

BMJ Open Effects of a carbohydrate-reduced high-protein diet delivered with meal kits to Danish people with type 2 diabetes: protocol for a 12-month randomised controlled trial

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ABSTRACT

Introduction The cornerstone in the management of type 2 diabetes (T2D) is lifestyle modification including a healthy diet, typically one in which carbohydrate provides 45%–60% of total energy intake (E%). Nevertheless, systematic reviews and meta-analyses of trials with low carbohydrate diets (which are increased in protein and/or fat) for T2D have found improved glycaemic control in the first months relative to comparator diets with higher carbohydrate content. Studies lasting ≥1 year are inconclusive, which could be due to decreased long-term dietary adherence. We hypothesise that glucometabolic benefits can be achieved following 12 months of carbohydrate-restricted dieting, by maximising dietary adherence through delivery of meal kits, containing fresh, high-quality ingredients for breakfast, dinner and snacks, combined with nutrition education and counselling.

Methods and analysis This protocol describes a 12-month investigator-initiated randomised controlled, open-label, superiority trial with two parallel groups that will examine the effect of a carbohydrate-reduced high-protein (CRHP) diet compared with a conventional diabetes (CD) diet on glucometabolic control (change in glycated haemoglobin being the primary outcome) in 100 individuals with T2D and body mass index (BMI) >25 kg/m². Participants will be randomised 1:1 to receive either the CRHP or the CD diet (comprised 30/50 E% from carbohydrate, 30/17 E% from protein and 40/33 E% from fat, respectively) for 12 months delivered as meal kits, containing foods covering more than two-thirds of the participants' estimated daily energy requirements for weight maintenance. Adherence to the allocated diets will be reinforced by monthly sessions of nutrition education and counselling from registered clinical dietitians.

Ethics and dissemination The trial has been approved by the National Committee on Health Research Ethics of the Capital Region of Denmark. The trial will be conducted in accordance with the Declaration of Helsinki. Results will be submitted for publication in international peer-reviewed scientific journals.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Maximised dietary adherence by providing participants with more than two-thirds of their estimated daily energy requirements, supported by frequent nutrition education and counselling.
- ⇒ No concomitant changes in competing lifestyle (eg, exercise or forced caloric restriction) or medication use.
- ⇒ Participants will be extensively studied including many state-of-the-art glucometabolic and cardiovascular outcomes.
- ⇒ The study design does not include hard outcomes.
- ⇒ Blinding of the study participants and study personnel will not be possible due to the nature of the intervention.

Trial registration number NCT05330247.

Protocol version The trial protocol was approved on 9 March 2022 (study number: H-21057605). The latest version of the protocol, described in this manuscript, was approved on 23 June 2023.

INTRODUCTION

The cornerstone in the management of type 2 diabetes (T2D) is lifestyle modification including adoption of a healthy diet, increased physical activity and weight loss.¹ Weight loss maintenance has, however, proved challenging and may only be achievable by a few highly motivated individuals.^{2,3} The beneficial effect of exercise can also be difficult to obtain in many T2D individuals due to a sedentary lifestyle and because of overweight, obesity or advancing age and the presence of musculoskeletal or other comorbidities.⁴ Previously, a calorie-restricted

low-fat diet, rich in low-glycaemic index carbohydrate, has been recommended for individuals with T2D, with a macronutrient distribution range of 45%–60 % of total energy intake (E%) from carbohydrate, 25–40 E% from fat and 10–20 E% from protein.⁵ However, in recent years, a carbohydrate-restricted eating pattern has been recognised by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) as a viable approach for achieving improvements in glycaemic control,^{6 7} although not recommended for all patients with T2D across the board.

Systematic reviews and meta-analyses of carbohydrate restriction for T2D have consistently concluded that these diets are more effective than comparator diets in improving glucometabolic control in the short-term (up until 6–12 months).^{8 9} Nevertheless, the effect of carbohydrate-restricted diets seems to diminish over time, most likely reflecting progressively decreasing dietary adherence, and studies exceeding 1 year in duration are inconclusive.^{8 9} More extreme carbohydrate restriction (eg, low (10–26 E%) or very low (<10 E%) carbohydrate intake) may offer the greatest metabolic improvements but may also be the most difficult to adhere to in the long term.^{10 11} The effects of carbohydrate-restricted diets are overall difficult to interpret due to heterogeneity in study designs, particularly differences between studies in dietary carbohydrate content, type of carbohydrate (eg, simple vs complex), lack of control over calorie restriction and subsequent weight loss, varied physical activity and/or discontinuation of antidiabetic medication. These differences could potentially confound the isolated effect of carbohydrate restriction.

We have previously investigated the effect of carbohydrate restriction in two meticulously controlled studies.^{12 13} In these studies, we sought to maximise dietary adherence by providing all meals to the participants. Moreover, we studied the effects of low carbohydrate diets under both weight maintenance and during matched weight loss to dissect the effect of replacing carbohydrate with protein and fat from those of changes in body weight. We found that a eucaloric carbohydrate-reduced high-protein (CRHP; 30/30/40 E% from carbohydrate/protein/fat) diet improved glycaemic control, dyslipidaemia and intra-hepatic fat content compared with an energy-matched conventional diabetes (CD; 50/17/33 E% from carbohydrate/protein/fat) diet over 6 weeks in individuals with T2D.¹² Although weight loss is considered to be the primary driver of these glucometabolic improvements, we found that a 6% weight loss induced by a CRHP diet improved glycaemia, dyslipidaemia and liver fat accumulation more than the same amount of weight loss induced by a CD diet.¹³ As such, diets restricted only moderately in carbohydrates (ie, 26–45 E%) may offer substantial and clinically significant improvements in metabolic function.

Identification of long-term efficacy, safety and feasibility of carbohydrate-restricted diets is essential for optimising dietary strategies in T2D. Maximising dietary adherence through full provision of precooked meals is not possible

in long-term and large-scale studies, besides not resembling usual nutritional care. Accordingly, feasible dietary approaches to properly support adherence to allocated diets (eg, provision of key ingredients and nutrition counselling) while ensuring options and flexibility for individual preferences are warranted.

