
Evidence Brief: Virtual Diet Programs for Diabetes

August 2020

Prepared for:

Department of Veterans Affairs
Veterans Health Administration
Health Services Research & Development
Service
Washington, DC 20420

Prepared by:

Evidence Synthesis Program (ESP)
Coordinating Center
Portland VA Health Care System
Portland, OR
Mark Helfand, MD, MPH, MS, Director

Authors:

Stephanie Veazie, MPH
Kathryn Vela, MLIS
Mark Helfand, MD MPH



U.S. Department of Veterans Affairs

Veterans Health Administration
Health Services Research & Development Service



PREFACE

The VA Evidence Synthesis Program (ESP) was established in 2007 to provide timely and accurate syntheses of targeted healthcare topics of importance to clinicians, managers, and policymakers as they work to improve the health and healthcare of Veterans. These reports help:

- Develop clinical policies informed by evidence;
- Implement effective services to improve patient outcomes and to support VA clinical practice guidelines and performance measures; and
- Set the direction for future research to address gaps in clinical knowledge.

The program is comprised of three ESP Centers across the US and a Coordinating Center located in Portland, Oregon. Center Directors are VA clinicians and recognized leaders in the field of evidence synthesis with close ties to the AHRQ Evidence-based Practice Center Program and Cochrane Collaboration. The Coordinating Center was created to manage program operations, ensure methodological consistency and quality of products, and interface with stakeholders. To ensure responsiveness to the needs of decision-makers, the program is governed by a Steering Committee comprised of health system leadership and researchers. The program solicits nominations for review topics several times a year via the [program website](#).

Comments on this evidence report are welcome and can be sent to Nicole Floyd, Deputy Director, ESP Coordinating Center at Nicole.Floyd@va.gov.

Recommended citation: Veazie S, Vela K, Helfand M. Evidence Brief: Virtual Diet Programs for Diabetes. VA ESP Project #09-199; 2020. Posted final reports are located on the ESP [search page](#).

This report is based on research conducted by the Evidence Synthesis Program (ESP) Coordinating Center located at the Portland VA Health Care System, Portland, OR, funded by the Department of Veterans Affairs, Veterans Health Administration, Health Services Research and Development. The findings and conclusions in this document are those of the authors who are responsible for its contents; the findings and conclusions do not necessarily represent the views of the Department of Veterans Affairs or the United States government. Therefore, no statement in this article should be construed as an official position of the Department of Veterans Affairs. No investigators have any affiliations or financial involvement (eg, employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties) that conflict with material presented in the report.

TABLE OF CONTENTS

Executive Summary	1
Key Findings	1
Introduction.....	6
Purpose.....	6
Background.....	6
Scope.....	8
Key questions.....	8
Eligibility criteria.....	9
Methods.....	10
Searches and Study Selection	10
Quality Assessment & Data Extraction	10
Strength of Evidence Assessment.....	10
Synthesis of Data	10
Results.....	12
Literature Flow.....	13
Part I: Programs Promoting a Named Diet	16
Overview.....	16
TeLiPro (Meal Replacement Diet).....	17
Virta Health (Ketogenic Diet).....	17
Low Carb Program (Low Carbohydrate Diet).....	19
Better Therapeutics (Plant-based Diet).....	20
Part 2: Programs that Promote Healthy Eating Based on Guidelines.....	21
u-Healthcare (US & South Korea Guidelines).....	22
ANODE (France Guidelines).....	23
Our Path (UK. Guidelines)	24
GlycoLeap (US and Singapore Guidelines).....	24
Part 3: Programs that Promote Healthy Eating Not Based on Named Diet or Guideline.....	25
Overview.....	25
My Dietitian.....	26
Noom Coach	27
Unnamed Programs.....	28
DiabMemory + Nutrinaut	28
Summary and Discussion.....	30

Limitations	31
Gaps and Future Research	32
Conclusions.....	34
Acknowledgments.....	35
Operational Partners.....	35
Key Informants	35
References.....	36

FIGURES AND TABLES

Table 1. Summary of Findings.....	3
Figure 1: Literature Flowchart	13
Table 3. Overview of Studies on Virtual Diabetes Diet Programs	14
Table 4. Detailed Findings from Studies of Named Diet Programs	16
Table 5. Detailed Findings From Studies of Programs That Promote Healthy Eating Based on Guidelines	21
Table 6. Detailed Findings From Studies of Programs That Promote Healthy Eating not Based on Diabetes or Dietary Guidelines.....	25

EXECUTIVE SUMMARY

Key Findings

- 15 studies (9 RCTs, 1 non-randomized controlled trial, 3 single-arm longitudinal studies, and 2 pre-post studies) evaluated 14 virtual diabetes diet programs with a coaching component.
- In a single study that was poorly controlled, selected participants (*ie*, those who were severely obese, interested in an intensive diabetes management program, and willing to adhere to the ketogenic diet) experienced improvements in weight and HbA1c after participating in the Virta Health program for 10 weeks and maintained improvements if they continued to participate in the program for 2 years. Some of these participants also stopped taking medications and reversed their diabetes.
- In 1 RCT, 1 longitudinal study, and 1 before-after study, participants in 3 other programs (TeLiPro, Low Carb Program, and Better Therapeutics) experienced improvements in 2 diabetes-related outcomes (*ie*, lowering HbA1c > .5%, weight loss > 5%, and/or diabetes medication cessation) between 3 months to 1 year after program initiation. In 5 RCTs, 1 longitudinal study and 1 before-after study, participants in 6 other programs (u-Healthcare, Our Path, GlycoLeap, Noom Coach, and 2 unnamed programs) experienced improvements in 1 diabetes-related outcome (either lowering HbA1c or weight loss) between 3 and 6 months after program initiation. Those who participated in Noom Coach also had higher rates of diabetes reversal than controls.
- Data on harms were sparse. Only studies of Virta Health, Better Therapeutics, and Noom Coach reported that no severe or serious treatment-related harms occurred.
- As health systems like the VA begin to implement virtual diabetes coaching programs, evaluations should emphasize creation of appropriate control arms; ensuring comparable long-term follow-up data; and attention to possible harms. Since evidence isn't clear which features of programs are most critical, a health system might also wish to compare virtual programs delivering different types of diets.

Background

The ESP Coordinating Center (ESP CC) is responding to a request for a rapid review on virtual diet programs for diabetes from the VA Health Services Research & Development (HSR&D). Findings from this evidence brief will be used to inform an evaluation of the Virta Health program among Veterans with type 2 diabetes.

Methods

To identify studies, we searched MEDLINE, CINAHL and Cochrane Central Register of Controlled Trials (CENTRAL). We used prespecified criteria for study selection, data abstraction, and rating internal validity and strength of the evidence. See our PROSPERO protocol for our full methods (Registration # CRD 42020180278).

In recent years, the ketogenic diet has become an increasingly popular option for people looking to lose weight, including those with type 2 diabetes. The ketogenic diet is a low carbohydrate, high fat diet, where approximately 70% of an individual's calories come from fat, 20% from protein, and 10% or less from carbohydrates. Proponents of the diet point to studies indicating it can help with weight loss, improve cholesterol and blood pressure, reduce the need for medications, and potentially reverse diabetes, while skeptics have pointed out there are no long-term (>1 year) studies on the ketogenic diet, so it is unclear whether these benefits are maintained over time and if there are any long-term risks.

Virta Health is an online platform that delivers a ketogenic diet intervention – as well as education, coaching and physician management of medications – for people with type 2 diabetes. In 2019, Virta Health and the VA initiated a pilot project in which 400 Veterans with type 2 diabetes were given access to the Virta Health program. On its website, Virta claims that 84% of Veteran patients on the Virta treatment for 90 days achieved glycemic outcomes below the diabetes threshold or at least a 1-point drop in HbA1c (a measure of blood sugar). No data from Virta's VA pilot project have been published, so this claim cannot be verified. A separate, single-center, open-label, nonrandomized controlled study that provides the only evidence about the Virta program indicates that program participants can lose weight, lower HbA1c, discontinue medications, and reverse diabetes. This study, which is expected to be completed in 2021, has important limitations, and it is unclear how this program compares to other programs that deliver similarly comprehensive, continuous remote care. If properly designed, the VA's ongoing evaluation of the Virta VA pilot could address important gaps in the evidence about Virta. Virta's ongoing evaluation might also close some gaps. Furthermore, the VA is contemplating expanding virtual diet programs and will need to design a prospective evaluation to assess the impact of whatever program is selected.

