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Randomized controlled trial of a web-based low carbohydrate diet intervention for adults with type 2 diabetes: The T2Diet study protocol

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Abstract

Introduction: Standard care for patients with type 2 diabetes (T2D) consists of routine physician appointments to monitor glycemic status and overall health. Dietary modification is an essential component of T2D management. Evidence suggests a low carbohydrate diet (LCD) provides better clinical outcomes for people with T2D compared to other diets. However, providing dietary support in face-to-face settings is challenged by issues of availability and accessibility. Digital interventions can help bridge this gap. The objective of this paper is to describe the protocol of a randomized controlled trial (RCT) of a web-based intervention that will evaluate the effectiveness of standard care plus web-based LCD intervention when compared to standard care only.

Methods and analysis: In a two-arm parallel RCT, 100 adults with T2D will be randomized to either a theoretically-informed 16-week automated web-based LCD intervention plus standard care or standard care only. LCD recommendations emphasize consuming nutrient-dense whole foods and encourage a daily carbohydrate goal of 50-100 grams, with an objective of achieving 10-<26% carbohydrates from total energy intake. Assessments will take place at baseline and 16-weeks. The primary outcome will be hemoglobin A1c (HbA1c). Additional data collected will include dietary intake, self-efficacy, weight and height, anti-diabetes medication and dosages, and diabetes-related comorbidities. Process evaluation will consist of a mixed-methods assessment of website engagement metrics, user experience, and participants' perspectives.

Ethics and dissemination: All study procedures have been approved by the Deakin University Human Research Ethics Committee (2020-349). Study findings will be disseminated widely through public, professional, and academic presentation and publication.

Trial registration: The trial has been prospectively registered with the Australian New Zealand Clinical Trials Registry (ACTRN12621000096853).

Keywords: Type 2 diabetes, low carbohydrate diet, glycemic control, self-management, web-based, HbA1c.

Strengths and limitations of this study

- To the best of our knowledge, this study is the first web-based study to evaluate the effectiveness of a low carbohydrate diet (10-<26% energy intake) on glycemic control in adults with type 2 diabetes.
- A key strength of the study is the randomized controlled design and robust outcome assessment using hemoglobin A1c that will minimize bias and maximize the validity of the study findings.
- One limitation is no long term follow up, as this was not feasible for this study.

Introduction

The global burden of T2D was estimated at 462 million individuals in 2017 [1]. Due to metabolic changes, T2D results in high glycemic status, frequently measured by HbA1c. The primary treatment goal is to assist people with T2D to achieve a HbA1c below 7.0% [2]. However, in 2020, estimates indicated 50% of adults with T2D had uncontrolled T2D, with HbA1c levels above the treatment goal [3]. Uncontrolled T2D significantly contributes to the development of diabetes complications and mortality [3]. Standard care for patients with T2D consists of routine health checks with a primary care physician to monitor glycemic status, diabetes complications and overall health [2, 4]. In addition, healthy behavior should be routinely encouraged before or in conjunction with pharmacological treatment if necessary [4].

Dietary modification plays an integral role in diabetes management, in improving glycemic control and overall health [2]. In terms of diet, a low fat, moderate-high carbohydrate diet has traditionally been a common dietary recommendation provided to people with T2D [4, 5]. However, a growing body of evidence has demonstrated a LCD, defined as 10-<26% carbohydrate of total energy intake [6, 7], may be more optimal for improving clinical outcomes in people with T2D [6, 8, 9]. Systematic reviews and meta-analyses of LCDs in people with T2D have demonstrated greater improvements in glycemic control, increases in HDL cholesterol,

decreases in triglycerides, reduced medication requirements [6, 8-11], and greater potential for diabetes remission [9].

LCD interventions for people with T2D have typically been delivered in face-to-face settings [8]. However, people with T2D face substantial challenges in accessing dietary support due to limited availability, accessibility, and cost barriers [2, 12-14]. Web-based interventions can bridge this gap, offering the potential for greater reach and accessibility, with the advantage of being convenient and on-demand to participants when required [15]. Systematic reviews of web-based comprehensive self-management interventions in people with T2D have demonstrated favorable improvements in glycemic control [16-18]. Preliminary evidence suggested web-based dietary interventions may be an effective way to support dietary change and improved glycemic status in adults with T2D [19]. Furthermore, web-based interventions in people with T2D have shown promise as a cost-effective option [20], with the capacity to be widely implemented to support routine primary care [21]. No RCT to date has assessed the effectiveness of a LCD intervention in individuals with T2D, delivered in a web-based setting.

The study protocol for a RCT of a web-based LCD program for adults with T2D is presented here. The primary aim of this study is to determine the effectiveness of a web-based LCD intervention on glycemic control in adults with T2D. We hypothesize that the web-based LCD intervention plus standard care will result in better glycemic control—lower HbA1c levels—at 16 weeks compared to standard care alone in adults with T2D. Secondary aims are to assess changes in dietary intake, self-efficacy, weight and body mass index (BMI), anti-diabetes medication and diabetes-related comorbidities; and to assess process outcomes related to user engagement and experience.

Methods

Study design

The T2Diet study is a 16-week two-arm parallel RCT that aims to investigate the effectiveness of a web-based LCD intervention plus standard care versus standard care alone on glycemic control in 100 Australian-based adults with T2D (Figure 1). A period of 16 weeks was chosen as

previous web-based dietary interventions demonstrated significant improvements in glycemic control could be achieved within this timeframe [19].

Inclusion criteria will be adults aged 40-89 years, the most highly affected demographic for T2D in Australia [22], with non-insulin-dependent T2D and self-reported HbA1c levels ≥7.0% within the previous six months; access to the Internet; an active email address; able to read and understand English; based in Australia; and willing and able to provide informed consent. Exclusion criteria will be people with type 1 diabetes, prediabetes or gestational diabetes; people with diagnosed renal or cardiovascular disease; people with a terminal disease or severe complications compromising the quality of life of the participant and their ability to participate according to the protocol; women who are pregnant or lactating; people who have undergone bariatric surgery; vegetarians or vegans; people currently on a weight loss program or who have taken a weight loss program within the past 3 months; people enrolled in other clinical studies; and people at risk of disordered eating, assessed during screening with the Eating Attitudes Test-26 [23, 24]. Participants identified with potential eating disorders will be referred to The Butterfly Foundation National Helpline [25]. Informed consent will be obtained from eligible participants prior to entry into the study.

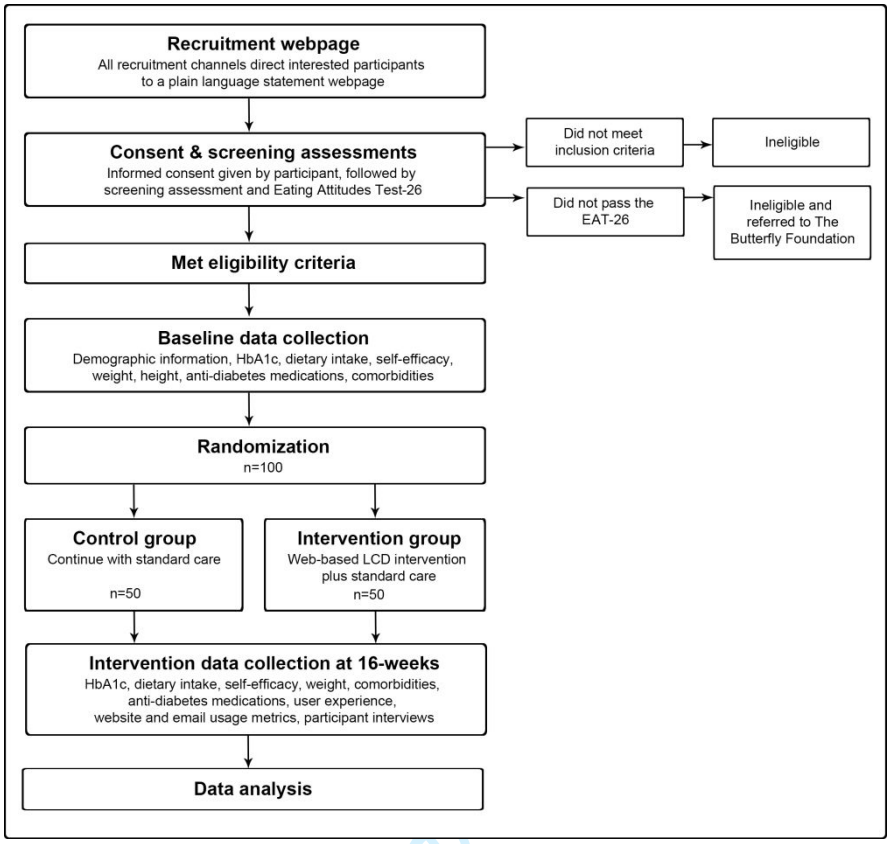

Figure 1. Study flow chart

Intervention

The intervention is a theoretically informed 16-week automated web-based LCD behavior change support program. Existing website resources were licensed for this study. Subsequently, four phases of inquiry were conducted with end-users (adults with T2D) to inform development of the new web-based dietary intervention. The weekly behavior change modules adopt various behavior change techniques [26] and were constructed upon a theoretical framework, consisting of: 1) self-efficacy theory [27]—self-efficacy being a key determinant of self-care behaviors and glycemic control in T2D [28-31]; 2) positive message framing—using language that communicates benefits rather than scare tactics [32, 33]; and, 3) principles of persuasive technology—using technology as a means of persuasively communicating intervention content [34].