Hence, the present study, we introduce a convenient solution that is new to research, although well known to consumers and the food service industry, for supporting nutrition-related lifestyle changes and dietary adherence in individuals with T2D. By initiating a meal kit delivery service comprising fresh, high-quality and nutrient-dense ingredients for breakfast, dinner and snacks alongside nutrition education and counselling, we aim to facilitate long-term dietary adherence to moderate carbohydrate restriction and propose this as a future addition to medical nutrition therapy for individuals with T2D.

OBJECTIVE AND HYPOTHESIS

The objective of this study is to investigate the effects of a CRHP diet compared with a CD diet, provided as a meal kit delivery service for 12 months in a free-living setting in individuals with T2D. We hypothesise that the meal kits together with nutrition education and counselling will facilitate long-term adherence and lead to CRHP improving glycaemic control, body weight and composition, ectopic fat accumulation, lipids and other biomarkers of cardiometabolic health to a greater extent than the CD diet after 12 months.

METHODS AND ANALYSIS

Study design, participants and outcomes

This study protocol describes a 12-month investigator-initiated, open-label, superiority, parallel-group, randomised controlled trial. Participants will be allocated to an eucaloric CRHP or CD diet in a 1:1 ratio, with no other changes made in competing lifestyle (eg, increased exercise or forced energy restriction) as part of the intervention. As such, this study represents solely a nutrition intervention trial exploring the effect of macronutrient distribution.

Study setting and timeline

The study is a collaboration between Copenhagen University Hospital Bispebjerg (Bispebjerg Hospital) and Aarhus University, primarily conducted at Bispebjerg Hospital. Most study visits will take place at the Research Unit at the Department of Endocrinology including recruitment of participants, study-related procedures such as nutrition counselling and telenutrition, physical examinations, blood sample collection, medical and metabolic tests, collection of questionnaires and body scans. Investigators at the Department of Food Science, Aarhus University, will virtually collect questionnaires and conduct interviews with the participants.

Study preparations were commenced in 2021 by drafting the protocol and securing funding. After acquiring the necessary approvals in April 2022 (including approval of the protocol by the local ethical committee), the study was initiated by recruitment and the first participant was enrolled in September 2022. Study conclusion with last participant's last visit is planned for January 2025.

Eligibility criteria

In total, 100 participants will be enrolled in the study. Eligible participants are adult men or postmenopausal women <76 years, diagnosed with T2D with a glycated haemoglobin (HbA_{1c}) level of 48–75 mmol/mol and a BMI>25 kg/m², who are being treated with or without glucose-lowering therapy limited to metformin, dipeptidyl peptidase 4 (DPP-4) inhibitors, sodium-glucose co-transporter 2 (SGLT-2) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists, provided they have been under a stable medication dosage for at least 3 months prior to enrolment. A full list of the eligibility criteria is provided in [box 1](#).

Recruitment

Study participants will be recruited from the Zealand Region and the Capital Region of Denmark via advertisement in online media, local newspapers and public bulletins. Potential participants will be prescreened by phone and, if interested and eligible, invited to a physical meeting (online supplemental figure S1). Here, they will receive information about the study, both in oral and written form and will be screened according to eligibility criteria. Prior to any study-related procedures, patients must give oral and written informed consent to participate (<https://videnskabsetik.dk/ansoegning-til-etisk-komite/samtykkeerklæringer-og-blanketter>). Final participation will depend on the results from a blood analysis and a medical examination.

Glucose-lowering therapy could be adjusted prior to enrolment in case of participants taking medications not permitted in the study and/or having an HbA_{1c} level<55 mmol/mol, in which case inclusion will be postponed ≥3 months.

Patient and public involvement

This study is designed and conducted without any involvement from participants or the public, although the diet interventions are influenced by previous experiences and patient feedback from the randomised controlled trials conducted by our research group.^{12 13} Study results will be disseminated to the participants directly by inviting them to a presentation and to the public through media coverage as much as possible.

Attrition

Drop-out

Participation in the study is voluntary, and withdrawal of consent is possible at any time. In such instances, reasons given for withdrawing will be evaluated for their relation to study diets. Participants who drop out will be lost at

Box 1 List of eligibility criteria

Inclusion criteria

- ⇒ Men aged 18–75 years or postmenopausal women aged ≤75 years, with menopause defined as >12 months without menses.
- ⇒ Diagnosed with type 2 diabetes and glycated haemoglobin between 48 and 75 mmol/mol.
- ⇒ Body mass index >25 kg/m².
- ⇒ No or ongoing therapy with glucose-lowering medication including metformin, dipeptidyl peptidase 4 inhibitors, sodium-glucose co-transporter 2 inhibitors and/or glucagon-like peptide 1 receptor agonists.
- ⇒ No smoking (at least the past year before study participation).
- ⇒ Acceptance of regulation of antidiabetic, antihypertensive and lipid-lowering medications by study endocrinologists only.

Exclusion criteria

- ⇒ Currently following a particular eating pattern or strong food preferences, not compatible with study participation.
- ⇒ Weight change ≥5% the preceding 3 months prior to screening.
- ⇒ Ongoing insulin or insulin analogue therapy.
- ⇒ Ongoing treatment with sulfonylureas and/or thiazolidinediones unless discontinuation is possible, in which case a 3-month wash-out is mandatory.
- ⇒ Severe gut disease including inflammatory bowel disease and mal-absorptive disorders.
- ⇒ Extensive intestinal surgery including bariatric surgery, small bowel resection and colectomy.
- ⇒ Severe heart disease including angina pectoris, coronary heart disease, congestive heart failure.
- ⇒ Renal impairment (estimated glomerular filtration rate <45 mL/min/1.73 m² or urine albumin/creatinine ratio >300 mg/g).
- ⇒ Severe hepatic impairment (from measures of alanine and aspartate aminotransferases).
- ⇒ Cancer, ongoing or within the past 5 years not including basal or squamous cell skin cancers.
- ⇒ Severe psychiatric disease including major depression, bipolar disorders and schizophrenia.
- ⇒ Ongoing systemic corticosteroid treatment.
- ⇒ Reported or documented food allergy or intolerance.
- ⇒ Reported or documented alcohol consumption exceeding the recommendations from The Danish Health Authorities of no more than 120 g weekly and 48 g daily (for men and women).
- ⇒ Anaemia (haemoglobin <7 mmol/L (113 g/L) for men and <6 mmol/L (97 g/L) for women).
- ⇒ Inability, physically and/or mentally, to comply with the study-related procedures.
- ⇒ Participation in other ongoing clinical trials.

follow-up and for logistic reasons, no effort will be made to continue collecting or acquiring data at future planned visits or end of treatment.