We conducted a rapid evidence review assessing the last 5 years of research on the Virta Health program and other similar programs, focusing on weight loss, HbA1c, and medication reduction, the outcomes that have been emphasized by Virta and proponents of other virtual programs. We also focused on harms. In addition to the study of Virta, we identified 9 RCTs, 3 single-arm longitudinal studies, and 2 pre-post studies of 13 other virtual diabetes diet programs (Table 1). Studies examined 3 types of programs:

1. Programs that promote a named diet (*ie*, one where certain categories of food or macronutrients are limited, such as the ketogenic diet, low carbohydrate diet, or plant-based diet).
2. Programs that promote healthy eating based on a diabetes or dietary guideline.
3. Programs that promote healthy eating not based on a named diet or guideline.

Overall, although the study of Virta had important limitations, it suggests that for some patients (*ie*, those who are severely obese, interested in an intensive diabetes management program, and willing to adhere to the ketogenic diet), participation in Virta Health is associated with improvements in diabetes outcomes such as weight and HbA1c at 10 weeks. Some participants of the program also stopped taking medications and reversed their diabetes. These outcomes were maintained for up to 2 years in patients who continue to participate in the intervention. Three other virtual diet programs for diabetes (TeLiPro, Low Carb Program, and Better

Therapeutics), all of which delivered a named diet, were associated with a clinically significant improvement in 2 diabetes outcomes (*ie*, lowering HbA1c $> .5\%$, weight loss $> 5\%$, and/or diabetes medication cessation) between 3 months and 1 year after initiation. Participants in 2 of these programs (TeLiPro and Low Carb Program) maintained improvements for 1 year (in 1 program the intervention ended at 12 weeks, and in the other the intervention continued for a year). Although benefits were more limited, 6 additional virtual diet programs (u-Healthcare, Our Path, GlycoLeap, Noom Coach, and unnamed programs from Wayne 2015 and Sun 2019) were associated with a clinically meaningful improvement in 1 diabetes-related outcome (either lowering HbA1c $> .5\%$ or weight loss $> 5\%$) between 3 and 6 months after initiation. In the Noom Coach study, more people reversed diabetes in the intervention group than the control group. Few studies reported on harms, but of those that did (Virta Health, Better Therapeutics, and Noom Coach), none found serious or severe treatment-related harms.

Table 1. Summary of Findings

Intervention category	Virtual diet programs	Changes in weight*	Changes in HbA1c*	Changes in medication use*	Harms	Strength of evidence (SOE) & limitations
Supporting evidence Total N						
Programs promoting a named diet 4 studies (1 RCT, 1 non-randomized controlled trial, 1 single-arm longitudinal, 1 pre-post) N = 1,669	<ul style="list-style-type: none"> • TeLiPro • Virta Health • Low Carb Program • Better Therapeutics 	↓3-12% (3 studies)	↓.8%-1.4% (4 studies)	9-40% of those taking diabetes medications at baseline stopped taking them (3 studies).	No serious treatment-related harms of Virta Health or Better Therapeutics (2 studies).	Low SOE <ul style="list-style-type: none"> • Each program only evaluated in 1 study. • 2 studies were uncontrolled • 1 controlled study had unequal groups at baseline and other important limitations including high attrition
Programs promoting healthy eating based on guidelines 5 studies (3 RCTs, 1 single-arm longitudinal, 1 pre-post) N = 1,268	<ul style="list-style-type: none"> • u-Healthcare • ANODE • Our Path • GlycoLeap 	↓2.5-8% (4 studies)	↓.4-1.1% (3 studies)	12% of ppts in u-Healthcare intervention reduced dosage of oral antidiabetic drugs or insulin (1 study).	NR	Low SOE <ul style="list-style-type: none"> • Each program only evaluated in 1 study (except u-Healthcare) • 2 studies were uncontrolled • High attrition and differential attrition between groups

Intervention category	Virtual diet programs	Changes in weight*	Changes in HbA1c*	Changes in medication use*	Harms	Strength of evidence (SOE) & limitations
Supporting evidence						
Total N						
Programs promoting healthy eating not based named diet or guidelines	<ul style="list-style-type: none"> • My Dietitian • Noom Coach • Diab Memory + NutriNaut • 3 unnamed programs 	↓ 1-4% (2 studies)	↓ .4-1.9% (4 studies)	15% reduced dosage of oral diabetes medication or insulin (1 study).	<i>No severe hypoglycemia or hospitalization occurred during Noom Care intervention (1 study).</i>	Low SOE <ul style="list-style-type: none"> • Each program only evaluated in 1 study • Studies were small • High attrition
6 studies (5 RCTs and 1 pre-post study)						
N = 462						

*Represents changes in outcomes experienced among intervention group participants from baseline to follow-up.

↓=decrease; ↑=increase; NR=Not reported; ppts = participants

Italics= Meets criteria for a minimum clinically important difference (ie, weight loss ≥ 5%, HbA1c reduction ≥ .5%, stopping any or all diabetes medications, no severe treatment-related harms)

There were limitations to our rapid review methods as well as limitations of the primary studies. One limitation is that we did not include studies older than 5 years. An additional limitation is that we had a single reviewer include studies and abstract data with second reviewer checking, which could have resulted in missing eligible studies or data. However, we made attempts to reduce this risk by establishing explicit inclusion criteria for studies and developing and using a piloted data abstraction tool.

In terms of primary study limitations, one-third (5/15) did not include a separate control group, and among those that did use a control group, half (5/10) used a control group that was not similar to the intervention group in terms of intensity. This made it impossible to determine what caused the differences in outcomes (*ie*, the diet, the coaching, the access to virtual tools to track outcomes, the frequent interactions with health care providers or coaches, or a combination of these components).

Our primary recommendations for the VA's retrospective evaluation of the initial group of Veterans enrolled in the Virta Health pilot project is to collect detailed information on participants' baseline characteristics (including BMI, HbA1c, lipid levels, duration of diabetes, and any comorbidities) and measure the same outcomes (weight, HbA1c, and diabetes medication cessation) at the same time points (3 months, 1 year, and 2 years) as the Virta study. We also recommend researchers use intent-to-treat analysis to assess the effectiveness of Virta among all participants who enrolled, and to consider stratifying by engagement in the program to determine the minimum level of engagement needed for a clinically meaningful change in outcomes.

Our primary recommendation for the prospective evaluation of Veterans that may enroll in an expanded virtual diet program in the future is to compare that program to a similarly intensive intervention, either a different commercial program based on a different dietary approach or one

delivered by VA staff (such as virtual health coaches). For both parts of the evaluation, we recommend that researchers capture a wide range of information on harms, including exacerbation or development of conditions such as diverticulitis.

By using a suitable comparator, we believe the VA evaluation could help determine whether the benefits of the virtual diet program are dependent primarily on the specific diet or on the remote continuous care intervention and coaching support. As Veterans' preferences for the type of diet they follow are likely to vary, a practical solution to improving diabetes care should include a variety of diet options if the particular diet is not the critical component of the intervention. This comparison could also inform how virtual diabetes programs might be adapted to meet the needs of a variety of Veterans with type 2 diabetes.

EVIDENCE BRIEF

INTRODUCTION

PURPOSE

The ESP Coordinating Center (ESP CC) is responding to a request from the Department of Veterans Affairs (VA) Health Services Research & Development (HSR&D) program for an evidence brief on the effectiveness and harms of Virta Health and other virtual diet programs which include a coaching component for type 2 diabetes. The VA is planning to evaluate the effect of Virta Health among Veterans, and findings from this review could help inform power estimations, possible comparators and outcomes, and length of follow-up, among other study features.

BACKGROUND

One in 4 Veterans has some form of diabetes, which is twice the rate seen in the general US population.^{1,2} Type 2 diabetes, characterized by insulin resistance that can result in deficiencies in insulin secretion, is the most common form of diabetes and is thought to be primarily caused by excess weight in the body.³ When untreated, type 2 diabetes can lead to microvascular complications including retinopathy (damage to the eyes that can result in blindness), nephropathy (damage to the kidneys that can result in kidney failure), and neuropathy (damage to the nerves in hands and feet that can result in amputation), as well as macrovascular complications including increased risk of heart disease, stroke, and coronary events such as heart attacks. Treatment of type 2 diabetes includes the self-management of lifestyle factors (*eg*, diet, exercise) to reduce or maintain weight, tracking of biomarkers (*eg*, blood glucose levels) that can indicate diabetes is worsening or uncontrolled, use of medications (*eg*, metformin, insulin) that augment insulin levels, increase sensitivity to insulin, or impart other glucose-lowering effects, and monitoring and treating diabetes-related complications.