Dietary recommendations

Intervention participants will receive web-based recommendations to consume an *ad libitum* LCD [10], and encouraged to consume between 50-100 grams carbohydrates per day [6]. The

overall goal is to achieve a low carbohydrate intake, defined as 10-<26% total energy intake [6, 7]. Web-based resources emphasize high consumption of non-starchy vegetables, adequate dietary fiber, and selection of nutrient-dense sources of lower carbohydrate foods [2]. Participants will be instructed to avoid or minimize high carbohydrate food and beverage sources such as added sugar, sugar-sweetened beverages [2, 5, 35], starchy foods [36, 37], and discretionary foods [2, 5, 35]. There will be no specific prescription for other macronutrients. However, based on estimated energy intake for the demographic of this study ranging from 1600 calories/6694 kilojoules to 2400 calories/10041 kilojoules [38], the protein and fat ranges are estimated to fall between 60-180 grams (15-30% estimated energy intake) and 80-200 grams (45-75% estimated energy intake), respectively [2, 39-41]. Web-based recommendations encourage nutrient-dense sources of protein and fat [36, 37], emphasizing consumption of polyunsaturated and monounsaturated fat [2, 35], and suggesting reduced-fat dairy may be preferred [42]. To facilitate implementation, skills-based resources such as recipes, information on T2D, food and beverage choices, menu examples, eating out tips, menu planning and food preparation tips, an interactive planner, and cooking demonstrations are provided.

Web-based intervention delivery

Intervention participants will be provided with login details for the study website to access the weekly modules and on-demand resources. The weekly modules consist of short videos with brief overviews, links to further resources, recipe suggestions, and action steps (Figure 2). These delivery methods, particularly the use of video, have been shown to address various levels of literacy [43], enhance engagement [44], and support health behavior change [45]. The weekly modules will be delivered sequentially, however, participants can continue to access any previous weeks' modules, along with accessing on-demand resources at any time. To prompt website usage and performance of behavioral actions, reminders will be sent to participants via email twice per week [43, 46]. It is estimated participants will login to the website once per week.

Adverse effects

Intervention participants will be provided with education about and resources on how to manage potential adverse effects of carbohydrate reduction, such as constipation, headache and brain fog,

halitosis, muscle cramps, tiredness and fatigue, hunger and cravings, and heart palpitations [37, 47]; temporary hypoglycemic-like symptoms; hypoglycemia, defined as a blood glucose level <70mg/dL/<4.0mmol/L; and to identify symptoms of ketoacidosis, for any participant taking sodium glucose cotransporter 2 inhibitor medications [2]. Participants will be able to report adverse effects via an online form. If participants request assistance, they will be directed to appropriate resources, and/or, advised to consult with their treating physician. Any adverse effects will be documented and reported with trial outcomes.

Standard care

Participants in both groups will be advised to continue with their standard care, defined by the Royal Australian College of General Practitioners [4], as routine appointments with their physician to monitor glycemic control, diabetes complications, and other health parameters.

Control condition

The control group will be standard care, as defined above. Participants in the control group will be on a waitlist and provided with the opportunity to participate in the intervention after completing the study.

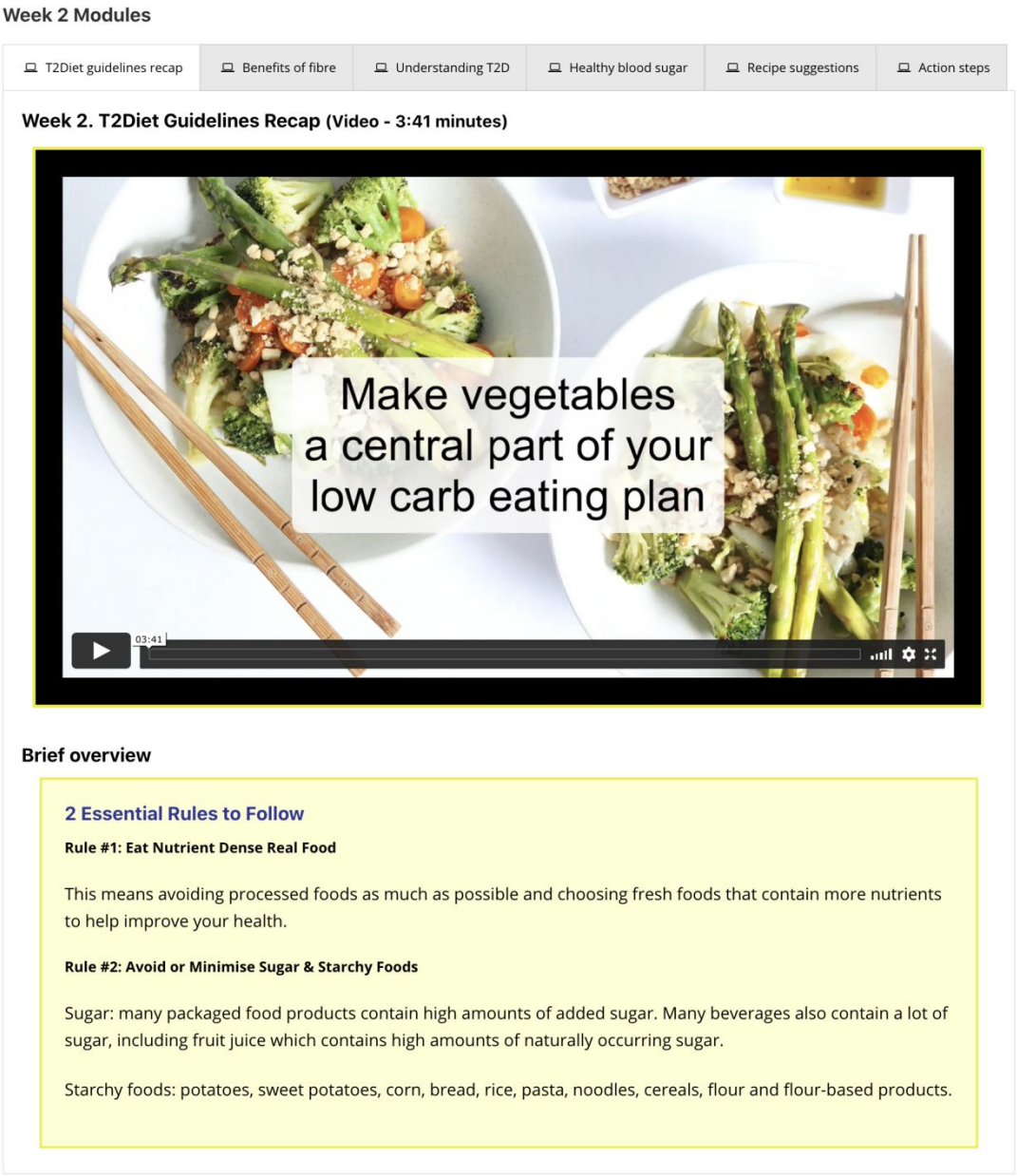

Figure 2: Presentation format of the weekly behavior change modules

Outcomes

Primary and secondary outcomes will be measured at baseline and immediately post-intervention (16 weeks). An overview of study measures, data collection instruments and their timepoints is presented in Table 1. The primary outcome will be glycemic control measured by the mean difference of change in HbA1c between intervention and control group from baseline to 16

weeks. For secondary outcomes, dietary intake data—food, beverages and dietary supplements, will be collected to assess participants' adherence to the recommended LCD. We will also explore improvements in the quality of the participants' diet such as changes in discretionary food intake and vegetable consumption, and changes to individuals' overall macro and micronutrient intake and food groups. In addition, we will explore the association between adherence to diet and glycemic control. Self-efficacy will be measured to assess whether participants' self-efficacy improves and whether self-efficacy predicts and promotes greater changes in glycemic control [28-31]. Weight and height will be collected to assess change in weight and BMI (kg/m^2). To assess confounding factors, anti-diabetes medication and dosages, and diabetes-related comorbidities [4] will be collected.

Process evaluation

Post-intervention, a mixed-methods approach [48] will be used to explore website utilization, user engagement and experience, in the intervention group only. Two forms of quantitative data will be collected: 1) website and email usage rates for frequency, intensity and duration metrics [49], collected for each week of the 16-week intervention; and 2) a self-administered questionnaire using the User Engagement Scale short form [50] and Honeycomb Model [51, 52]. To collect qualitative data, 20 participants [53] will be invited to attend a semi-structured phone interview. Process evaluation will be reported separately to the primary and secondary outcomes of this trial.

Table 1. Summary of outcome measures, data collection instruments and timepoint

Measures	Instrument	Timepoint

		Baseline	16 weeks
Demographic information	Structured questionnaire, self-reported via an online request form.	X	
Primary outcome			
Hemoglobin A1c (%)	Collected and assessed using the Nutripath Integrative Pathology Services HbA1c microsample self-administered postal test.	X	X
Secondary outcomes			
Dietary intake: food, beverage and dietary supplements	Assessed via self-reported 24-hour food recall using study-specific online questionnaire, analysis using FoodWorks professional nutrition software.	X	X
Self-efficacy	Self-reported via an online request form using the Diabetes Management Self-Efficacy Scale—Australian version [54].	X	X
Weight/BMI	Self-reported weight and height, via a study-specific online request form.	X	X
Confounders			
Anti-diabetes medication and dosages, and diabetes-related comorbidities	Self-reported, via a study-specific online request form.	X	X
Process outcomes (Intervention group only)			
Website utilization	Website and email usage metrics.	←	→
User engagement and experience	Self-reported using the User Engagement Scale short form [50] and Honeycomb Model [51, 52], via an online request form.		X
Participants' experience	Semi-structured phone interviews with up to 20 participants.		X

Sample size

A total of 100 participants (50 per group) will provide 80% power at *type I error of 0.05* to detect a between-group difference of 0.5% on HbA1c (primary outcome). In terms of clinical relevance, a decrease in HbA1c of 0.5% may avert cardiovascular disease events by 10% over 5

years [55]. An estimated 12% of diabetes-related deaths could be prevented by lowering HbA1c by a modest 0.1% [56]. The sample size is based on the following assumptions: a standard deviation of 0.9 HbA1c [57, 58], a pre-post intervention correlation of 0.5 [59], and a drop-out rate of 20% [60, 61]. The sample size calculation was conducted by an independent statistician using Stata's power twomeans command.

Recruitment

Enrolment of 100 participants will occur nationally across Australia using social media (primarily Facebook, Twitter and Linkedin); networking with colleagues and acquaintances; community publications, newsletters or radio; through diabetes clinics, community organizations, fitness centers or medical centers; snowballing; and if necessary, paid online advertising via Facebook. All recruitment channels will direct interested participants to a plain language statement webpage where participants can voluntarily provide their informed consent. After giving informed consent, participants are immediately redirected to the eligibility screening questionnaire. Eligible participants will then be required to complete all baseline measurements (Table 1) before being randomized to their allocated group. Following intervention completion at 16-weeks, participants will be required to complete the same measurements, excluding demographic details and height (Table 1). Recruitment started in February 2021 and is expected to be completed by December 2021.