Exclusion/protocol violation

Participants can be excluded from the study by the investigational team in the event of safety concerns or if severe or repeated protocol violations occur. These include strong opposition against following the allocated diet (not including decreasing adherence), motivation towards other eating patterns conflicting with the allocated diet, relocation to an

Box 2 List of exploratory outcomes, all evaluated as change between baseline and 12 months

Anthropometry, body composition and muscle function

- ⇒ Proportion achieving clinically significant weight loss (ie, >5% and >10% reduction of baseline body weight).
- ⇒ Body mass index.
- ⇒ Waist circumference (from MR scans).
- ⇒ Total and appendicular lean body mass, fat body mass and fat percentage measured by dual-energy X-ray absorptiometry.
- ⇒ Handgrip strength.
- ⇒ Muscular strength in lower extremities.

Glucose metabolism and glucoregulatory hormones

- ⇒ Proportion achieving adequate glycaemic control (glycated haemoglobin <48 mmol/mol).
- ⇒ Changes in glucose-lowering medication (dosage increases/decreases and drug start/termination).
- ⇒ Basal and postchallenge concentrations following an oral glucose tolerance test (OGTT) of glucose, insulin, C-peptide and insulin secretion rates.
- ⇒ Diurnal glucose profiles assessed from continuous glucose monitoring including 24-hour mean, time-in-range and glycaemic variability.
- ⇒ Homeostasis Model Assessment of insulin resistance and β -cell function.
- ⇒ Insulin sensitivity (by the Composite Index) and β -cell function (by the Insulinogenic Index, β -cell responsiveness to glucose and Disposition Index) derived from an OGTT.
- ⇒ Basal and postchallenge concentrations following an OGTT of incretin, satiety and gut hormones including glucagon-like-peptide 1 (GLP-1), glucose-dependent insulinotropic polypeptide, glucagon, peptide YY, cholecystokinin, gastrin and ghrelin.
- ⇒ Basal and postchallenge concentrations following an OGTT of growth hormone, insulin-like growth factor 1 and insulin-like growth factor binding protein 1.

Lipid deposition and metabolism and metabolic syndrome

- ⇒ Intrapaneatic, visceral and subcutaneous fat accumulation measured by MRI.
- ⇒ Basal and postchallenge concentrations following an OGTT of non-esterified fatty acids and triglyceride.
- ⇒ Fasting lipid profile including concentrations of total, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and non-HDL cholesterol, and apolipoproteins.
- ⇒ Lipoprotein density profiling including triglyceride-rich lipoproteins and subfractions of LDL and HDL particles.
- ⇒ Concentrations of ketone bodies.
- ⇒ Metabolic Syndrome Severity Z score (MetS-Z).
- ⇒ Change in lipid-lowering medication (dosage increase/decrease, drug start/termination).

Cardiovascular risk markers, liver fibrosis and renal function

- ⇒ Heart rate variability including state-of-the-art parameters of sympathetic and parasympathetic neural activity, evaluated over 24 hours and during day and night-time.
- ⇒ Systolic, diastolic and mean-arterial blood pressure, evaluated over 24 hours and during day and night-time.
- ⇒ Adipokines and markers of low-grade inflammation including leptin, adiponectin, tumour necrosis factor α , interleukin 6, C reactive protein.

Continued

Box 2 Continued

- ⇒ Measures of liver fibrosis including the aspartate aminotransferase to platelet ratio index and Fibrosis-4 index.
- ⇒ Renal function assessed from estimated glomerular filtration rate (based on cystatin C) and urinary albumin excretion.
- ⇒ Change in antihypertensive medication (dosage increases/decreases and drug start/termination).

Dietary adherence

- ⇒ Diurnal urinary excretion of urea.
- ⇒ Intake of macronutrients, that is, carbohydrate, protein, and fat (with and without alcohol included), extracted from 3-day food records.
- ⇒ Intake of total energy, alcohol, fibre, simple sugars and other food components extracted from 3-day food records.
- ⇒ Perceived dietary adherence measured by the Perceived Dietary Adherence Questionnaire.

Questionnaires and interviews

- ⇒ Physical activity by the long-form International Physical Activity Questionnaire.
- ⇒ Health-related quality of life (QoL) by the Short-Form 36 Health Survey, evaluated in its respective domains and its physical and mental component summary scores.
- ⇒ Diabetes-related emotional distress by The Problem Areas in Diabetes questionnaire.
- ⇒ Meal acceptance and subjective satiating capacity of meals following three morning and three evening meals.
- ⇒ Self-reported well-being, food-related QoL, variety-seeking behaviour, eating behaviours (emotional, retained and external) and drivers of food-related pleasure by various questionnaires.

area not supported by the meal kit delivery service, or repeated weekly alcohol consumption more than the national recommendation of maximum 120 g (or 48 g for 1 day) for men and women.

Outcomes

Primary outcome

The primary outcome is change in HbA_{1c} between baseline and 12 months.

Secondary outcomes

Secondary outcomes include changes in body weight and intrahepatic fat content between baseline and 12 months, in this order.

Exploratory outcomes

Due to the high complexity and costs of conducting a nutrition intervention by meal kit provision, several additional outcomes related to metabolic health will be included; however, the results will be interpreted with caution due to their exploratory nature. Exploratory outcomes are included in full in [box 2](#).