While there is widespread consensus that maintaining a healthy diet is a key part of diabetes management, there is no consensus on the ideal diet for diabetes. Guideline groups including the Department of Veterans Affairs/Department of Defense (VA/DOD), American Diabetes Association (ADA), and the Academy of Nutrition and Dietetics (the Academy) all recommend people with diabetes receive medical nutrition therapy (MNT) consisting of a nutrition assessment, diagnosis, intervention (including education and counseling), and monitoring/evaluation. However, they disagree on whether patients receiving MNT should follow a particular diet. The VA/DOD recommends that the Mediterranean diet (high intake of vegetables, fruits, nuts, unrefined grains, and olive oil; moderate intake of fish and poultry; low or moderate intake of wine; and low intake of red meat, processed meat, dairy, and sweets) be offered *first* to patients, then a low carbohydrate (14-45% of total calories) and/or low glycemic index diet be offered *second* if patients don't choose the Mediterranean diet.³ These recommendations emphasize that the chosen diet be tailored to patient preferences and needs. By contrast, both the Academy and ADA recommendations state that a variety of diets are acceptable for the management of diabetes, with the Academy emphasizing that personal preferences be considered and the ADA suggesting that clinicians focus on the common elements among diets for diabetes including emphasis of non-starchy vegetables, minimizing added sugars and refined grains, and choosing whole foods over highly processed foods.^{4,5}

In recent years, the ketogenic diet has become an increasingly popular option for people looking to lose weight, including those with type 2 diabetes.⁶ The ketogenic diet is a low carbohydrate, high fat diet, where approximately 70% of an individual's calories come from fat, 20% from protein, and 10% or less from carbohydrates.⁷ The ketogenic diet is distinct from other types of low carbohydrate diets (eg, Atkins, Paleo, and South Beach) as the majority of calories come from fat, rather than protein. The ketogenic diet dates back to the early 1900s when it was developed and used as a treatment for diabetes prior to the invention of insulin.⁸ Diets similar to ketogenic such as the very low carbohydrate diet are currently recommended by groups such as the National Institute for Health and Care Excellence (NICE) for instances in which patients need to lose weight rapidly, such as prior to joint replacement surgery or fertility treatments.⁹ The theory underlying the ketogenic diet is that restricting carbohydrates limits the body's access to glucose (the body's main source of energy) and forces it to burn stored fat (called ketones) instead.⁷ The process of burning ketones is called ketosis, and has been linked to a number of metabolic benefits.¹⁰ Proponents of the ketogenic diet cite studies indicating it can lead to weight loss, improve cholesterol and blood pressure, reduce the need for medications and reverse diabetes.^{11,12} There have also been anecdotal accounts that the ketogenic diet is easier to follow than other types of restrictive diets, since high fat foods such as fatty cuts of meat, eggs, and butter are allowed and there are no restrictions on the amount of calories consumed. However, skeptics have pointed out there are no long-term (> 1 year) studies of the effect of the ketogenic diet, so it is unclear whether these benefits are maintained over time, and if there are any long-term risks to patients with diabetes such as worsening of cardiovascular disease risk factors including LDL cholesterol, hypoglycemia (drop in blood glucose that can cause patients to pass out) or ketoacidosis (harmful levels of ketones in the blood that can cause diabetic coma or death).^{13,14}

A 2019 rapid response (review of reviews)¹⁵ by the Canadian Agency for Drugs and Technologies in Health (CADTH) provides the most recent and rigorous assessment of the effectiveness and harms of low carbohydrate diets (including the ketogenic diet) compared to control diets (no or minimal intervention) for diabetes. Due to the mixed findings of included systematic reviews, the report does not provide a definitive answer on the effectiveness and harms of these diets. The report looked at 10 systematic reviews published from January 2016 to October 2019. Because there were no primary studies that compared low carbohydrate diets to control diets, the most direct evidence comes from 3 network meta-analyses (NMA) conducted in 3 reviews. One NMA¹⁶ of 52 RCTs (duration 3-48 months) found that low carbohydrate diets *were not* significantly more effective than control diets at improving LDL cholesterol or HDL cholesterol, but *were* more effective at improving triglycerides (moderate strength of evidence). A second NMA¹⁷ of 10 trials (duration not reported) found that low carbohydrate diets *were not* significantly more effective than control diets at improving HbA1c, total cholesterol, HDL cholesterol, triglycerides, or BMI (strength of evidence not reported). A third NMA¹⁸ of 56 RCTs (duration 3-48 months) found that low carbohydrate diets *were* significantly more effective than control diets at improving HbA1c and fasting glucose (low strength of evidence).

Given the conflicting evidence on the ideal diet for improving outcomes for patients with type 2 diabetes, researchers continue to evaluate the effects of different diets on patient outcomes. In recent years, researchers, clinicians, and patients have become increasingly interested in using virtual tools such as apps, websites, and online patient portals as an alternative or additional modality for supporting diabetes self-management.¹⁹⁻²¹ Using virtual tools has the potential to increase patients' access to these interventions (as they can log into a virtual class or otherwise

access content at home rather than traveling to a clinic), adherence (since these types of interventions can be more easily adapted to patients' schedules, needs, and preferences than in-person interventions), as well as satisfaction with care. Virtual tools can also help patients with the burdensome process of tracking information related to their health, such as diet, physical activity, and biometrics like HbA1c, and provide additional avenues for communication and support, such as through texting with a dietitian or joining a group forum of other patients.

One such virtual program is Virta Health, an online platform that delivers a suite of services related to diabetes management, including nutrition and behavioral counseling focused on the ketogenic diet, as well as education, coaching, and physician management of medications (*ie*, titration of medications based on biomarker tracking).²² Virta Health's website states that it is a "proven treatment to reverse type 2 diabetes" and provides links to its peer-reviewed papers. In May 2019, the Department of Veterans Affairs (VA) initiated a pilot project in which 400 Veterans were given access to the Virta Health program with the goal of improving their diabetes-related outcomes. In November 2019, Virta Health stated on its website that of the first 104 patients enrolled in the pilot project, 84% had either a 1-point drop in HbA1c or had a drop below the clinical threshold for diabetes within 90 days, and 53% experienced a reduction in prescriptions for diabetes-specific medications.²³ No data from Virta's VA pilot project have been published, so this claim cannot be verified. A separate, single-center, open-label, nonrandomized controlled study provides the only evidence about the Virta program and indicates that program participants can lose weight, lower HbA1c, discontinue medications, and reverse diabetes.¹¹ This study, which is expected to be completed in 2021, has important limitations, and it is unclear how this program compares to other programs that deliver comprehensive, continuous remote care. If properly designed, the VA's ongoing evaluation of the Virta VA pilot project could address important gaps in the evidence about Virta. Virta's ongoing study might also close some gaps. The VA is also contemplating expanding virtual diet programs and will need to design a prospective evaluation to assess the impact of whatever program is selected.

This rapid evidence review was commissioned by the VA's Health Services Research & Development (HSR&D) program to help inform an evaluation of the Virta Health program among Veterans. The primary goal of this review is to assess the effectiveness and harms of all available virtual diabetes diet programs that include a coaching program on the three outcomes (weight loss, HbA1c, and medication reductions) that have been emphasized by Virta and proponents of other virtual programs. A secondary goal is to identify gaps in knowledge that could be informed by future research.

SCOPE

This rapid evidence review assesses the effectiveness and harms of virtual diabetes diet programs which include a coaching component among patients with type 2 diabetes.

KEY QUESTIONS

Key Question 1: Among adults with type 2 diabetes, what is the effectiveness of virtual diabetes diet programs which include a coaching component?

Key Question 2: Among adults with type 2 diabetes, what are the harms of virtual diabetes diet programs which include a coaching component?

ELIGIBILITY CRITERIA

The ESP included studies that met the following criteria:

- **Population:** Adults with type 2 diabetes
- **Intervention:** Diabetes diet program (*eg*, ketosis, low carb, *etc*) with coaching component (*eg*, patient provides diabetes-related information and receives personalized feedback from a provider or algorithm) delivered virtually. We considered a diet program to be one that delivers education or counseling related to diet.
- **Comparator:** Any, including no comparator
- **Outcomes:**
 - *Benefits:* Weight loss, HbA1c, medication reductions
 - *Harms:* Any (including hypoglycemia)
- **Timing:** Last 5 years (2015-2020)
- **Setting:** Any
- **Study design:** Any

METHODS

SEARCHES AND STUDY SELECTION

To identify articles relevant to the key questions, our research librarian searched Ovid MEDLINE, CINAHL, and Ovid CENTRAL databases as well as AHRQ, Cochrane, HSR&D, and Clinicaltrials.gov websites using terms for *type 2 diabetes*, *self-management*, *virtual programs*, and *diet* from January 2015 to April 2020 (see Supplemental Materials for complete search strategies). To accommodate our rapid timeline, we only searched for the most recent literature (*ie*, published in the past 5 years). Our rationale is that the technology supporting apps/online programs is rapidly changing, and an app/online program greater than 5 years old is unlikely to currently be available to patients. We limited the search to published and indexed articles involving human subjects available in the English language.

