characteristics including dietary data between groups will be assessed by independent student t-tests and chi-squared tests for continuous and categorical variables respectively. Intention-to-treat analysis (ITT) will be conducted including participants who completed the study irrespective of compliance. Changes over time (weeks 0-12 and 12-24) between the intervention groups will be assessed using a linear mixed effects model with treatment as a between-subject factor, and time as the repeated measurement. Where appropriate, any difference in baseline characteristics will be controlled for in the analysis. Where there is a significant main effect, post-hoc comparisons will be performed with Bonferroni adjustments for multiple comparisons to determine differences between group means. Associations of change between variables will be analysed using Pearson correlations. Statistical significance will be set at $P < 0.05$. Statistical analyses will be performed using SPSS version 21.0 (SPSS In., Chicago, IL).

Discussion

With the prevalence of T2DM rapidly rising, evidence for lifestyle interventions which favourably impact glycaemic control and improve health outcomes are urgently needed.

A paucity of studies have evaluated the effects of energy-restricted HP diets when combined with physical activity as part of a holistic lifestyle modification program on health outcomes in

a population with T2DM, despite evidence suggesting benefits in other populations. Even fewer studies have investigated the effects of dietary patterns in an energy-balanced weight maintenance state without the influence of weight loss. This protocol paper describes the methodology used in this study to compare the effects of isocaloric, HP and SP diets combined with moderate exercise on glycaemic control, cardiometabolic risk factors, food cravings, cognitive function and psychological wellbeing in adults with T2DM. Most previous studies evaluating HP diets focus primarily on weight loss and metabolic outcomes during an energy-restricted state. Our study will extend this knowledge to investigate whether the benefits observed after weight loss continue during a 12 week energy-balanced weight maintenance phase. This work will also extend our understanding of these dietary patterns on cognitive performance which is an important health outcome in this patient population that has not been examined to date. The results will be of interest to clinicians, researchers and dietitians working in the areas of diabetes and obesity and also policy makers and regulatory bodies.

Abbreviations

ARENA: Alliance for Research in Exercise, Nutrition and Activity; BMI: body mass index; BP: blood pressure; CSIRO: Commonwealth Scientific and Industrial Research Organisation; D-39: Diabetes-39 Quality of Life Questionnaire; DEXA: dual energy x-ray absorptiometry; DQES: Dietary Questionnaire for Epidemiological Studies; FCI: Food Craving Inventory; G-FCQ-S: General Food Craving Questionnaire-State; G-FCQ-T: General Food Craving Questionnaire-Trait; HbA1c: glycosylated haemoglobin; HC: Higher-carbohydrate; HDL: high-density lipoproteins; HP: higher-protein; ITT: intention-to-treat; kg: kilogram; kJ: kilojoule; LDL: low-density lipoproteins; LSEQ: Leed's Sleep Evaluation Questionnaire; MES: medication effect score; PAID: Problems Areas in Diabetes; PSS: Perceived Stress Scale; RPE: rate of perceived exertion; T2DM: type 2 diabetes mellitus

Competing interests

NAW is supported by a post-graduate research scholarship from the Pork Co-operative Research Centre (Pork CRC), an Australian Government funding initiative. All other authors declare no personal or financial conflicts of interest.

Authors' contributions

KJM initiated the study. KJM, PRCH, JDB, MN, GDB, AMC, GP and NAW designed the study. LD and HC planned, designed and programmed the cognitive battery. KJM, PRCH, JDB, MN, GDB and AMC secured the funding. NAW and KAD collected data. NAW prepared the manuscript and all authors critically revised the manuscript for intellectual content. At time research was conducted KJM was a NHMRC Industry Research Fellow (399396).

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Participant Reimbursements

Apart from the provided study foods mentioned, each participant received \$50 at the end of the study (or pro-rata) to cover travel and parking costs. No additional payments were made.

Study Status: Data collection has been completed.

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