Study intervention

CD and CRHP dietary patterns

The meal kits will be produced and delivered twice weekly by an established company specialising in meal kit delivery services (Skagenfood A/S, Strandby, Denmark).

Table 1 Macronutrient composition and quality of a conventional diabetes (CD) and a carbohydrate-reduced high-protein (CRHP) diet

Macronutrient	CD diet	CRHP diet
Carbohydrate, total	50 (48–52) E%	30 (28–32) E%
Dietary fibre	Min 2.0 g/MJ	Min 2.0 g/MJ
Added sugar	Max 8 E%	Max 5 E%
Protein, total	17 (15–19) E%	30 (28–32) E%
Fat, total	33 (31–35) E%	40 (38–42) E%
Saturated and trans fatty acids	Max 10 E%	Max 13 E%
Monounsaturated fatty acids	10–15 E%	10–20 E%
Polyunsaturated fatty acids	5–15 E%	5–15 E%

Dietary requirements of a daily CD or CRHP diet. For carbohydrate, protein and fat each meal had to be ± 2 energy percent (E%) of the targeted E%.

The eucaloric diets, provided free-of-charge for 12 months, cover more than two-thirds of the total individual estimated daily energy requirements for body weight maintenance ($\sim 20\%$ for breakfast, $\sim 35\%$ for dinner and $\sim 10\%$ for snacks). To allow for options and flexibility, participants will be responsible for lunch ($\sim 35\%$ of total daily energy intake) while still required to adhere to the macronutrient distribution. Lunch and dinner can be interchanged if deemed necessary, for example, when going out for dinner, further enhancing adaptability of the diet to daily life.

The CRHP/CD diets comprise 30/50 E% from carbohydrate, 40/33 E% from fat and 30/17 E% from protein (table 1). To meet most energy needs, both diets have three calorie levels (2100, 2500 or 2900 kcal) not differentiating in the quality of carbohydrate, protein and fat except minor differences reflecting the overall difference in macronutrients found naturally in foods. Participants are assigned to the calorie level that matches their estimated energy requirements more closely, thus allowing for ad libitum dieting by changeable serving sizes and individual needs and preferences. The design of the diets, especially the three calorie levels, dietary patterns and macronutrient distribution ranges for carbohydrate, protein and fat is based on results and experience from previous studies.^{12 13}

Meal plans

The meal plans reflect a healthy eating pattern, taking cultural and sustainable choices into consideration, rotating every 3 weeks, repeated over the entire 12-month trial period, additionally changing ingredients throughout the seasons. Culturally appropriate substitutes for specific ingredients are made available with ethnic groups in mind, although optional for all participants.

Recipes are created by dietitians and chefs in accordance with the recommended calories and macronutrients; hence participants are advised not to add other ingredients to their meal, except various listed spices. However, preparation and cooking methods are optional, provided that all ingredients are used, making the meals adjustable for different lifestyles and individual preferences. An overview of meals along with examples and pictures are provided in online supplemental table S1 and figures S2 and S3, respectively.

Satiation, servings and portion sizes

Emphasis is on recognising the feeling of satiation and not overeating, which for many can be troublesome. Participants are instructed to eat every meal until they feel satiated, without trying to finish the entire serving if there is too much food. If a meal serving contains too much food, participants are instructed to eat an equal amount of each part of the meal, for example, two-thirds of the meat, two-thirds of the vegetables and two-thirds of the side dish. Participants must consider this before they start eating, to avoid eating, for example, all meat or salad. Advice is given to begin by portioning the serving, and start eating one portion first, for example, half of the prepared food, continuously assess hunger, and decide whether to eat the remaining portion or perhaps halve it again. Meals are for participants only; if living with a partner or other cohabitants, advice is given on how to cook meals and dine together while adhering to the diet and ensuring the desired macronutrient distribution.

Participants who consistently experience that they receive too much or too little food in the meal kits will be assigned to a different calorie level if possible or instructed to either increase or decrease the serving size, swap with another meal with a different calorie content or combine, for example, different snacks with or without breakfast or dinner.

Timing and frequency of meals

Timing or frequency of certain meals is flexible and adaptable, to align with individual preferences. Although a sufficient intake of calories with the advised macronutrient distribution at each meal is pivotal to assure satiety, participants are advised to avoid consciously restricting food intake or overeating, or eating ultra-processed hyperpalatable snacks.¹⁴ The provided snacks can be eaten at any time of the day.

Recipes

Besides the meal plan recipes, participants receive supplemental recipes, as well as seasonal and holiday recipes, supporting individual needs for serving sizes and reinforcing individual choices and adherence to the intervention (online supplemental table S2). The recipe booklet also includes a thorough introduction with nutrition information, cooking methods, measurement units, food storage tips, a list of shelf stable foods from the meal kits, macronutrient distribution and meal energy distribution.

It was sought to keep the recipes simple, however, to ensure nutrient-dense meals consisting of many vegetables, beans, lentils and starchy vegetables, some recipes are somewhat laborious, estimating that overall 1–1.5 hours daily will be spent on cooking.

The meal plans can be different from what participants are familiar with, considering recipes, ingredients, meal frequency and timing, hence a period of adjustment is warranted. Participants must try all recipes and ingredients at least once, except if substitutions are necessary due to cultural or medical reasons. In such instances, or if participants develop strong aversion to certain foods, substitutes for these ingredients or dishes are found, however, participants need to purchase suitable substitutes themselves.

Excess food

Weighing all ingredients is important to ensure the correct macronutrient distribution. In the recipes, it will be specified whether to use excess food for example, meat, beans on another day. In case of leftover food, participants are instructed to either freeze or store it in the fridge, and use in other recipes, for example, lunch. Lunch recipes have been developed with this in mind. Many vegetables and fruits can also be pickled or preserved in other ways. This way, both participants and others can benefit from any excess food.