Assignment of interventions

Participants will be randomized in a 1:1 ratio to standard care (control group) or standard care plus web-based LCD intervention (intervention group) using block randomization with varying random block sizes and stratified by age and gender. A computer-generated predetermined randomization schedule will be produced and held off-site by an independent statistician, who will indicate the group allocation as eligible participants are recruited. The group allocation will be concealed from researchers and participants until all baseline measures have been collected and the independent statistician has conducted the randomization. Outcome assessors and data analysts will be blinded to group allocation.

Data collection tools

Aside from HbA1c, all points of data collection will occur online through structured questionnaires with self-reported entries, for both groups. Demographic information such as age, gender, duration of T2D, family history of T2D, country of birth, employment status, education level, relationship status, and smoking status will be collected at baseline for descriptive purposes.

HbA1c will be assessed using Nutripath Integrative Pathology Services HbA1c microsample test, a self-administered test that will be mailed to participants and back to the pathology service. HbA1c is the most common clinical biomarker used to assess glycemic control in RCTs that include people with T2D [8].

Dietary intake will be assessed using 24-hour food recall, a comprehensive self-report instrument that is considered highly robust [62]. An online 24-hour food recall questionnaire will collect participants' self-report of foods, beverages, and supplements consumed in the previous 24-hour period. Submissions will be reviewed and if necessary, participants will be contacted for additional detail. FoodWorks professional nutrition analysis software for Australia and New Zealand will be used for assessment.

Self-efficacy will be measured using the Diabetes Management Self-Efficacy Scale—Australian version [54], which has been validated for use in people with T2D in Australia. The scale contains 20 questions rated on a 10-point scale. Responses are then summed to present a single self-efficacy score. Higher scores indicate greater self-efficacy.

Self-reported weight and height, anti-diabetes medication and dosages, and diabetes-related comorbidities will be collected. Online self-reported weight and height has been demonstrated to be a valid method [63]. The checklist of comorbidities was drawn from the Royal Australian College of General Practitioners guidelines on general practice management of T2D [4].

Participant retention and withdrawal

To accommodate any loss, multiple imputations will be used to handle the missing data (either as primary or sensitivity analysis), using available data to minimize potential bias of estimated intervention effects due to non-random attrition. In addition, when measurement data is

due/overdue, emails and/or text message reminders and phone calls to participants will be made. All participants completing this study will receive a $30AUD shopping voucher. Participants are free to withdraw from the study for any reason, up until data analysis commences.

Data management and protection against bias

Significant measures have been put in place to ensure robust data management and integrity and protect against bias. Primary outcome reports and self-reported data files will be downloaded in their wholly original unmodified form by the principal investigator and securely stored in a location inaccessible to other research team members. These original data files will not be modified. Copies of original data files will be provided to research team members as required. Data that requires manual entry will be crosschecked against copies of the original data files by a second research team member. An independent statistician will be provided with a copy of the original or crosschecked data files to collate and clean the dataset in preparation for data analysis. Once complete, the coded, de-identified dataset will be securely stored by the principal investigator, as the lockdown dataset files, in a location inaccessible to other research team members. These lockdown dataset files will not be modified. Copies of the lockdown dataset will be shared with research team members as required. A dedicated study statistician will be provided with a copy of the lockdown dataset files to conduct the data analysis independently.

Monitoring

Overall study monitoring occurs via monthly meetings involving the research team members.

Data availability statement

Data will be available upon reasonable request.

Statistical methods

All data will be imported into Stata for quantitative analysis. Baseline characteristics will be presented using descriptive statistics. The mean and standard deviation, or median and range, will be used to describe continuous variables. Frequencies and/or percentages will be used to

describe categorical variables. Intervention effects (i.e., mean difference between intervention and control group) at 16 weeks will be evaluated by implementing an ANCOVA model for each outcome with the 16-week value of the outcome as the dependent variable, and treatment group and baseline outcome score as independent variables, and adjusting for stratification variables (age and gender). Multiple imputation techniques with missing at random assumption will be used to impute missing data due to dropouts or withdrawals to comply with the intention-to-treat approach. Sensitivity analysis will be performed to evaluate missing at random assumption for missing observation pattern. Subgroup analysis will be conducted with the duration of diabetes and gender. For the duration of diabetes, a median split will be used to define subgroups. P-value 0.05 will be used as the level of significance for the primary outcome and all secondary outcomes. Cohen's D effect size will be calculated and reported. For all continuous outcomes, data will be explored for deviation from the normal distribution assumptions. If necessary, a transformation of data (e.g., log transformation) or a non-parametric approach may be considered.

Patient and public involvement

Participants (adults with T2D) were engaged in four iterative phases of user-centered inquiry involving group discussions, which informed the development of the new web-based dietary intervention. Intervention participants will be involved in feedback during process evaluation.

Ethics and dissemination

All study procedures have been approved by the Deakin University Human Research Ethics Committee (2020-349). Any protocol amendments will be submitted for approval to the ethics committee prior to implementation and communicated via an update of the Australian and New Zealand Clinical Trial Registry.

Key audiences this research may benefit include the general public, researchers, clinicians, policymakers, and healthcare organizations [64-66]. Various methods may be used to disseminate the findings, including peer-reviewed publication, presentations, consumer and professional publication, and social media [66, 67]. Participants involved in the study will be

sent a summary report of the study's main outcomes via email. In any dissemination of research findings, participants' identities will remain confidential.

Discussion

This study will conduct a RCT of standard care alone versus standard care plus web-based LCD intervention in adults with T2D, with the primary intervention objective of improving glycemic control. To meet the needs and context of end-users who will participate in the study, user-centered principles and involvement of end-users in numerous rounds of feedback and iterative development were employed. The weekly behavior change modules apply various behavior change techniques and were constructed upon a theoretical framework to help strengthen communication of the intervention, address literacy levels, and maintain engagement. In addition, the email reminder notifications aim to boost website usage and motivation to participate.

This study will be the first RCT of a LCD intervention for adults with T2D, delivered in a web-based setting. The findings will contribute valuable insights into whether a LCD is effective when delivered in a web-based environment; and whether such an intervention could be considered to support T2D management more broadly. Further, this study will contribute new knowledge to inform future digitally-delivered dietary interventions that could be used to reach a greater number of people with T2D and other health conditions across Australia and internationally.

Acknowledgment

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Conflicts of Interest

JD is co-owner of Diabetes Meal Plans, a web-based nutrition support service for people with type 2 diabetes and prediabetes, who licensed the web-platform for this study.

Authorship

JD conceived and designed the study and wrote the manuscript. SI, EG, KB made critical contributions to the study design and provided critical input and revisions to the manuscript. MM contributed to the study design and provided critical revisions of the manuscript. All authors provided final approval for submission of the manuscript.