Additional citations were identified from hand-searching reference lists and consultation with content experts. We also developed a list of companies who are currently marketing virtual diabetes diet programs to people with type 2 diabetes (Better Therapeutics, CappaHealth [My Dietitian], Diabetes.co.uk [Low Carb Program], Diab Memory, Noom [Noom Coach], Second Nature [Our Path], and Virta Health) from our list of included studies. We contacted these companies to request unpublished data.

Study selection was based on the eligibility criteria described above. Titles, abstracts, and full-text articles were reviewed by 1 investigator and checked by another. All disagreements were resolved by consensus.

QUALITY ASSESSMENT & DATA EXTRACTION

We used Cochrane's Risk of Bias 2 Tool to rate the internal validity of controlled trials.²⁴ We rated the internal validity of cohort studies, longitudinal single-armed studies, and pre-post studies based on the Cochrane ROBINS-I.²⁵ We abstracted data from all studies and results for each included outcome. All data abstraction and internal validity ratings were first completed by one reviewer and then checked by another. All disagreements were resolved by consensus.

STRENGTH OF EVIDENCE ASSESSMENT

We informally graded the strength of the evidence based on the AHRQ Methods Guide for Comparative Effectiveness Reviews.²⁶ This approach incorporates 4 key domains: risk of bias (includes study design and aggregate quality), consistency, directness, and precision of the evidence. Strength of evidence is graded for each key outcome measure and ratings range from high to insufficient, reflecting our confidence that the evidence reflects the true effect.

SYNTHESIS OF DATA

Due to heterogeneity in participant characteristics, intervention components and length of follow-up, we synthesized results narratively. In our synthesis, we highlighted which programs demonstrated a *clinically meaningful change* on weight loss, HbA1c, or medication reduction, without harms. Table 2 outlines what we considered to be a *clinically meaningful change* for each outcome. Although HbA1c reduction $\geq .5\%$ is not a clinically meaningful outcome in and

of itself, we have included it here as HbA1c level has been shown to be directly related to diabetes-related complications.²⁷

Table 2. Definitions of Clinically Meaningful Change by Outcome

Outcome	Clinically meaningful change
Weight loss	Weight loss \geq 5% from baseline ²⁸
Reversal of diabetes	Lowering HbA1c to level $<$ 6.5% (diagnostic threshold for type 2 diabetes) without medications
HbA1c	Lowering of HbA1c level \geq .5% from baseline ²⁷
Medication reduction	Discontinuation of ANY diabetes-related medication Discontinuation of ALL diabetes-related medication
Harms	Serious or severe treatment-related adverse events

In our synthesis, we also comment on whether participants were in the normal weight range (BMI 18.5 to $<$ 25 kg/m²), overweight (BMI 25 to $<$ 30), obese (BMI 30 to $<$ 40), or severely obese (BMI 40 or higher) at baseline according to CDC guidelines.²⁹ We discuss results from intent-to-treat analyses unless otherwise described. The complete description of our full methods can be found on the PROSPERO international prospective register of systematic reviews (<http://www.crd.york.ac.uk/PROSPERO/>; registration number CRD 42020180278).

RESULTS

The literature flow diagram (Figure 1) summarizes the results of the search and study selection processes. Among 622 potentially relevant citations, we included 18 articles of 15 studies (9 RCTs,³⁰⁻³⁸ 1 non-randomized trial,^{11,39-41} 3 single-arm longitudinal studies,⁴²⁻⁴⁴ and 2 pre-post studies^{45,46}) of 14 virtual diabetes diet programs (TeLiPro,³⁰ Virta Health,^{11,39-41} Low Carb Program,⁴² Better Therapeutics,⁴⁵ u-Healthcare,^{32,33} ANODE,^{31,43} Our Path (Second Nature),⁴⁶ GlycoLeap,⁴⁶ My Dietitian,³⁴ Noom Coach,³⁵ DiabMemory + Nutrinaut,⁴⁴ and 3 unnamed programs).³⁶⁻³⁸ Studies varied considerably in terms of the diet program provided; as a result, we organized our results into 3 parts: *part 1*— programs promoting a named diet; *part 2*— programs that promote healthy eating based on a diabetes or dietary guideline; and *part 3*— programs that promote healthy eating not based on a named diet or guideline.

Across studies, participant characteristics were heterogenous: mean baseline BMI ranged from 27 to 40 kg/m², HbA1c from 5.9% to 9.1%, and length of time diagnosed with diabetes from 3 to 17 years. Study size ranged from 24 to 1,000 participants. Outcomes were measured between 10 weeks and 2 years after program initiation, although most studies measured outcomes at either 3 months, 6 months, or 1 year. Detailed study-level data abstraction and quality assessment appear in the Supplementary Materials. Table 3 provides a high-level overview of each program—including program features; whether the program was associated with clinically meaningful improvements in weight, HbA1c, and medication use without severe or serious harms; and the number and types of studies evaluating each program.

From our outreach to companies marketing virtual diabetes programs to patients, we only received a response from Virta Health. We have incorporated a summary of findings from relevant conference abstracts provided by Virta in the “Virta Health” section, but did not formally include these articles in our report.