Drinks

Tap water and sparkling water with or without flavour are recommended as primary drinks. Coffee and tea with or without a little skimmed or low-fat milk, but without added cream or sugar, is allowed. Alcoholic beverages are permitted within the recommendations from the Danish Health Authorities, still taking the calorie and carbohydrate content into consideration. Artificial sweeteners are permitted, although avoiding artificially sweetened beverages as much as possible is recommended due to risk of sugar cravings for some individuals.¹⁵ Attention must be paid to the nutrition label when choosing such drinks, as some may still contain a significant number of calories.

Calorie level

The individual estimated total daily energy requirement is calculated using resting energy expenditure derived from the Henry Equation¹⁶ or the Mifflin-St Jeor Equation¹⁷ when BMI < 30 or ≥ 30 kg/m², respectively, multiplied by an estimated physical activity level derived from MET values from a physical activity questionnaire collected at baseline and individual lifestyle considerations.¹⁸ Participants are instructed to maintain their usual exercise activities throughout the intervention period.

Dietary adherence

By combining partial food provision by meal kits with monthly nutrition counselling and support from study staff, adherence to the diets is expected to be high. We aim to validate this quarterly by use of 3-day weighed food records, where participants record all foods and

drinks, preferably weighed prior to consumption using a portable weighing scale (or otherwise estimated) into an electronic diet registration tool (MADLOG, Madlog ApS, Kolding, Denmark). Participants are advised to take photographs of the recorded foods and drinks to substantiate the food records. Furthermore, food frequency questionnaires and diet history interviews will be performed at the quarterly study visits, and dietary adherence evaluated by study staff and registered clinical dietitians (RCDs). Food records will be evaluated during the nutrition counselling sessions and advice will be given by RCDs on how to improve adherence when needed. If follow-up is deemed necessary, extra counselling or follow-up calls will be planned with participants. Additionally, adherence to assigned study diets will be assessed by analysing diurnal urinary excretion of urea, which is used as a surrogate marker for protein intake.

Nutrition education and counselling

After the allocated diet is revealed, participants receive their recipe booklet and a pamphlet with general information about nutrients. Hereafter, prior to the start of the intervention participants receive their first nutrition counselling (figure 1). All these sessions are conducted on an individual basis and held by RCDs. In the first session, the RCD collects nutrition assessment data along with diet history, explains dietary considerations and answers questions regarding the allocated diet. The next nutrition counselling sessions are scheduled 3 weeks after the first delivery of meal kits and monthly thereafter. Monthly counselling sessions will address how to adhere to the allocated macronutrient distribution, especially concerning the self-selected lunch meals, as well as how to navigate the food environment during, for example, holidays, weddings and birthdays. Importantly, as diets are expected to induce satiety, counselling will emphasise how to achieve the advised macronutrient distribution if participants cannot eat the planned serving size. Throughout the study, participants will give feedback on the meal kit recipes and, if necessary, specific food items can be substituted or other minor changes made to maintain a high degree of dietary adherence.

Holidays, travels and sick days

Short vacations away from home (not receiving or bringing the meal kits) are permitted and plans will be made individually. In case of illness or other conditions not related to the intervention, participants will be advised to contact the investigational team after consulting their general practitioner, to discuss a plan for managing sick days and reschedule study visits if necessary.

Changes in medication

Two experienced endocrinologists will be responsible for titrating the pharmacological treatment during the duration of the study, both of whom will be blinded to participants' diet allocation. If possible, glucose-lowering medication will be kept constant during the entire study

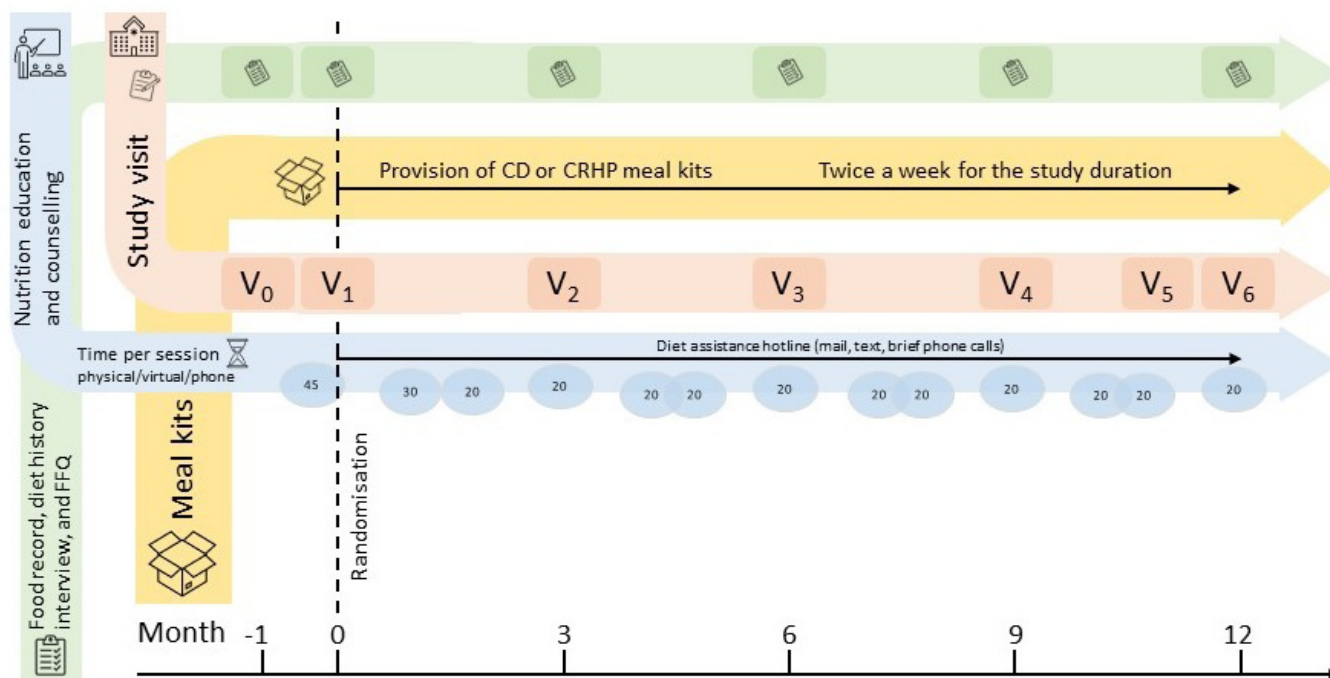


Figure 1 Overview of study visits, meal kit provision, nutrition education and counselling and evaluation of dietary adherence. For nutrition counselling sessions, attendance during first two sessions is preferred physical, thereafter virtual sessions or by phone are allowed. CD, conventional diabetes; CRHP, carbohydrate-reduced high-protein; FFQ, Food Frequency Questionnaire.