Abbreviations

BMI: body mass index

T2D: type 2 diabetes

HbA1c: hemoglobin A1c

LCD: low carbohydrate diet

RCT: randomized controlled trial

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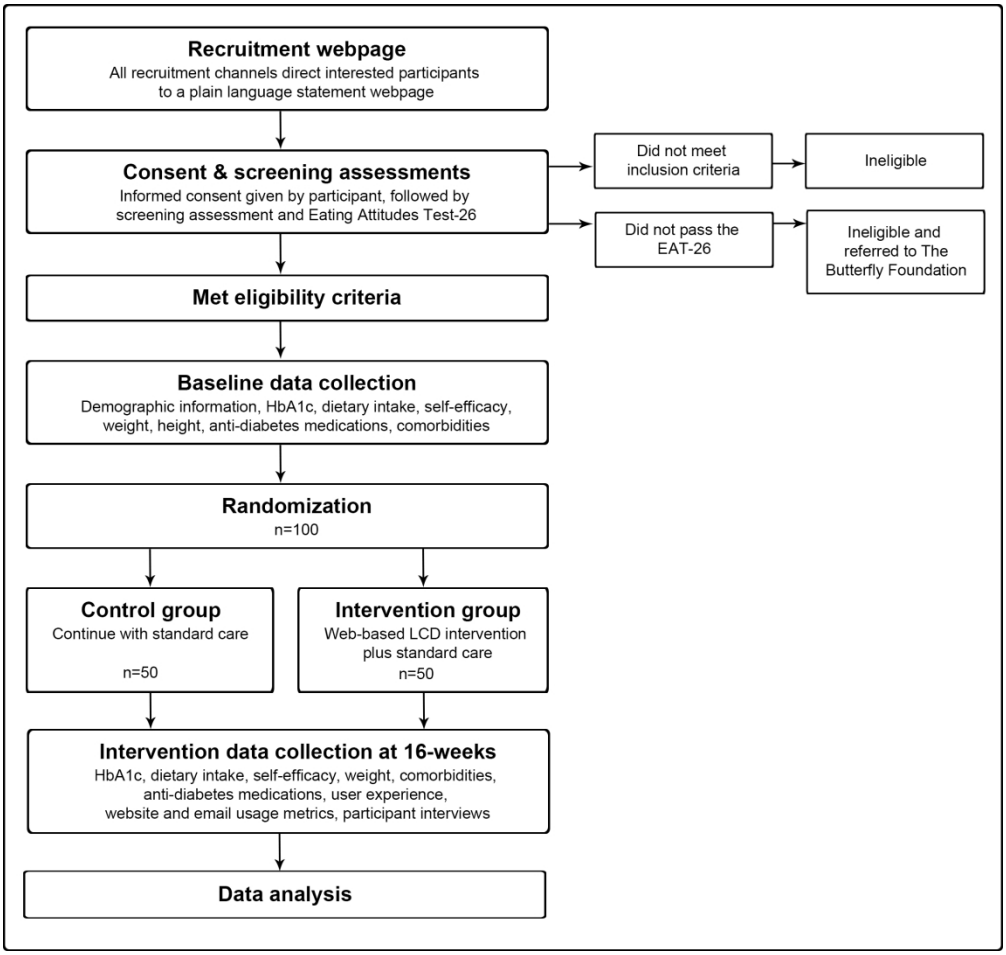
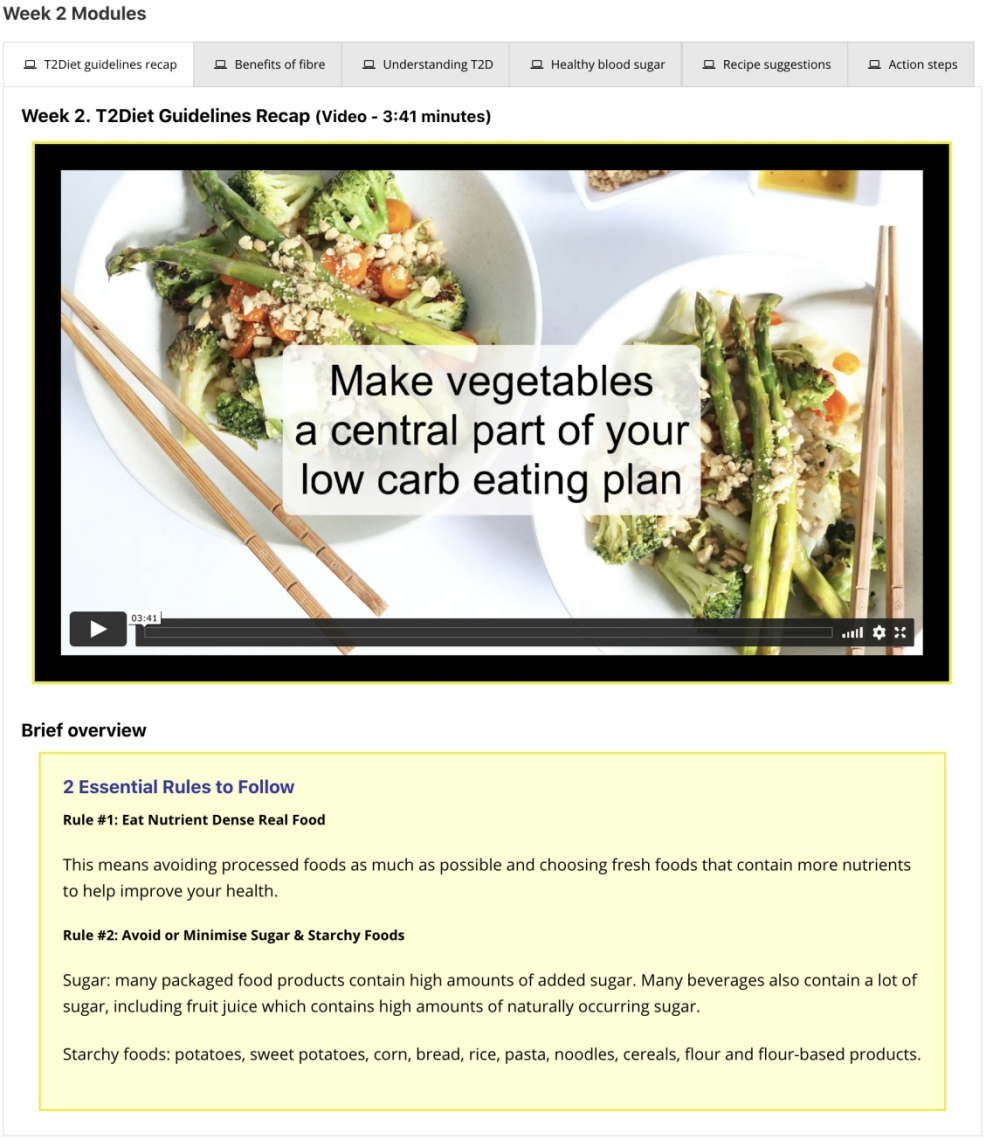


Study flow chart

201x190mm (300 x 300 DPI)



Presentation format of the weekly behavior change modules

324x372mm (144 x 144 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	____1__
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_____2_____
	2b	All items from the World Health Organization Trial Registration Data Set	____NA_____
Protocol version	3	Date and version identifier	____NA_____
Funding	4	Sources and types of financial, material, and other support	_____16_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_____1_____
	5b	Name and contact information for the trial sponsor	_____1_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	___NA_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_____14_____

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
	6b	Explanation for choice of comparators	3-4
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4, 11
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7-8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9-10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10, 11

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	11
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	12
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	11-12
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11-12
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	11-12
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	13
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	7
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	14

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	13
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	16
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Attached
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

PLAIN LANGUAGE STATEMENT AND CONSENT FORM

TO: Participants

Plain Language Statement

Date:

Full Project Title: Web-based diet intervention for adults with type 2 diabetes

Principal Researcher: Dr Shariful Islam

Student Researcher: Jedha Dening

Associate Researcher(s): Professor Kylie Ball, Dr Elena George

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Join this new study for adults with type 2 diabetes in Australia

You are invited to participate in the 16-week T2Diet study—an evidence-based eating program for adults with type 2 diabetes.

The 16-week program is provided to you online so you can participate from home. Participation is voluntary. Participation is free.

You can participate in this study if:	You **CANNOT** participate in this study if:
• You are an adult between 40-89 years with non-insulin-dependent type 2 diabetes • If one of your HbA1c tests within the previous 6 months was equal to or above 7.0% / 53 mmol/mol • Have an active email address • Have access to a computer and the internet • Are able to read and understand English • Are located in Australia • Are willing to use a finger-prick HbA1c self-test kit to take a blood sample at home (There will be no cost to you) • Are willing to complete the required tests and questionnaires outlined below, which will help us make our scientific assessment of the program	• You are a person with type 1 diabetes, prediabetes or gestational diabetes • You have been diagnosed with renal disease or cardiovascular disease • You have a disease or complication that may interfere with your participation, for example, cancer, proliferative retinopathy, or severe neuropathy. • You are a woman who is pregnant or lactating • You have undergone bariatric surgery • You are vegetarian or vegan • You are currently on a weight loss program or who have taken a weight loss program within the past 3 months • You are currently enrolled in other clinical studies • You have, or are at risk of, an eating disorder

Please view this entire page with information about the study. If you agree to participate, please click the button at the bottom of the page to complete the consent process.

Purpose of this study

The purpose of this research is to determine whether the web-based T2Diet program is effective for helping adults with type 2 diabetes in Australia improve their eating plan and improve blood sugar levels.

Methods

To help us determine the effectiveness of the web-based T2Diet program, we need to compare the changes in blood sugar levels in people who participate in the web-based T2Diet program, or in people who follow their standard care.

This means there will be two groups in this study:

Group 1) Will be allocated to the 16-week T2Diet program right away.

Group 2) Will be asked to continue with their standard care, however, you will be able to take the 16-week T2Diet program after the study is complete. This means Group 2 is on a 'waiting list' and will have to wait until after we've collected all the data from study participants before you are able to take the 16-week T2Diet program.

If you choose to participate, you could be allocated to Group 1 or Group 2. You can't choose which group to be in and you won't know up front. If you choose to join the study, you will be allocated to Group 1 or Group 2 randomly.

Regardless of which group you are allocated to, your participation is *very* important to help us determine whether this web-based eating program could be beneficial to support adults with type 2 diabetes in Australia to achieve better blood sugar control.

What your participation will involve

When you join this study, you will be randomly allocated to Group 1 (T2Diet program right away) or Group 2 (wait list).

Both groups will be required to provide us with information to help us make our scientific assessments of the 16-week program. Your personal identity will remain confidential.

Please view the information below that explains each test or questionnaire we will ask you to do.

Eligibility/ Eating Attitudes Questionnaire

Before entering the study, all participants will be required to confirm their eligibility by taking a short questionnaire, along with an Eating Attitudes Questionnaire

These two questionnaires will take approximately 10 minutes. You will be asked to complete these questionnaires via an online form after you provide your consent to participate.

Demographic information

We will ask you to complete an online form to provide demographic information such as age, gender, duration of diabetes, family history of diabetes, country of birth, employment status, highest level of education, relationship status, current medication, smoking status, and existing health conditions.

This questionnaire takes 5-10 minutes. You will only need to take this questionnaire once at the beginning of the study. At the end of the study, we will only ask you about your current medication and health conditions. Your personal identity always remains confidential.

HbA1c to measure your blood sugar levels

We will send you a HbA1c self-test kit that you can use at home to take a blood sample. We will need to provide the test company with your personal details (name, DOB, phone, address, email, gender) so they can ship the test kit to you.

The HbA1c test will involve following the instructions provided to take a finger-prick blood sample. After you take the blood sample, you will need to return it to the pathology lab within 24-hours in the reply-paid envelope provided.

This is the most important test as it will help us determine any changes in your blood sugar levels over time. You would need to return the test kit to the lab in the reply-paid envelope within 24-hours after taking your blood sample. We will test your HbA1c before participating in the study and 16 weeks later (2 tests). There will be no cost to you.

Report your food and beverage intake over a 24-hour period

We'll ask you to complete an online guided questionnaire that will prompt you to enter all the foods and beverages you consumed in a 24-hour period, including listing any supplements you take.

This questionnaire takes 30 minutes. It is the longest test you will need to take for the study.

If there are missing entries or details from your food diary that need to be clarified, the researchers or their research assistant may contact you via phone or email.

We will ask you to take the food questionnaire 2 times, before participating in the study and 16 weeks later.

Report your weight and height

We ask you to complete an online form so you can share both your weight and height.

We will ask you to report your height in centimetres and your body weight in kg.

This self-report will take 5 minutes.

We will ask you to report your height 1 time and weight 2 times, before participating in the study and 16 weeks later.

Take a diabetes management questionnaire

This questionnaire asks you about a range of factors related to your diabetes management.

This questionnaire takes 5-10 minutes.

We will ask you to take the diabetes management questionnaire 2 times, before participating in the study and 16 weeks later.

Share your experience of participation (Group 1 only)

We will ask you to complete an online questionnaire where you can use a scale to rate your experience of using the program and website.

This questionnaire takes 5-10 minutes.

We only ask participants in Group 1 to complete this at the end of the study.

Join a phone interview after the study (Group 1 only - OPTIONAL)

After the study we are interested to interview participants in Group 1 to learn more about their experience during the T2Diet study. This would involve joining a 20-30 minute phone interview with a researcher who will ask you a series of questions.