LITERATURE FLOW

Figure 1: Literature Flowchart

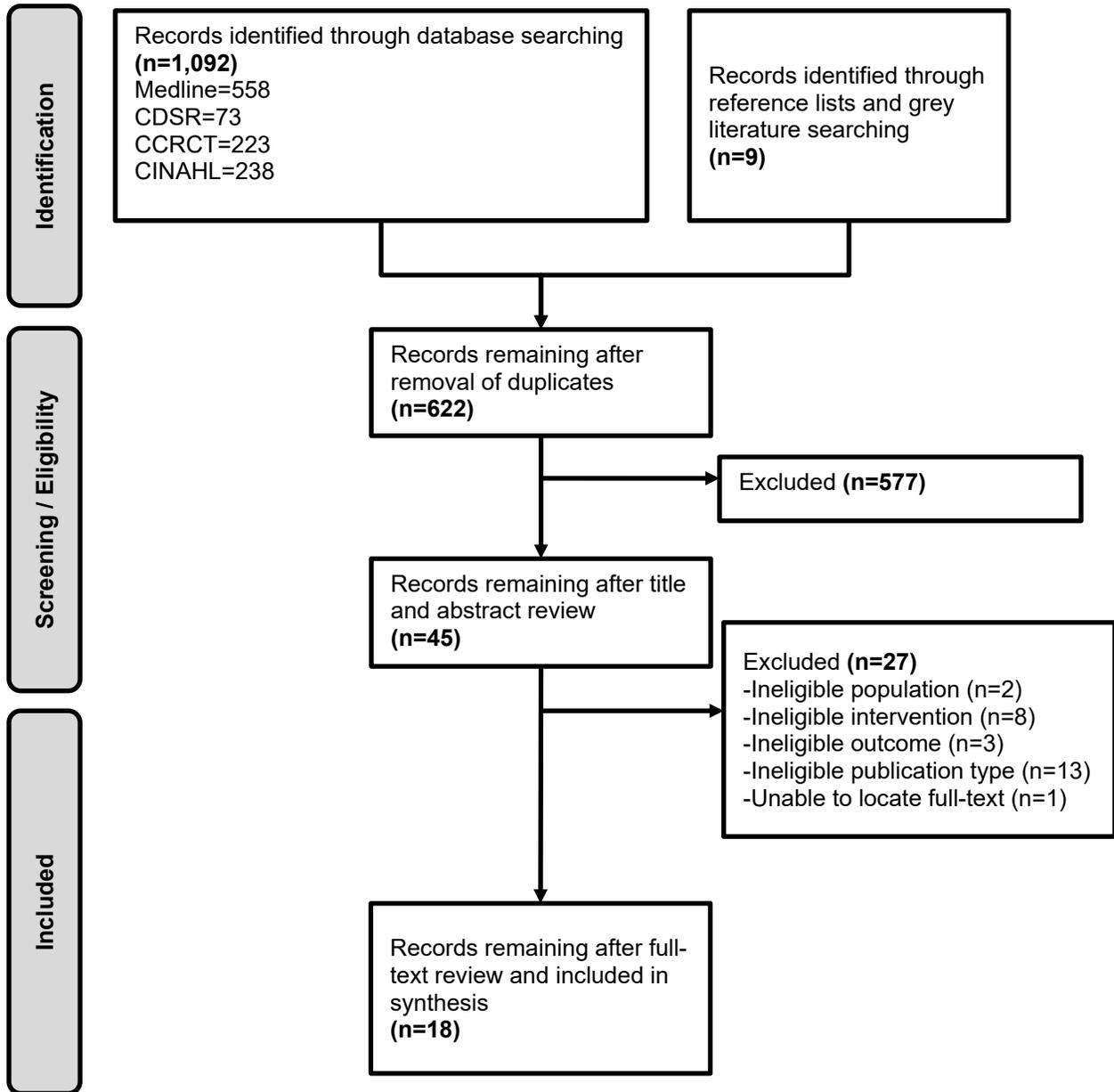


Table 3. Overview of Studies on Virtual Diabetes Diet Programs

Program	Diet	Coaching		Additional features of program					Outcomes					Number and type of studies			
		Health coach by person	Health coach by algorithm	Educational classes/	Health data tracking	Medication management	Peer support	Physical activity	Weight >5% ↓	HbA1c ↓ >.5%	Stopped medications	No harms found	Maintained 1+ years	RCT	Non-randomized controlled	Single-arm longitudinal	Pre-post
Programs promoting a named diet																	
TeLiPro ³⁰	Meal replacement	•			•				√	√			√	1			
Virta Health ^{11,39-41}	Ketogenic	•		•	•	•	•		√	√	√	√	√		1		
Low Carb Program ⁴⁷	Low carbohydrate		•	•	•	•			-	√	√		√			1	
Better Therapeutics ⁴⁵	Plant-based	•		•	•		•	•		√	√	√					1
Programs promoting healthy eating based on guidelines																	
u-Healthcare ^{32,33}	US and South Korea guidelines		•		•			•	-	√				2			
ANODE ^{31,43}	France guidelines		•	•	•				-	-				1			
Our Path (Second Nature) ⁴⁶	UK guidelines	•		•	•		•	•	√				√			1	
GlycoLeap ⁴⁶	US and Singapore guidelines	•		•	•			•	-	√							1



Program	Diet	Coaching		Additional features of program					Outcomes					Number and type of studies			
		Health coach by person	Health coach by algorithm	Educational classes/	Health data tracking	Medication management	Peer support	Physical activity	↓ Weight >5%	↓ HbA1c >.5%	Stopped medications	No harms found	Maintained 1+ years	RCT	Non-randomized controlled	Single-arm longitudinal	Pre-post
Programs promoting healthy eating not based named diet or guidelines																	
My Dietitian ³⁴	Meal tracking	•			•		•	•	-				-	1			
Noom Coach ³⁵	Diet education & tracking	•		•	•			•		√		√		1			
Unnamed program (Wayne 2015) ³⁸	Diet counseling & tracking	•		•	•			•	-	√				1			
Unnamed program (Sun 2019) ³⁶	Diet counseling & tracking	•			•			•		√				1			
Unnamed program (Von Storch 2019) ³⁷	Diet counseling & tracking	•			•			•		-				1			
DiabMemory + Nutrinaut ⁴⁴	Diet counseling & tracking	•			•			•		-							1

• denotes this feature was present. Outcomes √= target achieved; - = target not achieved; blank= not measured.
 For HbA1c, target was achieved if mean HbA1c ↓ .5% at follow-up in the intervention group. For weight, target was achieved if mean weight ↓ 5% at follow-up in intervention group. For medications, target was achieved if any intervention participants stopped taking medications. For harms, target was achieved if no serious or severe diabetes-related harms were reported by intervention participants. For maintenance, target was achieved if any benefits in weight, HbA1c, or weight were maintained for 1+ years.



PART I: PROGRAMS PROMOTING A NAMED DIET

Overview

Four studies (1 RCT,³⁰ 1 non-randomized trial,^{11,39-41} 1 single-armed longitudinal study,⁴² and 1 pre-post study⁴⁵) examined virtual diet programs promoting named diets where certain categories of food or macronutrients were limited. Named diets included a meal replacement diet,³⁰ a ketogenic diet,^{11,39-41} a low carb diet,⁴² and a plant-based diet⁴⁵ (Table 4). Overall, virtual programs based on named diets were associated with weight loss (3-12%), HbA1c reductions (.8-1.4%), and reductions in medication use (9-40% of those taking diabetes medications at baseline stopped taking them) with no treatment-related harms. By comparison, those receiving usual care did not experience improvements in any of these measures. In 1 study, improvements in the intervention group were maintained for 1 year even after the intervention ended at 12 weeks; in a second study, improvements were maintained for 1 year when participants continued to receive the intervention; and in a third study, improvements were maintained for 2 years when participants continued to receive the intervention. Overall, we have low confidence in these findings as each program was only evaluated in a single study, only 2 studies had separate control groups, and in 1 controlled study those in the intervention group were considerably different (*ie*, higher BMI, lower rates of insulin use) than those in the control group at baseline, among other important limitations.

Table 4. Detailed Findings from Studies of Named Diet Programs

Study Characteristics	Weight Loss	HbA1c Reduction	Medication use	Serious or severe harms
TeLiPro ³⁰ 12-week meal replacement program (I) vs routine care (C) RCT (N = 202)	<ul style="list-style-type: none"> • 12 wks: ↓6% (I) vs no change (C) • 6 mo & 1 yr: weight loss maintained 	<ul style="list-style-type: none"> • 12 wks: ↓1.1% (I) vs no change (C) • 6 mo & 1 yr: HbA1c reductions maintained 	NR	NR
Virta Health ^{11,39-41} 2-year continuous care intervention based on ketogenic diet (I) vs usual care (C) Non-randomized trial (N =349)	<ul style="list-style-type: none"> • 10-11 wks: ↓7% (I) • 1 yr: ↓12% (I) vs no change (C) • 2 yrs: ↓10% (I) vs no change (C) 	<ul style="list-style-type: none"> • 10-11 wks: ↓1% (I) • 1 yr: ↓1.4% (I) vs no change (C) • 2 yrs: ↓1% (I) vs no change (C) 	<ul style="list-style-type: none"> • 10-11 wks: 9% stopped taking medication (I) • 1 yr: ↓27% taking metformin (I) vs no change (C) • 2 yrs: ↓13% taking insulin (I) vs no change (C) 	<ul style="list-style-type: none"> • 10-11 wks: No hypoglycemia (I) • 1 yr: No metabolic acidosis (I & C)
Low Carb Program ⁴² 1-year low carbohydrate diet program Single-arm longitudinal study (N = 1,000)	1 yr: ↓3.3%	1 yr: ↓.8%	1 yr: 40% stopped taking hypoglycemia medication	NR
Better Therapeutics ⁴⁵ 12-week plant-based diet program	NR	3.5 mo: ↓.8%	3.5 mo: 17% decreased dosage or stopped taking 1 or more diabetic medications.	3.5 mo: no treatment-related adverse events.

Study Characteristics	Weight Loss	HbA1c Reduction	Medication use	Serious or severe harms
Pre-post study (N =118)				

↓=decrease; ↑=increase; I= intervention; C=Control; NR=Not reported; *Italics*= *Meets criteria for a minimum clinically important difference*

TeLiPro (Meal Replacement Diet)

Study Design

A RCT³⁰ (N = 202) conducted in Germany evaluated the effect of the TeLiPro intervention, a 12-week, virtual, meal-replacement diet intervention. Participants were recruited from attending physicians or newspaper articles. In this intervention, participants consumed a meal-replacement product (dissolvable in water) for 3 meals/day, gradually decreasing the proportion of meals that came from meal replacements over a 12-week period. Coaching consisted of a weekly call from a diabetes coach (20 min duration). Participants also received devices to help them self-monitor glucose levels, weight, and physical activity, and measurements were automatically transferred to a personalized online portal. The control group received routine care every 3 months from a physician. At baseline, participants weighed on average between 35.3 kg/m² (intervention) and 37 kg/m² (control), had an average HbA1c level between 8.2% (control) and 8.4% (intervention), had been diagnosed with diabetes for 11 years, and were taking at least 2 diabetes medications. Outcomes were measured at 12 weeks, 6 months, and 1 year.