period. However, to ensure safety participants will be instructed to perform self-monitoring of blood glucose at home once weekly after the first 3 months of intervention. In the event of repeated fasting glucose levels >11.1 mmol/L or any diabetes-related symptoms (eg, fatigue, polyuria, thirst and confusion), participants will be referred to the study endocrinologists where necessary changes in medication will be assessed. To accommodate further safety concerns, if HbA_{1c} levels are above 58 mmol/mol following 6 months of intervention, glucose-lowering medication will in most cases be intensified. The choice of therapy will be in accordance with current national guidelines as well as guidelines from the EASD and the ADA. During the study, if possible, all medications with known effects on lowering blood pressure and lipids will be kept constant. However, any cases of severe hypotension or hypertension, or hyperlipidaemia as judged by the study endocrinologists (from symptoms or routine measurements after 6 months), will be remedied by optimising pharmacological therapy. Of note, the treatment of participants with highly elevated blood pressure and lipids will be optimised prior to study enrolment.

Assignment of intervention

Randomisation and allocation

Participants will be randomised in blocks of random size in a 1:1 ratio to the CRHP or the CD diet. Randomisation will be performed by a third-party person (without other affiliation to the study) by using the R extension package ‘blockrand’ to generate a randomisation list from a prespecified seed. Only the third-party person will

be allowed access to the randomisation list and participants will be allocated in the order of inclusion into the study. The allocation will not be revealed to the participants or investigators until after baseline measurements are completed. At this point, a double-sealed envelope marked with their randomisation number, containing a printed paper with the allocated diet (CD or CRHP), will be provided to the participants.

Blinding and unblinding

Participants and the investigators responsible for study coordination will, due to the nature of the intervention, not be blinded to the diet allocation. Such blinding will be performed whenever possible for staff conducting laboratory analyses, assessors of the MR scans and the personnel performing the dual-energy X-ray absorptiometry (DXA) scans and tests of muscular strength. The endocrinologists responsible for the pharmacological regulations during the study will also be blinded to the participants’ allocation, although unblinding is possible in the event of a severe adverse event or when it is deemed necessary by the endocrinologists.

Data collection and management

Assessments

A large examination programme including several days of examinations, conducted over 3 weeks, will be performed at baseline and end of treatment following 12 months of intervention, whereas some assessments will be repeated at every study visit, including baseline and months 3, 6, 9 and 12. An overview is provided in figure 1 and table 2.

Table 2 Schedule of study-related procedures and assessments

	Enrolment	Baseline		Intervention period				
Study visits		V ₀	V ₁	V ₂	V ₃	V ₄	V ₅	V ₆
Time points (month)		-1	0	3	6	9	11	12
Enrolment								
Eligibility screening	√							
Informed consent	√							
Optimising medications	(√)							
Randomisation			√					
Assessments								
Demographics	√							
Continuous glucose monitoring		√					√	
Diurnal urine collection		√		√	√	√	√	
Diurnal blood pressure		√					√	
Holter monitoring		√					√	
MR imaging		√					√	
DXA scan		√					√	
Muscle strength tests		√					√	
Anthropometry including body weight	√		√	√	√	√		√
Fasting blood sampling			√	√	√	√		√
Oral glucose tolerance test			√					√
Questionnaires		√	√	√	√	√		√
Interviews		√	√		√			√
Adherence to study protocol								
Food records		√		√	√	√		√
Diet history interviews and FFQ		√		√	√	√	√	
Query of adverse events				√	√	√	√	√
Query of medication changes	√	√		√	√	√	√	
Query of alcohol consumption	√	√		√	√	√	√	

Overview of study-related procedures and assessments conducted during the study duration. Baseline (V₀-V₁) and end of treatment (V₅-V₆) measurements were performed over a 3-week period for logistic reasons.
DXA, dual-energy X-ray absorptiometry; FFQ, Food Frequency Questionnaire.

Food records

Adherence to allocated diets will be evaluated according to intake of macronutrients on quarterly visits by use of 3-day weighed food records. Food records will be evaluated for total energy, macronutrients, alcohol and other food components important for dietary quality, for example, fibre, simple sugars, saturated and monounsaturated fat.

Anthropometry

Body weight will be measured on a calibrated scale (Tanita WB-110MA, Tanita, Tokyo, Japan) to the nearest 0.1 kg at the quarterly study visit. Height will be measured to the nearest 0.1 cm by a wall-mounted stadiometer (KERN MSF 200N, KERN & SOHN, Balingen-Frommern, Germany) at baseline. BMI will be calculated as weight divided by height in metres squared. Waist circumference will be measured in a supine position at the level of the lumbar vertebrae L3 (from MR scans) at baseline and at the end of treatment.

Body composition

DXA scans (Lunar iDXA, GE HealthCare, Madison, Wisconsin, USA) will be performed following an overnight (10-hour) fast to measure total body composition including lean body mass, fat mass and whole-body fat percentage.