We will take an audio recording of the phone interview so we don't forget anything that you said and can refer to the recordings later. The audio recordings will then be transcribed and used to help us learn about your experience in the study. Your comments may be used to publish study results but your identity and personal details will always remain confidential.

Benefits and risks to you

The direct benefit to you is that you get to participate in this new program, either now (Group 1) or in future (Group 2), which may help you improve your blood sugar levels and eating plan. Access to this new program is not available anywhere else. Participation is free.

Regardless of whether you're in Group 1 or Group 2 (waiting list), your participation in this research is *very* important, because no web-based study such as this has yet been conducted. This means the results of this study will make a valuable contribution to knowledge that may be used to better support you and other people with type 2 diabetes across Australia.

Potential risks include short-term physical pain or discomfort in taking some of the tests or questionnaires.

For example:

- You may experience short-term pain and discomfort when self-administering the HbA1c finger-prick test.
- You may feel uncomfortable when we ask you to fill in the online forms to share your demographic information such as how long you have had type 2 diabetes, your age, gender, ethnicity, relationship status, employment status and so forth.
- You may feel uncomfortable when we ask you some personal questions related to your eating attitudes, diet, weight or height.
- You may experience short-term physical discomfort when you modify your eating plan. These may include constipation, bad breath, headaches, muscle cramps, tiredness and fatigue, hunger and cravings, or hypoglycaemia. These symptoms are rare but they can occur in some people. We will provide you with education on what the potential symptoms are and how to minimise or manage them.
- If you choose to participate in an interview after the program you may feel uncomfortable

during the interview process. The interviewer will discuss how the interview works and you can pass on any questions you do not want to answer. Participation in an interview is voluntary.

If you experience distress of any kind, please contact the free counseling and support services listed below:

beyondblue
www.beyondblue.org.au
1300 22 4636

Lifeline Australia
www.lifeline.org.au
13 11 14

Your privacy and confidentiality

Your privacy and confidentiality are very important to us.

Participation in this research study is completely voluntary. If you do not wish to take part you are not obliged to, and this decision will not be held against you in any way.

If you decide to take part and later change your mind, you are free to withdraw from the project at any stage up until data analysis commences.

With your permission, the information collected will be retained to ensure that the results of the research project can be measured properly. You should be aware that any information collected by the research team will form part of the research project results. If you withdraw, the information collected will be stored securely but will not be used.

Any information obtained in connection with this research project that can identify you will remain strictly confidential and will only be used for the purpose of conducting the research project. All your results will be labeled with a unique ID code. The researchers will have access to your details and the results obtained from the study, which will be held securely at the Institute for Physical Activity and Nutrition (IPAN), Deakin University. In addition, the HbA1c test company, Nutripath, will be provided with your personal details (name, address, phone, email, DOB, gender) in order to collect your blood sample and assess the results of your HbA1c test. Nutripath data is protected, managed and stored in reference to ISO15189 standards.

Your usage of the website may include provision of a username and password, your email address, tracking of your IP address and website usage. This information is accessible by the research and development team only. To protect your privacy, this website (https://T2Dietstudy.com.au) is hosted on a secure dedicated server, which has DDOS protection and an IP-based firewall. The website is further protected by a private certified Secure Sockets Layer (SSL) and via a restricted access software for participant login and usage purposes. After the study your information will be deleted from the website.

To comply with government requirements all data will be stored securely for a period of 15 years after final publication. It will then be destroyed.

Compensation for your time

All participants completing this study will receive a $30 Coles or Woolworths voucher.

Declaration of funding

Funding for this project has been secured from IPAN PhD student fund (A$ 2500/year awarded to Jedha Dening 2019-2021), a National Heart Foundation Vanguard Grant and an NHMRC Emerging Leader Fellowship grants (Dr Shariful Islam). These funds will be sufficient to purchase the HbA1c test kits, qualitative data transcription and providing participants with $ 30 gift voucher for participation.

Declarations of interests

This research is being conducted by Jedha Dening who is a PhD Candidate at Deakin University. Jedha is also the co-owner of Diabetes Meal Plans (DMP), a web-based type 2 diabetes nutrition service, who licensed the web-platform for this study.

Distribution of the study results

Results of the study will be published in scientific journals and presented in conferences. If you wish to access to the results, you may contact the researchers in the future.

Your information will be non-identifiable in any publication.

Where appropriate or if the opportunity arises, the results of this study may also be disseminated or discussed across social media, in press releases, via consumer or professional publications (online or print), or via radio or TV media.

No identifiable information will be included in any study publication or media. Your details will always remain confidential.

Your access to study results

The HbA1c test company will send you the HbA1c self-test kits and when you post them back using the reply-paid envelope, the company will process the results and we will notify you of the result by email.

At the end of the study, we will email you an overall summary of the findings and outcomes of the research.

Complaints

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about your rights as a research participant, then you may contact:

The Human Research Ethics Office, Deakin University, 221 Burwood Highway, Burwood Victoria 3125, Telephone: 9251 7129, research-ethics@deakin.edu.au

Please quote project number 2020-349

Your consent

If you wish to participate in this study, please click the button below to complete the consent process.

After you provide your consent, you will be redirected to another web form to fill in the eligibility and eating attitudes questionnaires.

After you complete the questionnaires, the researchers will be in touch with you to discuss the next steps.

CLICK HERE TO COMPLETE YOUR CONSENT TO PARTICIPATE

PLAIN LANGUAGE STATEMENT AND CONSENT FORM

TO: PARTICIPANT

Consent Form

Date:

Full Project Title: Web-based diet intervention for adults with type 2 diabetes

Reference Number:

T2Diet Study Participant Consent Form

Please check the boxes below to indicate your acknowledgement:

- I have read the information provided and I understand the study and what my participation involves.
- I am aware I will be randomly allocated to Group 1 (T2Diet program right away) or Group 2 (wait list).
- The researcher has agreed not to reveal my identity and personal details. My identity will remain confidential.
- I give permission for my personal details (name, email, address, DOB, phone, gender) to be shared with the HbA1c test company so they can ship the HbA1c self-test kits to me.
- I give permission for the HbA1c test company to provide the results of my HbA1c tests to the researchers involved in this study.
- I give permission for my data to be reidentified by the research team in the event that there is missing information (e.g., in my self-reported food intake), and to be contacted by the researcher or their research assistant for the purposes of clarifying that information.
- I freely agree to participate in this study according to the conditions outlined.

If you would like to participate in an interview after the study to share your experience during the T2Diet study, please check the boxes below, otherwise leave blank.

- Yes, I give permission to be contacted after the study to attend an interview
- I am aware that my participation in an interview will involve an audio recording and I give my consent to record the interview session. My personal identity will remain confidential.

Please enter your full name

……

Please provide your email address

……

Please provide your mobile phone number
……

Date
……

By clicking the button below, you acknowledge that your participation in the study is voluntary, you are 18 years of age or above, and that you are aware that you may choose to terminate your participation in the study at any time before data analysis commences, and for any reason.

By clicking the button below, you provide your consent to be contacted by the researchers and participate in this study.

- I consent to participate

After you provide your consent above, **please click the arrows below**, you will now be redirected to another page to fill in a questionnaire to confirm your eligibility to participate.

PLAIN LANGUAGE STATEMENT AND CONSENT FORM

TO: Participants

Withdrawal of Consent Form

(To be used for participants who wish to withdraw from the project)

Participation in this research study is completely voluntary. You are free to withdraw from the project at any stage up until data analysis commences.

If you withdraw, the information collected will be stored securely but will not be used.

Project title: Web-based diet intervention for adults with type 2 diabetes

Please enter your full name

……

Email address

……

Date

……

Please check the box below to withdraw your consent, then click the arrow below to submit this form.

- ○ I hereby wish to WITHDRAW my consent to participate in the above research project and understand that such withdrawal WILL NOT jeopardise my relationship with Deakin University or the researchers.

BMJ Open

Randomized controlled trial of a web-based low carbohydrate diet intervention for adults with type 2 diabetes: The T2Diet study protocol

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Randomized controlled trial of a web-based low carbohydrate diet intervention for adults with type 2 diabetes: The T2Diet study protocol

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Abstract

Introduction: Type 2 diabetes (T2D) management frequently involves a multidisciplinary care team. However, standard care for T2D patients is the central role of the general practice physician, and consists of routine appointments to monitor glycemic status and overall health. Dietary modification is an essential component of T2D management. Evidence suggests a low carbohydrate diet (LCD) provides better clinical outcomes for people with T2D compared to other diets. However, providing dietary support in face-to-face settings is challenged by issues of availability and accessibility. Provided in conjunction with standard care, digital interventions can help bridge this gap. The objective of this paper is to describe the protocol of a randomized controlled trial (RCT) of a web-based intervention that will evaluate the effectiveness of standard care plus web-based LCD intervention when compared to standard care only.

Methods and analysis: In a two-arm parallel RCT, 100 adults with non-insulin-dependent T2D aged between 40-89 years will be randomized to either a theoretically-informed 16-week automated web-based LCD intervention plus standard care or standard care only. LCD recommendations emphasize consuming nutrient-dense whole foods and encourage a daily carbohydrate goal of 50-100 grams, with an objective of achieving 10-<26% carbohydrates from total energy intake. Assessments will take place at baseline and 16-weeks. The primary outcome will be hemoglobin A1c (HbA1c). Additional data collected will include dietary intake, self-efficacy, weight and height, anti-diabetes medication and dosages, and diabetes-related comorbidities. Process evaluation will consist of a mixed-methods assessment of website engagement metrics, user experience, and participants' perspectives.

Ethics and dissemination: All study procedures have been approved by the Deakin University Human Research Ethics Committee (2020-349). Study findings will be disseminated widely through public, professional, and academic presentation and publication.

Trial registration: The trial has been prospectively registered with the Australian New Zealand Clinical Trials Registry (ACTRN12621000096853).

Keywords: Type 2 diabetes, low carbohydrate diet, glycemic control, self-management, web-based, HbA1c.