Results

Intervention group participants lost on average of 6% of their body weight at 12 weeks and maintained these reductions at 6 months and 1 year, while the control group did not lose weight at any time point. The intervention group also reduced their HbA1c level by 1.1% (8.4% to 7.3%) at 12 weeks, while the control group experienced no change. HbA1c reductions were generally maintained, although both intervention and control groups had an increase of 0.1-0.2% HbA1c at 6 months and 12 months. The study did not report medication use or harms.

Limitations

High rates of attrition (44% of control participants and 25% of intervention group participants did not complete data assessments at 1 year) were a major limitation of this study, although intent-to-treat analyses were used to account for missing data.

Virta Health (Ketogenic Diet)

Study Design

A non-randomized clinical trial^{11,39-41} (N = 349) conducted in the US comparing Virta Health (a virtual intervention based on the ketogenic diet) to usual care. One of these articles describe pre-post differences in the intervention arm at 10-11 weeks,³⁹ while the others describe between-group differences at 1 year^{11,40} and 2 years.⁴¹ In the study, eligible participants chose to enroll in the Virta Health program (a “continuous care intervention” that provided support from a personal health coach as well as physician-directed medication management, diabetes education, data tracking, and peer support) or to receive usual care (care from a PCP or endocrinologist with counseling from an RD according to ADA recommendations). Goals of the ketogenic diet were to consume < 30 g carb, 1.5 g/kg protein, dietary fats to satiety, 3-5 servings non-starchy

vegetables, and to intake adequate mineral and fluids each day. Personal health coaching was available through 1-on-1 texting. At baseline, participants in the intervention group (N = 262) had an average BMI of 40.4 kg/m² (severely obese) and 30% were taking insulin, while those in the control group (N = 87) had an average BMI of 36.7 kg/m² (obese) and 46% were taking insulin. Length of time diagnosed with diabetes (8 years) and HbA1c (7.6%) were similar between groups. Participants received the intervention for 2 years, although the frequency of classes (delivered either in person or virtually) decreased over time. Data was collected at 10-11 weeks, 1 year, and 2 years.

Results

Those in the intervention group lost 7% of their body weight at 10-11 weeks,³⁹ 12% at 1 year,¹¹ and generally maintained the weight loss at 2 years,⁴¹ while those in the usual care group did not lose weight at 1 or 2 years. Intervention group participants also lowered their HbA1c levels by 1% (7.6% to 6.6%)³⁹ at 10-11 weeks, by 1.4% at 1 year,¹¹ and maintained reductions at 2 years, while those in the usual care group did not experience any reductions in HbA1c. Additionally, there was an increase in the percentage of people in the intervention group who successfully reversed their diabetes (defined as HbA1c <6.5% without medications or with just metformin) at 2 years (12% to 54%), while there was a decrease in the control arm (16% to 9%).⁴¹ The percentage of participants in the intervention group taking any diabetes medication (except metformin) decreased from 57% to 30% at 1 year and the percentage taking insulin decreased from 30% to 17% at 1 year, compared to no change in the control group.¹¹ Authors reported no participants in the intervention group experienced hypoglycemia during the first 10-11 weeks, and no participants experienced metabolic acidosis in either group in the first year. Attrition was 26% in the intervention group and 22% in the control group at 2 years.

Additional data are available on participants in Virta Health's non-randomized controlled trial via conference abstracts, but these data have not been peer-reviewed.⁴⁸⁻⁵⁰ We briefly discuss these findings here, but do not formally include the abstracts or evaluate study quality given the more limited information available in abstracts. Readers should interpret these results with caution. In one abstract,⁴⁸ Virta Health program participants who completed outcome assessments at 3.5 years lowered their HbA1c by 0.6% (7.4% to 6.8%) and lost 9% of body weight (117 to 106.5 kg) from baseline. In addition, the percentage of participants that were not taking diabetes medication increased from 15% to 33%, and 45% of participants had lowered HbA1c < 6.5% with the use of metformin or no medication. Overall, these results indicate the benefits of the program are maintained long-term in this selected population, although there is some rebound effect as both HbA1c and weight were higher at 3.5 years than at 1 or 2 years. A second abstract⁴⁹ examined predictors of HbA1c reduction and weight loss, and found that early nutritional ketosis (measured as percentage of blood beta-hydroxybutyrate (BHB) readings ≥ 0.5 mm) was a predictor of weight loss and HbA1c reduction, but engagement in the app (measured as percentage of days participants messaged their coach and logged ≥ 1 biomarker or symptom) was not. A third abstract⁵⁰ found that shorter diabetes duration and lower HbA1c at baseline were associated with success lowering of HbA1c < 6.5% with either metformin or no medication.

Limitations

This study had several major limitations. The first was the use of non-randomized methods to assign participants into groups, resulting in measurable and potentially unmeasurable differences which make it difficult to establish causality between the intervention and outcomes. The control

group was designed to be a “reference for typical disease treatment and progression over 1 year within the same geographical, health care, and laboratory locations” as the intervention group.¹¹ The control group had a “separate information session and informed consent” process, although they were notified that the trial had an intervention arm and could participate in that arm if they liked.¹¹ The result of having a non-randomized process for assigning patients to groups is that the groups were different at baseline in several measurable ways. Those in the intervention group had a higher average BMI and a lower proportion who used insulin (although authors controlled for BMI and insulin use, among other baseline participant characteristics, in between-group analyses). An additional concern with non-randomly assigning people to groups is that the groups could be different in non-measurable ways – such as the intervention group being more motivated to lose weight and therefore choosing to be in a more intensive intervention.

The second major limitation is that researchers revised the study’s Clinicaltrials.gov protocol²² over time without providing a justification for why changes were made, which could have contributed to reporting bias. A comparison of the originally submitted Clinicaltrials.gov protocol from August 2015 versus a revised version from January 2018 indicates that researchers lengthened the study follow-up period (from 2 years to 5 years), added 3 secondary purposes (to compare in-person versus web-based delivery of education content, to explore relationships in LDL cholesterol and carotid intima media thickness, and to evaluate whether health outcomes are maintained and what the economic effects are over 5 years), and specified that at the 3-month time point, outcomes would *only* be collected in the intervention arm. Making unjustified changes to a protocol can lead to reporting bias, as it can make it appear that researchers intended to measure a certain outcome or to evaluate a certain question, when in reality, it was the result of an interim analysis or other factors. The August 2018 revision that clarified that 3-month outcomes would only be measured in the intervention group is especially problematic as it occurred *after* the first article³⁹ on this study was published in August 2017 examining 10-11 week outcomes in the intervention group only.

The third major limitation of this study is that results are spread out over 6 published articles (4 that were included and 2^{51,52} that were not), which could have contributed to publication bias. While unique outcome data are presented in each article, some outcomes are reported in multiple studies (such as 1-year outcomes, which were the focus of the Hallberg 2018 article³⁹ but were also reported in the Athinarayanan 2019 article⁴¹ which examined whether outcomes were maintained at 2 years). Publishing multiple articles on a single study, sometimes referred to as data fragmentation or “salami-slicing,” can lead to publication bias and has been discussed frequently in editorials as a common but problematic practice.^{53,54} In terms of this study, splitting outcomes across 6 articles is an issue because 1) it makes it appear to a casual reader that there are more data supporting the intervention than there truly are and 2) it makes it difficult to see the “big picture” of how the intervention impacted the researcher’s primary outcomes of interest.

Low Carb Program (Low Carbohydrate Diet)

Study Design

A single-arm, longitudinal study⁴² (N = 1,000) conducted in the UK evaluated the effects of the online Low Carb Program, a low carbohydrate intervention that also included automated feedback and tracking of health data. Patients were recruited from convenience samples following the 2015 online launch of the Low Carb Program. Goals of the low carbohydrate diet

were to restrict carbohydrates based on visual plate method and increase intake of green vegetables as well as low-glycemic index fruits and fats. Coaching consisted of weekly automated emails based on program use. Participants were encouraged to have regular contact with their health care providers to adjust medications in weeks 1, 2, and 10, although these providers were not part of the Low Carb program. Participants received 10 weeks of educational coursework, but could continue to access the coursework, track data, and access a discussion board for up to a year. At baseline, participants weighed an average of 89.6 kg, had a HbA1c of 7.8% and many had comorbidities including hypertension (40%) and high cholesterol (35%). Outcomes were measured at 1 year.