Fat distribution

MRI (Ingenia Ambition 1.5 T X, Philips, Philips Healthcare, Best, The Netherlands) will be performed in the morning after breakfast (and any medication) at the Department of Radiology at Bispebjerg Hospital, to assess fat content stored in the liver, subcutaneously and viscerally (at the level of lumbar vertebrae L3-L5) as well as in the pancreas and psoas major muscle (segmented in one slice where pancreas is most visible and midst lumbar vertebrae L3 level, respectively). Chemical shift encoding-based water-fat imaging (6-point mDIXON Quant sequence package) will be used to assess

liver, subcutaneous and visceral fat. Based on a semiautomated segmentation approach (Mirada DBx V.1.2.0, Mirada Medical Imaging Software Applications), pancreatic fat and fat in the psoas major muscle will be assessed using a fat fraction sequence whereas visceral fat will be assessed by calculating its volume in the entire abdominal cavity at L3–L5.

Fasting blood samples

Fasting blood samples will be collected to evaluate glycaemic control, markers of glucose and lipid metabolism, renal function, low-grade inflammation, and hormonal and nutritional status. Samples will be handled appropriately and stored at -80°C until analysis.

Continuous glucose monitoring

A precalibrated continuous glucose monitoring (CGM) system (Freestyle Libre Pro iQ, Abbott Diabetes Care, Alameda, California, USA) providing interstitial glucose readings every 15 min will be used to evaluate diurnal glucose profiles including summary metrics of daily glycaemia and glycaemic variability. The sensors will be inserted on the upper arm for a maximum of 14 days, of which all days after excluding the initial 24 hours will be included in the analysis.

Blood pressure

Ambulatory blood pressure monitoring (OnTrak 90227, Spacelabs Healthcare, Snoqualmie, Washington, USA) with recordings every 30 min during daytime (7:00–22:00) and every 60 min during nighttime will be included to evaluate 24-hour blood pressure.

Holter monitoring

Holter monitors (Bittium Faros 360, Bittium, Oulu, Finland) worn by the participants for 48 consecutive hours will be used to evaluate heart rate variability.

Oral glucose tolerance test

A 4-hour oral glucose tolerance test will be performed after an overnight (10-hour) fast. A baseline venous blood sample will be collected and a 75 g glucose solution (Rapi-lose, Penlan Healthcare, Weybridge, UK) will be ingested over 5 min. Thereafter, blood samples will be collected at time points 10, 20, 30, 45, 60 and then every 30 min for the next 3 hours.

Diurnal urine sampling

Participants will collect 24-hour urine specimens at home according to instructions; urine will be kept cooled and for a maximum of 1 day until returned. Urine will be assessed for excretion of urea as a marker of protein intake and other biomarkers of renal function.

Muscle strength

Handgrip strength will be measured using a hand dynamometer (SAEHAN SH5001, SAEHAN, Masan, Korea) where participants are encouraged to squeeze as forcefully as possible, alternating between hands, each tested at minimum three times.¹⁹ Physical performance will be

measured by sit-to-stand time²⁰ and the 30s chair-stand test, to assess muscle strength and function of lower extremities.^{21 22} With verbal encouragement, participants will get up and sit down on a chair five times as fast as possible and as many times as possible for 30s without using their arms.

Questionnaires

Four questionnaires will be filled out at Bispebjerg Hospital, including Danish versions of the International Physical Activity Questionnaire Long Form,^{23 24} the Health Literacy Questionnaire,^{25 26} the Perceived Dietary Adherence Questionnaire—a Food Frequency Questionnaire (online supplemental material) and the Problem Areas In Diabetes Scale.^{27 28} The Department of Food Science at Aarhus University will be responsible for collecting questionnaire responses from participants using an online programme (Compusense Cloud software, Compusense, Guelph, ON, Canada). Participants will fill out two groups of questionnaires: the first evaluating meal acceptance, appetite and satiety sensations, and well-being, and the second health status,²⁹ food-related quality of life, variety seeking tendencies,³⁰ eating behaviour,³¹ and food-related pleasure.³²

Interviews

The Department of Food Science at Aarhus University will conduct interviews with participants by telephone or via video conferencing (Zoom, Zoom Video Communications, San Jose, California, USA). The interviews will be recorded by use of a dictaphone or an online recording app for later data analysis (thematic analysis). The interview at baseline will focus on expectations from participation in the trial. The three following interviews will focus on the diet intervention experience.

Data management

Participants will be identified by a study ID throughout the study with an encrypted identification key stored securely and separately from the participants' data linking the ID to the personal information. All data generated from study-related procedures at Bispebjerg Hospital will be entered into electronic case report forms using a secure web-based system (REDCap, Vanderbilt University, Nashville, Tennessee, USA) hosted by the Capital Region of Denmark. Relevant documents will also be stored physically under lock and key. Data generated by investigators at the Department of Food Science at Aarhus University will be stored on secure servers.

All biological material (whole blood, plasma, serum and urine) will be stored in a research biobank under lock and key in freezers located at Bispebjerg Hospital in pseudoanonymised form, by labelling samples with study IDs. The research biobank will be terminated on 31 December 2032, the latest, at which time all biological material will be destroyed following current standards regarding clinical trials.

Data collection will be conducted in accordance with Danish Law as declared in the Data Protection Act. The physiological, biological and personal information collected and transferred for analysis during the study will be kept confidential and in accordance with the General Data Protection Regulation.

Statistical considerations

Sample size calculation

Sample size is calculated in relation to HbA_{1c} as the study's primary outcome. Based on previous nutrition intervention trials of similar experimental diets,³³ we assumed an SD of 10 mmol/mol in change in HbA_{1c} during 1 year, thereby calculating a need of 37 completing participants in each group in order to detect a difference in HbA_{1c} of 7 mmol/mol with 80% power and a two-sided α -level of 0.05. This difference in HbA_{1c} is considered clinically relevant. To account for a drop-out rate of 20%, found in similar studies,³³ and for a possibly smaller effect size, we decided to include 100 participants in the study.

Statistical analysis plan

Intention-to-treat (ITT) analyses including all available data from all randomised participants will be conducted to estimate the effect of prescribing/encouraging a CRHP eating pattern but may differ from the actual effect of the eating pattern in the presence of imperfect adherence to the diet by the participant. The treatment effect (CRHP vs CD) will be reported as an estimated marginal mean with corresponding two-sided 95% CI and p value and considered statistically significant if the 95% CI does not include 0. All statistical analyses and graphical work will be performed by using R (R, Boston, Massachusetts, USA).