Strengths and limitations of this study

- To the best of our knowledge, this is the first RCT to evaluate the effectiveness of a web-based low carbohydrate diet (10-<26% energy intake) intervention on glycemic control in adults with type 2 diabetes.
- A key strength of the study is the randomized controlled design and robust outcome assessment using hemoglobin A1c that will minimize bias and maximize the validity of the study findings.
- One limitation is no long term follow up, as this was not feasible for this study.

Introduction

The global burden of T2D was estimated at 462 million individuals in 2017 [1]. Due to metabolic changes, T2D results in high glycemic status, frequently measured by HbA1c. The primary treatment goal is to assist people with T2D to achieve a HbA1c below 7.0% [2]. However, in 2020, estimates indicated 50% of adults with T2D had uncontrolled T2D, with HbA1c levels above the treatment goal [3]. Uncontrolled T2D significantly contributes to the development of diabetes complications and mortality [3]. Management of T2D frequently involves engagement of a multidisciplinary healthcare team to ensure the needs of individuals are met comprehensively. However, the general practice physician (GP) plays the central role in providing standard care for T2D management [4]. Standard care for patients with T2D consists of routine health checks with their GP to monitor glycemic status, diabetes complications and overall health [2, 4]. In addition, guidelines suggest healthy behavior should be routinely encouraged before or in conjunction with pharmacological treatment if necessary [2, 4].

Dietary modification plays an integral role in diabetes management, in improving glycemic control and overall health [2]. In terms of diet, a low fat, moderate-high carbohydrate diet has traditionally been a common dietary recommendation provided to people with T2D [4, 5]. However, a growing body of evidence has demonstrated that LCDs, defined as 10-<26% carbohydrate of total energy intake [6, 7], may be more optimal for improving clinical outcomes in people with T2D [6, 8, 9]. LCDs had previously been viewed as controversial. However, the growing body of evidence has prompted updates across international diabetes care guidelines, which have acknowledged LCDs as a safe and viable dietary option for people with T2D [2, 10-12]. Systematic reviews and meta-analyses of LCDs in people with T2D have consistently demonstrated greater improvements in glycemic control, increases in HDL cholesterol, decreases in triglycerides, reduced medication requirements [6, 8, 9, 13, 14], and potential for diabetes remission [9]. In addition, significant improvements have been demonstrated in people with T2D provided with LCD recommendations through routine clinical care [15].

LCD interventions for people with T2D have typically been delivered in face-to-face settings [8]. However, people with T2D face substantial challenges in accessing dietary support due to limited availability, accessibility, and cost barriers [2, 16-18]. Provided in conjunction with standard care, web-based interventions can help bridge this gap, offering the potential for greater reach and accessibility, with the advantage of being convenient and on-demand to participants when required [19]. Systematic reviews of web-based comprehensive self-management interventions in people with T2D have demonstrated favorable improvements in glycemic control [20-22]. Preliminary evidence suggested web-based dietary interventions may be an effective way to support dietary change and improved glycemic status in adults with T2D [23]. Furthermore, web-based interventions in people with T2D have shown promise as a cost-effective option [24], with the capacity to be widely implemented to support routine primary care [25]. No RCT to date has assessed the effectiveness of a LCD intervention in individuals with T2D, delivered in a web-based setting.

The study protocol for a RCT of a web-based LCD program for adults with T2D is presented here. The primary aim of this study is to determine the effectiveness of a web-based LCD intervention on glycemic control in adults with T2D. We hypothesize that the web-based LCD

intervention plus standard care will result in better glycemic control—lower HbA1c levels—at 16 weeks compared to standard care alone in adults with T2D. Secondary aims are to assess changes in dietary intake, self-efficacy, weight and body mass index (BMI), anti-diabetes medication and diabetes-related comorbidities; and to assess process outcomes related to user engagement and experience.

Methods

Study design

The T2Diet study is a 16-week two-arm parallel RCT that aims to investigate the effectiveness of a web-based LCD intervention plus standard care versus standard care alone on glycemic control in 100 Australian-based adults with T2D (Figure 1). A period of 16 weeks was chosen as previous web-based dietary interventions demonstrated significant improvements in glycemic control could be achieved within this timeframe [23].

Inclusion criteria will be adults aged 40-89 years, the most highly affected demographic for T2D in Australia [26], with self-reported non-insulin-dependent T2D and self-reported HbA1c levels ≥7.0% within the previous six months; access to the Internet; an active email address; able to read and understand English; based in Australia; and willing and able to provide informed consent. All eligible participants with self-reported HbA1c levels ≥7.0% within the previous six months will be included, once baseline HbA1c measurements are conducted any reports returned as normal ≤5.6% [2] will result in participants being excluded. Exclusion criteria will be people with type 1 diabetes, prediabetes or gestational diabetes; people with diagnosed renal or cardiovascular disease; people with a terminal disease or severe complications compromising the quality of life of the participant and their ability to participate according to the protocol; women who are pregnant or lactating; people who have undergone bariatric surgery; vegetarians or vegans; people currently on a weight loss program or who have taken a weight loss program within the past 3 months; people enrolled in other clinical studies; and people at risk of disordered eating, assessed during screening with the Eating Attitudes Test-26 [27, 28]. Participants identified with potential eating disorders will be referred to The Butterfly Foundation National Helpline [29]. Informed consent will be obtained from eligible participants prior to entry into the study.

Figure 1. Study flow chart

Intervention

The intervention is a theoretically informed 16-week automated web-based LCD behavior change support program. Existing website resources were provided for this study. Subsequently, four phases of inquiry were conducted with end-users (adults with T2D) to inform development of the new web-based dietary intervention. The weekly behavior change modules adopt various behavior change techniques [30] and were constructed upon a theoretical framework, consisting of: 1) self-efficacy theory [31]—self-efficacy being a key determinant of self-care behaviors and glycemic control in T2D [32-35]; 2) positive message framing—using language that communicates benefits rather than scare tactics [36, 37]; and, 3) principles of persuasive technology—using technology as a means of persuasively communicating intervention content [38].

Dietary recommendations

Intervention participants will receive web-based recommendations to consume an *ad libitum* LCD [13], and encouraged to consume between 50-100 grams carbohydrates per day [6]. The overall goal is to achieve a low carbohydrate intake, defined as 10-<26% total energy intake [6, 7]. Web-based resources emphasize high consumption of non-starchy vegetables, adequate dietary fiber, and selection of nutrient-dense sources of lower carbohydrate foods [2]. Participants will be instructed to avoid or minimize high carbohydrate food and beverage sources such as added sugar, sugar-sweetened beverages [2, 5, 39], starchy foods [15, 40], and discretionary foods [2, 5, 39]. There will be no specific prescription for other macronutrients. However, based on estimated energy intake for the demographic of this study ranging from 1600 calories/6694 kilojoules to 2400 calories/10041 kilojoules [41], the protein and fat ranges are estimated to fall between 60-180 grams (15-30% estimated energy intake) and 80-200 grams (45-75% estimated energy intake), respectively [2, 42-44]. Web-based recommendations encourage nutrient-dense sources of protein and fat [15, 40], emphasizing consumption of polyunsaturated and monounsaturated fat [2, 39], and suggesting reduced-fat dairy may be preferred [45]. To facilitate implementation, skills-based resources such as recipes, information

on T2D, food and beverage choices, menu examples, eating out tips, menu planning and food preparation tips, an interactive planner, and cooking demonstrations will be provided.

Web-based intervention delivery

Intervention participants will be provided with login details for the study website to access the weekly modules and on-demand resources. The weekly modules consist of short videos with brief overviews, links to further resources, recipe suggestions, and action steps (Figure 2). These delivery methods, particularly the use of video, have been shown to address various levels of literacy [46], enhance engagement [47], and support health behavior change [48]. The weekly modules will be delivered sequentially, however, participants can continue to access any previous weeks' modules, along with accessing on-demand resources at any time. To prompt website usage and performance of behavioral actions, reminders will be sent to participants via email twice per week [46, 49]. It is estimated participants will login to the website once per week.

Adverse effects

Intervention participants will be provided with education about and resources on how to manage potential adverse effects of carbohydrate reduction, such as constipation, headache and brain fog, halitosis, muscle cramps, tiredness and fatigue, hunger and cravings, and heart palpitations [15, 50]; temporary hypoglycemic-like symptoms; hypoglycemia, defined as a blood glucose level <70mg/dL/<4.0mmol/L—emphasized for any participant taking sulfonylurea medications [51]; and to identify symptoms of ketoacidosis, for any participant taking sodium glucose cotransporter 2 inhibitor medications [2, 51]. Participants will be able to report adverse effects via an online form. If participants request assistance, they will be directed to appropriate resources, and/or, advised to consult with their treating physician. Any adverse effects will be documented and reported with trial outcomes.

Intervention group follow-up

Approximately three days after being provided with login details for the study website, intervention group participants will be followed up by email or phone to draw their attention to the potential adverse effects of carbohydrate reduction, cautions regarding medications, and to

encourage participants to discuss their participation in the study with their GP and healthcare team. Participants will be able to download a study information letter they can give to their GP or healthcare team.

Standard care

Participants in both groups will be advised to continue with their standard care, defined by the Royal Australian College of General Practitioners [4], as routine appointments with their physician to monitor glycemic control, diabetes complications, and other health parameters.

Control condition

The control group will be standard care, as defined above. Participants in the control group will be on a waitlist and provided with the opportunity to participate in the intervention after completing the study.

Figure 2: Presentation format of the weekly behavior change modules

Outcomes

Primary and secondary outcomes will be measured at baseline and immediately post-intervention (16 weeks). An overview of study measures, data collection instruments and their timepoints is presented in Table 1. The primary outcome will be glycemic control measured by the mean difference of change in HbA1c between intervention and control group from baseline to 16 weeks. For secondary outcomes, dietary intake data—food, beverages and dietary supplements, will be collected to assess participants' adherence to the recommended LCD. We will also explore improvements in the quality of the participants' diet such as changes in discretionary food intake and vegetable consumption, and changes to individuals' overall macro and micronutrient intake and food groups. In addition, we will explore the association between adherence to diet and glycemic control. Self-efficacy will be measured to assess whether participants' self-efficacy improves and whether self-efficacy predicts and promotes greater changes in glycemic control [32-35]. Weight and height will be collected to assess change in

weight and BMI (kg/m^2). Anti-diabetes medication and dosages and diabetes-related comorbidities [4] will be collected to assess changes.