Results

Participants lost on average of 3.3% of their body weight at 1 year, which was not a clinically meaningful change. However, those who completed the program (*ie*, finished all 10 educational modules) did have a clinically meaningful reduction in weight (8%) while those who partially completed or did not complete the program had no change in weight. At 1 year, participants lowered their HbA1c on average by 0.8% (7.8% to 7%), with a dose-response relationship between completion of the program and outcomes (completers lowered HbA1c by 1.2%, partial completers by 0.6%, and non-completers had no change). At 1 year, 40% of those who were prescribed hypoglycemia medications at baseline stopped taking 1 or more medications.

Limitations

The major limitation of this study was the lack of control group, making it impossible to determine if the intervention caused outcomes, or other potential confounders or co-occurring interventions. Additional methodological limitations include poor adherence to the intervention (only 52% of participants completed all 10 educational modules) and high attrition (30% of participants did not report outcomes at 1 year), although authors used intent-to-treat analyses to account for missing data and explored differences for completers, partial completers, and non-completers.

Better Therapeutics (Plant-based Diet)

Study Design

A pre-post study⁴⁵ (n=118) conducted in the US examined the effect of a 12-week app-based intervention (Better Therapeutics) that promoted a plant-based diet. Participants were recruited through advertisements on Facebook and Craigslist. Once enrolled, participants were encouraged to use the meal planning feature of the app (5 min/week), review educational materials on culinary or health topics (15-20 mins/week) and report meals (1-2 min/day). Health coaching was provided for 30 minutes every 2 weeks by phone, and a clinical team was available for additional support when needed. Additional features of the intervention included access to support groups and encouraging participants to monitor weight and engage in physical activity. At baseline, participants had an average BMI of 38.1 kg/m² (obese), HbA1c of 8.1%, and had been diagnosed with diabetes for 2.6 years. Outcomes were measured at 3.5 months.

Results

Weight loss was not reported in this study. However, at 3.5 months, participants lowered their HbA1c by an average of 0.8% (8.1% to 7.3%) and 17% reported either reduced dosage or

stopped taking their diabetic medications altogether. Authors reported no treatment-related adverse events occurred.

Limitations

The major limitation of this study was the lack of a control group that could rule out the possibility that effects were due to confounding or co-interventions. A minor limitation was that HbA1c was self-reported (rather than measured via a glucometer that automatically transferred readings to the study team) increasing the potential risk for measurement error or bias.

PART 2: PROGRAMS THAT PROMOTE HEALTHY EATING BASED ON GUIDELINES

Overview

Five studies (3 RCTs,³¹⁻³³ 1 single-arm longitudinal study,⁴³ and 1 pre-post study⁴⁶) evaluated 4 virtual diabetes diet programs (u-Healthcare,^{32,33} ANODE,³¹ Our Path,⁴³ and GlycoLeap⁴⁶) that promoted healthy eating based on national dietary or diabetes guidelines (Table 5). Overall, virtual healthy-eating programs based on guidelines had mixed effects on weight, with only OurPath demonstrating a clinically significant effect (7% reduction at 1 year). The u-Healthcare and GlycoLeap programs were both associated with > 0.5% decreases in HbA1c between 3-9 months, although clinically significant improvements were *also* seen in the u-Healthcare study's control group at 3-6 months. No studies evaluated the percentage of participants who stopped using diabetes medications- although the u-Healthcare study noted that 12% reduced their medication dosage. None of these studies reported on harms, so it is unclear if there are any potential downsides to these virtual programs. Overall, we have low confidence in these findings as each program was only evaluated in 1 study (with the exception of u-Healthcare which was evaluated in 2), only 3 studies had separate control groups, and 2 of the 3 controlled studies had either high attrition (> 20%) or differential attrition between groups.

Table 5. Detailed Findings From Studies of Programs That Promote Healthy Eating Based on Guidelines

Study Characteristics	Weight Loss	HbA1c Reduction	Medication use	Serious or severe harms
u-Healthcare ^{32,33} 6-month therapeutic lifestyle intervention w/ counseling (I) vs counseling alone (C) 2 RCTs (N=70 & N=100)	<ul style="list-style-type: none"> • 3 mo: NR • 6 mo: ↓2% (I) vs 0% (C) 	<ul style="list-style-type: none"> • 3 mo: ↓.8% (I) vs ↓.8% (C) • 6 mo: ↓.7%-1.1% (I) vs ↓.2-.5% (C) 	6 mo: 12% of ppts reduced dosage of oral antidiabetic drugs or insulin (I) vs no change (C)	NR
ANODE ³¹ 16-week nutritional support & education intervention (I) based on guidelines vs usual care (C) RCT (N= 102)	16 wks: ↓2.5% (I) vs no change (C)	16 wks: ↓.4% (I) vs ↑.2% (C)	NR	NR

Study Characteristics	Weight Loss	HbA1c Reduction	Medication use	Serious or severe harms
Our Path (now Second Nature) ⁴³ 3-month behavior coach program Single-arm, longitudinal study (N=896)	<ul style="list-style-type: none"> • 6 mo: ↓8% • 12 mo: ↓7% 	NR	NR	NR
GlycoLeap ⁴⁶ 6-month meal tracking intervention based on US & Singapore's guidelines Pre-post study (N=100)	9+ mo: ↓2.5%	9+ mo: ↓1%	NR	NR

↓=decrease; ↑=increase; I= intervention; C=Control; NR=Not reported; *Italics= Meets criteria for a minimum clinically important difference*

u-Healthcare (US & South Korea Guidelines)

Study Design

Two RCTs (N = 70³³ and N = 100³²) conducted in South Korea evaluated the u-Healthcare program, a therapeutic lifestyle program focused on diabetes management, compared to usual care. One RCT³³ (*ie*, Kim 2015) evaluated a version of u-Healthcare that had a voice inception software similar to speech-to-text where participants could verbally report their blood glucose to a device and it would record it, while the other RCT³² (*ie*, Lim 2016) did not include this software. Participants were recruited from an outpatient clinic of a university hospital. In both RCTs, intervention and control groups received the same diet and exercise counseling intervention prior to randomization. This counseling was characterized as meeting standards set by the American Diabetes Association and the Korean Diabetes Association in both studies, and Lim 2016 described the counseling as involving an individual assessment of dietary habits, nutritional education from a dietitian, recommendations to monitor blood glucose at least 8 times a week, and check-ins at 3 and 6 months. In both studies, the intervention group had access to the u-Healthcare system that helped them to track their blood glucose, submit it to a study database, and receive feedback from an algorithm, as well as track physical activity. Control group participants monitored blood glucose and physical activity without access to this system.

At baseline, participants had an average BMI ranging from 25.1 kg/m² to 25.9 kg/m² (overweight), HbA1c from 7.9% to 8.7%, and had been diagnosed with diabetes for 14.4 to 16.6 years (all participants were 60+ years old, per study eligibility criteria) depending on the study and group. Many participants also had comorbidities (46-51% hypertension; 66%-71% dyslipidemia, 14-26% CVD; retinopathy 14%; and neuropathy 10-18%) depending on the study and group. Outcomes were measured at 3 and 6 months.

Results

All findings in this section are from pre-protocol analyses. In Kim 2015,³³ intervention group participants lost 2% of their body weight while control group participants did not lose any weight

at 6 months- neither represented a clinically significant change. Lim 2016³² did not measure weight loss, although intervention participants lowered their BMI (26.3 to 25.7 kg/m²) at 6 months. This change was not seen for the control group (26.8 to 26.5 kg/m²).

In both studies, intervention participants experienced reductions in HbA1c at follow-up; however, results in control groups were mixed. In Kim 2015,³³ both groups experienced clinically meaningful reductions in HbA1c, although the intervention group had greater reductions at 6 months (-1.1% [8.6% to 7.5%] in intervention vs -0.5% [8.7% to 8.2%] in control). In Lim 2016,³² HbA1c was lowered by 0.7% at 3 months in the intervention group which was maintained at 6 months (8% to 7.3%)- a clinically meaningful change. In the control group, HbA1c was lowered at 3 months (number not reported) but rebounded at 6 months to a value that was not clinically different from baseline (8.1% to 7.9%).

Lim 2016³² reported that 12% of intervention group participants reduced their dosage of oral antidiabetic drugs or insulin compared to no change in the control group. Harms were not reported in either study.

Limitations

This study had minor limitations, primarily from reporting per-protocol results instead of intent-to-treat results. In Kim 2015,³³ only 3% of participants dropped out, so per-protocol analyses likely provide a good estimate of the effect of assignment to intervention. However, for Lim 2016³² between 14-16% of participants dropped out and although authors conducted both per-protocol and intent-to-treat analyses, most of the reported data is from per-protocol analysis. Per-protocol results may be biased as they do not account for people who dropped out of the study.