Primary outcome

A constrained linear mixed model (cLMM) will be used to model the mean HbA_{1c} (including data in original form) over time within each diet group while adjusting for important covariates including sex, age, BMI, T2D duration, insulin resistance by the $HOMA2_{IR}$ index and glucose-lowering medications (metformin, DPP-4 inhibitors, SGLT-2 inhibitors and GLP-1 receptor agonists).³⁴ The cLMM will include nine mean parameters (a single at baseline and one for each group and follow-up time point) and an unstructured pattern stratified by treatment group to model the residual variance within individuals. Missing data are handled by the cLMM using a full information approach.³⁵ The estimated marginal mean difference in changes from baseline to 12 months of follow-up between the two groups will be tested using a Wald test on the appropriate parameter of the cLMM (interaction group and 12 months).

Secondary outcomes and exploratory outcomes

Similar cLMMs as for the primary outcome will be used to model mean change in body weight and intrahepatic fat content over time while adjusting for covariates, estimating a total of nine (five time points) and three (two

time points) mean parameters, respectively, based on data included in original and log-transformed form, respectively.

Additional exploratory outcomes will be analysed using the cLMM, similarly as for the primary outcome, when continuous or using Fischer's exact test when categorical where the existence of an association between the outcome and the group variable will be assessed. For secondary and exploratory outcomes, p values and CIs will not be corrected for multiplicity in their hypothesis testing since these will be hypothesis-generating analyses instead of confirmatory analyses.

Per-protocol analyses

Per-protocol (PP) analyses³⁶ will be conducted to evaluate the diet effect on glucometabolic outcomes including the change in HbA_{1c} , body weight and hepatic fat content. Compared with ITT analysis, the effect is now evaluated conditional on dietary adherence. Adherence is defined based on food records and solely on carbohydrate intake with no requirements for the intake of protein and fat. Carbohydrate intake (averaged over months 9 and 12) in the range of 20–40 E% for the CRHP diet and 45–60 E% for the CD diet will qualify for inclusion in the PP analyses.

Furthermore, PP analyses will be performed to evaluate glucometabolic outcomes unaffected by changes in medication, by only including participants who had stable glucose-lowering and lipid-lowering medications throughout the study duration.

Superiority and non-inferiority testing

Our statistical analyses test for superiority, but if they fail to reject the null hypothesis, non-inferiority tests will be conducted secondarily for the primary and secondary outcomes, using the non-inferiority margin of 3 mmol/mol for HbA_{1c} change, 5 kg for weight loss and 25% relative change in intrahepatic fat. No adjustment for multiple testing is needed when switching between superiority and non-inferiority testing.³⁷

Qualitative data

The interviews will form the basis for a thematic analysis, following the six recommended phases of Braun and Clarke.³⁸

ETHICS AND DISSEMINATION

The study is approved by the National Committee on Health Research Ethics of the Capital Region of Denmark and will be conducted in accordance with the Declaration of Helsinki II as well as in accordance with the International Conference on Harmonisation–Good Clinical Practice standards to the extent that is considered relevant for a non-medical intervention. The study is registered with ClinicalTrials.gov (NCT05330247). All study results, whether positive, negative or inconclusive, will be published in line with Consolidated Standards

of Reporting Trials guidelines in peer-reviewed international scientific journals, presented at national and international scientific conferences and communicated as far as possible to the broader population including individuals with T2D, relevant policy and health services, and other stakeholders.

Safety considerations

The diets employed in this study are believed to be safe and not assumed to convey risks of adverse events. Nevertheless, all adverse events or side effects will be recorded throughout the study (and reported to the authorities) according to onset, intensity and relation to study diets, and necessary care and treatment will be given. Despite an overall aim to keep medication affecting the outcomes of the present study (ie, blood glucose, lipids and blood pressure) unchanged, any disease progression or changes in these will be handled appropriately by the study endocrinologists as described previously.

In theory, severe carbohydrate restriction may be associated with hypoglycaemia but, for the present eucaloric CRHP diet that has a moderate content of carbohydrate (expected daily intake in the range of ~150 g/day for the lowest calorie level, online supplemental table S3), hypoglycaemic risk is minimal, particularly in the absence of adjuvant therapy with sulfonylureas and/or insulin as in the present population. Nevertheless, if symptoms of hypoglycaemia (eg, hunger, sweating, dizziness, increased heart rate and confusion) occur, participants will be instructed to measure blood glucose and take appropriate measures. If clinically significant hypoglycaemia (defined as blood glucose <3.0 mmol/L) is assessed to be caused by improved glycaemic control through study participation, glucose-lowering medication will be adjusted. Also, previous literature has advocated against increasing intakes of fat and protein in people with T2D due to adverse effects on dyslipidaemia and renal disease, respectively, however, later meta-analyses have not validated these concerns.^{8 11 39} Collectively, we expect both diets to be safe.

The risks associated with study participation and its related procedures are minimal but may include minor bruising, haematomas or infectious risk from blood sampling, placement of peripheral venous catheter and insertion of CGM sensor. These are insignificant and largely overshadowed by the expected health improvements from the experimental diets.

Novelty and expected impact

We expect the present study to provide evidence that long-term carbohydrate restriction is feasible through the proper support of partial meal provision combined with nutrition education and counselling and prove advantageous compared with a traditional diet in the treatment of T2D, without the need for additional lifestyle changes, for example, concomitant exercise training or forced calorie restriction. The magnitude and duration of meal kit provision presented in this study is unique

and has, to our knowledge, not been conducted before in previous studies, even though provision of meal kits is easily implemented and represents an already established and feasible way of dining, familiar to the Danish as well as other Western populations. Thus, in the event of favourable results of moderate carbohydrate restriction on long-term efficacy and safety, upscaling to larger studies or clinical implementation is possible, which may pave the way for a paradigm shift in the dietary management of T2D.

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