Process evaluation

Post-intervention, a mixed-methods approach [52] will be used to explore website utilization, user engagement and experience, in the intervention group only. Two forms of quantitative data will be collected: 1) website and email usage rates for frequency, intensity and duration metrics [53], collected for each week of the 16-week intervention; and 2) a self-administered questionnaire using the User Engagement Scale short form [54] and Honeycomb Model [55, 56]. To collect qualitative data, a maximum of 20 participants [57] will be invited to attend a semi-structured phone interview. Process evaluation will be reported separately to the primary and secondary outcomes of this trial.

Table 1. Summary of outcome measures, data collection instruments and timepoint

Measures	**Instrument**	**Timepoint**	
		Baseline	**16 weeks**
Demographic information	Structured questionnaire, self-reported via an online request form.	X	
Primary outcome			
Hemoglobin A1c (%)	Collected and assessed using the Nutripath Integrative Pathology Services HbA1c test.	X	X
Secondary outcomes			
Dietary intake: food, beverage and dietary supplements	Assessed via self-reported 24-hour food recall using study-specific online questionnaire, analysis using FoodWorks professional nutrition software.	X	X
Self-efficacy	Self-reported via an online request form using the Diabetes Management Self-Efficacy Scale—Australian version [58].	X	X
Weight/BMI	Self-reported weight and height, via a study-specific online request form.	X	X
Anti-diabetes medication and dosages	Self-reported, via a study-specific online request form.	X	X
Exploratory outcome			
Diabetes-related comorbidities	Self-reported, via a study-specific online request form.	X	X
Process outcomes (Intervention group only)			
Website utilization	Website and email usage metrics.	◄	►

User engagement and experience	Self-reported using the User Engagement Scale short form [54] and Honeycomb Model [55, 56], via an online request form.		X
Participants' experience	Semi-structured phone interviews with up to 20 participants.		X

Sample size

A total of 100 participants (50 per group) will provide 80% power at *type I error of 0.05* to detect a between-group difference of 0.5% on HbA1c (primary outcome). The sample size is based on the following assumptions: a standard deviation of 0.9 HbA1c [59, 60], a pre-post intervention correlation of 0.5 [61], and a dropout rate of 20% [62, 63]. The effect size of 0.5% was chosen as it is considered a clinically meaningful HbA1c reduction [64]. This may seem large for a relatively short intervention. However, it is not vastly different to previous LCD studies in people with T2D, where 6-month durations with smaller sample sizes demonstrated reductions in HbA1c of approximately 0.6% [59, 60, 65]. Previous LCD studies have indicated low dropout rates (<10%) [60, 65] and the average dropout across five web-based dietary interventions in people with T2D was approximately 22% [23]. Therefore, a 20% dropout was considered reasonable for this study. The sample size calculation was conducted by an independent statistician using Stata's power twomeans command.

Recruitment

Enrolment of 100 participants will occur nationally across Australia using social media (primarily Facebook, Twitter and Linkedin); networking with colleagues and acquaintances; community publications, newsletters or radio; through diabetes clinics, community organizations, fitness centers or medical centers; snowballing; and if necessary, paid online advertising via Facebook. All recruitment channels will direct interested participants to a plain language statement webpage where participants can voluntarily provide their informed consent. After giving informed consent, participants are immediately redirected to the eligibility screening questionnaire. Eligible participants will then be required to complete all baseline measurements (Table 1) before being randomized to their allocated group. Following intervention completion at 16-weeks, participants will be required to complete the same measurements, excluding

demographic details and height (Table 1). Recruitment started in February 2021 and is expected to be completed by December 2021.

Assignment of interventions

Participants will be randomized in a 1:1 ratio to standard care (control group) or standard care plus web-based LCD intervention (intervention group) using block randomization with varying random block sizes and stratified by age and gender. A computer-generated predetermined randomization schedule will be produced and held off-site by an independent statistician, who will indicate the group allocation as eligible participants are recruited. The group allocation will be concealed from researchers and participants until all baseline measures have been collected and the independent statistician has conducted the randomization. Post intervention outcomes, except the primary outcome, will be assessed via participant self-report. Primary outcome assessment will be blinded as HbA1c samples are assessed by the pathology lab with no disclosure of group allocation. Data analysts will be blinded to group allocation.

Data collection tools

Aside from HbA1c, all points of data collection will occur online through structured questionnaires with self-reported entries, for both groups. Demographic information such as age, gender, duration of T2D, family history of T2D, country of birth, employment status, education level, relationship status, and smoking status will be collected at baseline for descriptive purposes.

HbA1c will be assessed by Nutripath Integrative Pathology Services. Participants will be sent the HbA1c microsample self-administered test. Participants unable to collect a sufficient self-administered sample will be sent the HbA1c pathology-assisted blood draw test. In both instances, the HbA1c test kits will be mailed to participants and back to the pathology service. HbA1c is the most common clinical biomarker used to assess glycemic control in RCTs that include people with T2D [8].

Dietary intake will be assessed using 24-hour food recall, a comprehensive self-report instrument that is considered highly robust [66]. An online 24-hour food recall questionnaire will collect

participants' self-report of foods, beverages, and supplements consumed in the previous 24-hour period. Submissions will be reviewed and if necessary, participants will be contacted for additional detail. FoodWorks professional nutrition analysis software for Australia and New Zealand will be used.

Self-efficacy will be measured using the Diabetes Management Self-Efficacy Scale—Australian version [58], which has been validated for use in people with T2D in Australia. The scale contains 20 questions rated on a 10-point scale. Responses are then summed to present a single self-efficacy score. Higher scores indicate greater self-efficacy.

Self-reported weight and height, anti-diabetes medication and dosages, and diabetes-related comorbidities will be collected. Online self-reported weight and height has been demonstrated to be a valid method [67]. The checklist of comorbidities was drawn from the Royal Australian College of General Practitioners guidelines on general practice management of T2D [4]. Reductions in anti-diabetes medication are commonly reported in LCD studies in people with T2D [8, 13, 14]. It has been noted that this reflects an underestimation in the overall benefits of LCDs [68, 69]. Thus, consideration of the influence of medication requirements needs to be taken into account. The Medication Effect Score will be used to quantify and summarize the changes in anti-diabetes medication [70].

Participant retention and withdrawal

To accommodate any loss, multiple imputations will be used to handle the missing data (either as primary or sensitivity analysis), using available data to minimize potential bias of estimated intervention effects due to non-random attrition. In addition, when measurement data is due/overdue, emails and/or text message reminders and phone calls to participants will be made. All participants completing this study will receive a $30AUD shopping voucher. Participants are free to withdraw from the study for any reason, up until data analysis commences.

Data management and protection against bias

Significant measures have been put in place to ensure robust data management and integrity and protect against bias. Primary outcome reports and self-reported data files will be downloaded in

their wholly original unmodified form by the principal investigator and securely stored in a location inaccessible to other research team members. These original data files will not be modified. Copies of original data files will be provided to research team members as required. Data that requires manual entry will be crosschecked against copies of the original data files by a second research team member. An independent statistician will be provided with a copy of the original or crosschecked data files to collate and clean the dataset in preparation for data analysis. Once complete, the coded, de-identified dataset will be securely stored by the principal investigator, as the lockdown dataset files, in a location inaccessible to other research team members. These lockdown dataset files will not be modified. Copies of the lockdown dataset will be shared with research team members as required. A dedicated study statistician will be provided with a copy of the lockdown dataset files to conduct the data analysis independently.

Monitoring

Overall study monitoring occurs via monthly meetings involving the research team members.

Data availability statement

Data will be available upon reasonable request.

Statistical methods

All data will be imported into Stata for quantitative analysis. Baseline characteristics will be presented using descriptive statistics. The mean and standard deviation, or median and range, will be used to describe continuous variables. Frequencies and/or percentages will be used to describe categorical variables. Intervention effects (i.e., mean difference between intervention and control group) at 16 weeks will be evaluated by implementing an ANCOVA model for each outcome with the 16-week value of the outcome as the dependent variable, and treatment group and baseline outcome score as independent variables, and adjusting for stratification variables (age and gender). Multiple imputation techniques with missing at random assumption will be used to impute missing data due to dropouts or withdrawals to comply with the intention-to-treat approach. Sensitivity analysis will be performed to evaluate missing at random assumption for missing observation pattern. Subgroup analysis will be conducted with the duration of diabetes and gender. For the duration of diabetes, a median split will be used to define subgroups. P-value

0.05 will be used as the level of significance for the primary outcome and all secondary outcomes. Cohen's D effect size will be calculated and reported. For all continuous outcomes, data will be explored for deviation from the normal distribution assumptions. If necessary, a transformation of data (e.g., log transformation) or a non-parametric approach may be considered.

Patient and public involvement

Participants (adults with T2D) were engaged in four iterative phases of user-centered inquiry involving group discussions, which informed the development of the new web-based dietary intervention. Intervention participants will be involved in feedback during process evaluation.

Ethics and dissemination

All study procedures have been approved by the Deakin University Human Research Ethics Committee (2020-349). Any protocol amendments will be submitted for approval to the ethics committee prior to implementation and communicated via an update of the Australian and New Zealand Clinical Trial Registry.

Key audiences this research may benefit include the general public, researchers, clinicians, policymakers, and healthcare organizations [71-73]. Various methods may be used to disseminate the findings, including peer-reviewed publication, presentations, consumer and professional publication, and social media [73, 74]. Participants involved in the study will be sent a summary report of the study's main outcomes via email. In any dissemination of research findings, participants' identities will remain confidential.

Limitations and strengths

One limitation is this study will not collect biomarkers related to cardiometabolic risk, which was beyond the scope of this trial. While more research is needed in this area, the overall evidence suggests LCDs may be associated with cardiovascular benefits, as commonly a reduction in triglycerides and an increase in HDL cholesterol are observed [6, 8, 13, 68, 69]. For LDL cholesterol, the evidence remains unclear due to mixed reports [9, 75-77]. In addition, blood pressure can be influenced by LCDs [78]. Given this web-based dietary intervention will be provided in conjunction with standard care, biomarkers such as lipid profiles and blood

pressure would continue to be routinely monitored by the participants GP or healthcare team. The short duration of this trial is also a potential limitation. However, the duration was justified based on previous web-based dietary interventions [23], and given this will be the first RCT of a web-based LCD intervention, determining effectiveness prior to allocating additional time and resources will be important. Another potential limitation is the study will not measure other lifestyle-related factors such as physical activity or psychological well-being [2]. The intervention was not designed to influence these outcomes, and any differences should be adequately addressed through random distribution in an RCT design. In addition, improvements related to hunger and satiety have been previously noted in LCD studies [68, 69], though will not be collected for this trial. This study also has significant strengths. While only one primary biomarker will be included, it will enable this research to be conducted remotely. This makes the study highly feasible during COVID-19 when restrictions of movement and face-to-face contact can be limited. In addition, remote delivery will increase the capacity to include participants from wide geographical locations, which will be of benefit given support for people with T2D in rural and remote areas is less accessible [79]. Furthermore, the RCT design, allocation concealment and blinding are key strengths that will minimize bias and maximize the validity of the study findings.

Discussion

This study will conduct a RCT of standard care alone versus standard care plus web-based LCD intervention in adults with T2D, with the primary intervention objective of improving glycemic control. To meet the needs and context of end-users who will participate in the study, user-centered principles and involvement of end-users in numerous rounds of feedback and iterative development were employed. The weekly behavior change modules apply various behavior change techniques and were constructed upon a theoretical framework to help strengthen communication of the intervention, address literacy levels, and maintain engagement. In addition, the email reminder notifications aim to boost website usage and motivation to participate.

This study will be the first RCT of a LCD intervention for adults with T2D, delivered in a web-based setting. The findings will contribute valuable insights into whether a LCD is effective

when delivered in a web-based environment; and whether such an intervention could be considered to support T2D management more broadly. Further, this study will contribute new knowledge to inform future digitally-delivered dietary interventions that could be used to reach a greater number of people with T2D and other health conditions across Australia and internationally.

Acknowledgment

We thank Dr Gavin Abbott and Professor Ralph Maddison from Deakin University Institute of Physical Activity and Nutrition for their contributions.

Funding

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Conflicts of Interest

JD is co-owner of Diabetes Meal Plans, a web-based nutrition support service for people with type 2 diabetes and prediabetes, who licensed the web-platform for this study.

Authorship

JD conceived and designed the study and wrote the manuscript. SI, EG, KB made critical contributions to the study design and provided critical input and revisions to the manuscript. MM contributed to the study design and provided critical revisions of the manuscript. All authors provided final approval for submission of the manuscript.

Abbreviations

BMI: body mass index

GP: general practice physician

HbA1c: hemoglobin A1c

LCD: low carbohydrate diet

RCT: randomized controlled trial

T2D: type 2 diabetes

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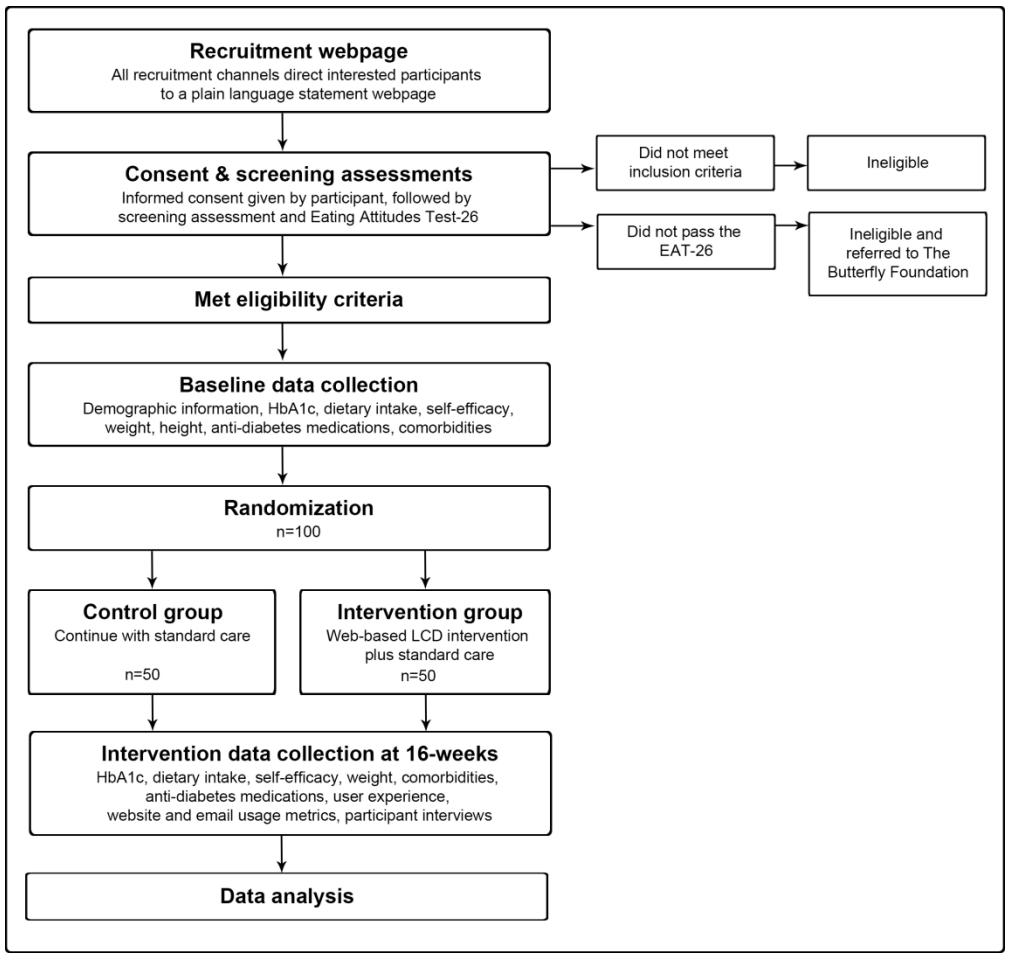
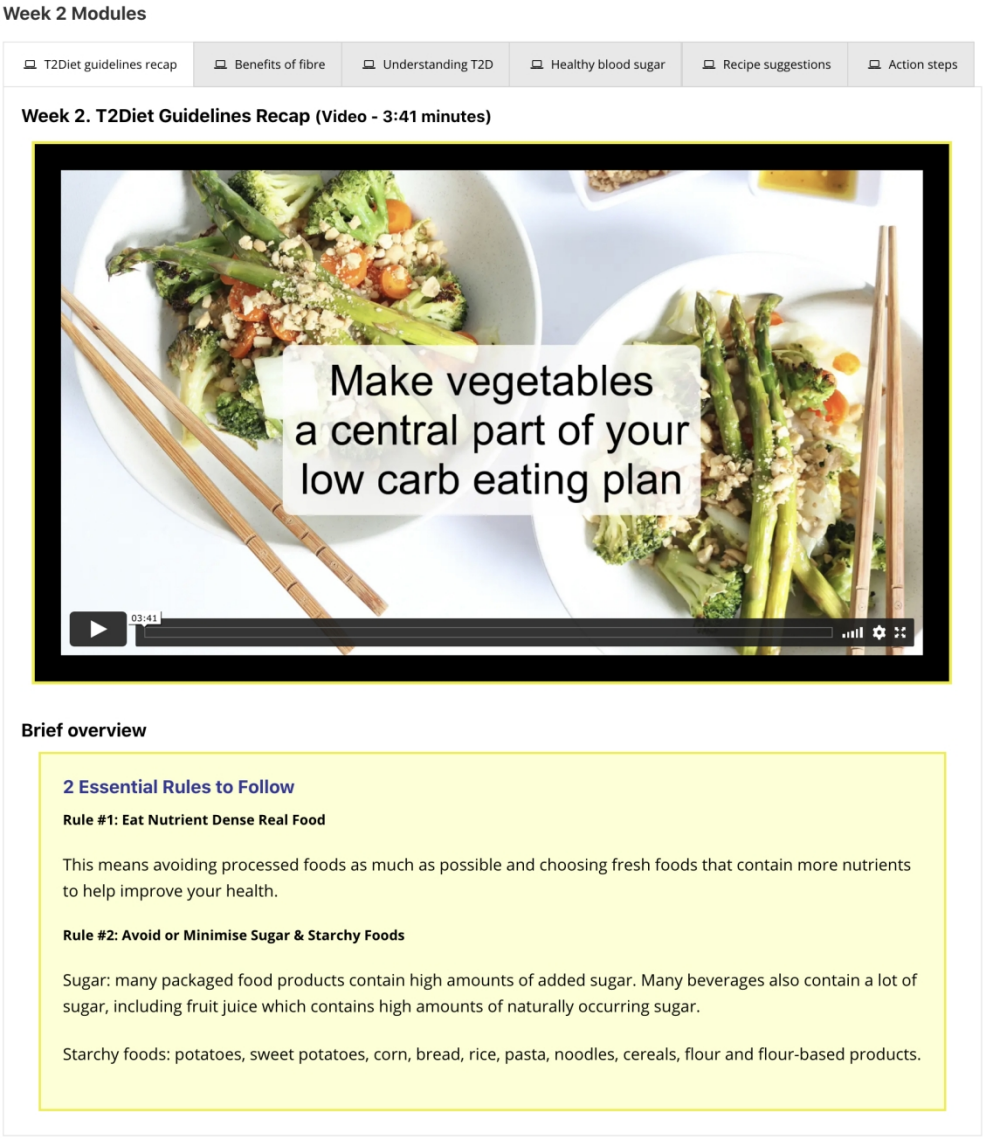


Study flow chart

201x190mm (300 x 300 DPI)



Presentation format of the weekly behavior change modules

324x372mm (144 x 144 DPI)

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	NA
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 17
	5b	Name and contact information for the trial sponsor	NA
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	NA
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	14

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-5
	6b	Explanation for choice of comparators	3-5
Objectives	7	Specific objectives or hypotheses	4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4, 5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5, 11
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	6-8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8-10, 12-13
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	__11_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	___11_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_11-12_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_11-12_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11-12_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	___12_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	____NA_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_12-14_____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	____13_____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13-14
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	7
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	15

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.