ANODE (France Guidelines)

Study Design

An RCT³¹ (N = 120) conducted in France evaluated ANODE, an online nutritional support tool designed to improve diet and physical activity according to France's National Nutrition and Health program guidelines, versus usual care with a GP or specialist. Participants were recruited from media advertising or directly referred by their caregivers. Intervention participants completed 4 online educational modules on diet and physical activity (1- self-monitoring diet and physical activity; 2- nutritional assessment; 3- balanced diet menu generator; and 4- physical activity education and prescription). Coaching consisted of participants entering their meal information into the support tool and received automated feedback summarizing the amounts of macro-nutrients consumed (fat, saturated fat, protein, salt, carbohydrates) as well as advice on how to achieve a balanced diet. Human contact was limited to a hotline support in case of technical issues. At baseline, participants had a BMI of 33.4 kg/m² (obese) and HbA1c of 7.2% (diabetes duration not reported). Outcomes were measured at 16 weeks.

Results

Intervention group participants lost on average 2.5% of their body weight at 16 weeks, which was not a clinically meaningful change (by contrast, control group participants did not lose weight). Those in the intervention group lowered their HbA1c by 0.4% (from 7.2% to 6.8%) which was also not a clinically meaningful change (by contrast, those in the control group had an average increase of HbA1c of 0.2%). Medication use and harms were not reported.

Limitations

This study had minor limitations: participants and coaches were aware of the assigned intervention during the trial, and attrition was higher in the intervention versus control group (11 vs 5 participants) due to lack of interest.

Our Path (UK. Guidelines)

Study Design

A single-arm, longitudinal study⁴³ (N = 896) conducted in the UK evaluated the Our Path (now known as Second Nature) program, a 3-month, app-based, behavior change program. Participants in this study either paid for the app or were referred from their general practitioner (GP) for treatment of type 2 diabetes (in which case, the app was free). Participants in this intervention reviewed educational articles on nutrition and health topics (10-15 min/article), were matched to a 10-person peer support group, had the option to text a health coach (a registered dietitian or nutritionist) 1-on-1 through the app, and received a physical activity tracker and a scale. Health coach advice was informed by the National Institute of Health and Care (NICE) guidelines. The intervention was split into 2 parts: a 12 week “core” phase that was more intensive, and a “sustain” phase where participants could no longer text a health coach but could access other features of the app. Of the 896 participants who completed data assessments at 6 and 12 months (an inclusion criterion for the study), 52% had type 2 diabetes and received access to the program through their GP. At baseline, participants with type 2 diabetes had an average BMI of 33.4 kg/m² (obese).

Results

At 6 months, participants with type 2 diabetes lost an average of 8% of their body weight and maintained the weight loss at 1 year. HbA1c, medication use, and harms were not reported. Authors noted that 56% of participants with type 2 diabetes lost >5% of their body weight at 1 year, and 25% lost > 10%.

Limitations

Results from this study (N = 896) represented only those who took part in the program who completed 6- and 12-month weight readings, which was about 25% of the total population who participated in the Our Path program during the study time period. Therefore, results likely reflect people who were more engaged with the program. The lack of control group also makes it difficult to determine if it was the intervention or a confounder/cointervention that drove the change in outcomes.

GlycoLeap (US and Singapore Guidelines)

Study Design

A pre-post study⁴⁶ (N = 100) conducted in Singapore evaluated 6 months of access to GlycoLeap, an online lifestyle management intervention. Participants were recruited from a single community health care facility. Intervention participants tracked meals and interacted with health coaches who provided recommendations, encouragement, and personalized feedback on progress. Twenty-four educational lessons on diabetes and self-management were available to participants based on the 7 healthy self-care behaviors recommended by American Association

of Diabetes Educators. After participants entered their meal information online, health coaches rated each meal for nutritional content on a 1 to 5 scale based on Singapore's Health Promotion Board's national dietary guidelines. Additional features of the program included tracking of weight, blood glucose, and physical activity. At baseline, participants had an average BMI of 29.8 kg/m² (overweight), HbA1c of 8.8%, and had been diagnosed with diabetes for 9.3 years. Outcomes were measured after the 6-month intervention, although the actual time point varied for each individual (eg, weight and HbA1c was measured between 12-38 weeks after intervention).

Results

Intervention participants reduced their HbA1c by 1% (8.8% to 7.8%) which was a clinically meaningful change. However, they only lost an average of 2.5% of their body weight (although authors note that 17% of participants did lose > 5%). Medication use and harms were not reported by the study.

Limitations

This study had major limitations, most notably a lack of control group that could have ruled out the possibility effects were due to confounders or co-interventions. In addition, the large period in which outcomes were measured (12-38 weeks after intervention) makes it difficult to interpret the meaning of the data reported.

PART 3: PROGRAMS THAT PROMOTE HEALTHY EATING NOT BASED ON NAMED DIET OR GUIDELINE

Overview

Six studies (5 RCTs³⁴⁻³⁸ and 1 pre-post study)⁴⁴ evaluated 6 virtual diabetes diet programs (My Dietitian,³⁴ Noom Coach,³⁵ Diab Memory + Nutrinaut,⁴⁴ and 3 programs³⁶⁻³⁸ that were unnamed) that promoted healthy eating but were not based on a named diet or guideline (Table 6). Overall, 2 RCTs^{34,38} evaluated the impact of 2 programs (My Dietitian and an unnamed program by Wayne 2015) on weight, neither of which showed a clinically significant reduction at any time point. Four RCTs³⁵⁻³⁸ evaluated the impact of 4 programs (Noom Coach as well as unnamed program by Wayne 2015, Sun 2019, and Van Storch 2019) on HbA1c: 3 RCTs showed both intervention and control groups had reductions > 0.5% in HbA1c while the other RCT did not show improvements in either group. Medication use was not reported in any of these studies, and only 1 RCT (of the Noom Coach program) indicated the intervention was not associated with harms. Overall, we have low confidence in these studies' findings as each program was only evaluated in 1 study, studies were small, and several studies had high rates of attrition.

Table 6. Detailed Findings From Studies of Programs That Promote Healthy Eating not Based on Diabetes or Dietary Guidelines

Study Characteristics	Weight Loss	HbA1c Reduction	Medication use	Serious or severe harms
My Dietitian ³⁴ 1-year online weight-loss intervention (I) vs usual care (C)	<ul style="list-style-type: none"> • 3 mo: ↓2% (I) vs 2% (C) • 1 yr: ↓4% (I) vs 2% (C) 	NR	NR	NR

Study Characteristics	Weight Loss	HbA1c Reduction	Medication use	Serious or severe harms
1 RCT (N=61)				
Noom Coach ³⁵ 12-week app-based diabetes management intervention with training from nurse (I) vs training from nurse alone (C) 1 RCT (N= 40)	NR	3 mo: ↓1.9% (I) vs 1% (C)	15% (I) and 20% (C) reduced their dosage of oral antidiabetic agents or insulin	<i>No severe hypoglycemia or hospitalization.</i>
Unnamed program (Wayne 2015) ³⁸ 6-month self-management intervention with vs without mobile phone support RCT (N=131)	6 mo: ↓1% (I) vs no change (C)	6 mo: ↓.7% (I) vs ↓1% (C)	NR	NR
Unnamed program (Sun 2019) ³⁶ 6-month app-based diet tracking + counseling intervention vs same intervention without use of app or continuous feedback RCT (N=91)	NR	<ul style="list-style-type: none"> • 3 mo: ↓.8% (I) vs .7% (C) • 6 mo: ↓1% (I) vs .7% (C) 	NR	NR
Unnamed program (Von Storch 2019) ³⁷ 12-month telemedicine-assisted lifestyle management program vs usual care RCT (N=115)	NR	3 mo: ↓.4% (I) vs no change (C)	NR	NR
Diab Memory + Nutrinaut ⁴⁴ 3-month app-based diet tracking + counseling intervention Pre-post study (N=24)	NR	3 mo: no change	NR	NR

↓=decrease; ↑=increase; I= intervention; C=Control; NR=Not reported; *Italics= Meets criteria for a minimum clinically important difference*

My Dietitian

Study Design

One RCT³⁴ (N = 61) conducted in the UK evaluated My Dietitian, a 1-year, online weight-loss program, compared to usual care. Participants were recruited from general practices within 2 counties. Intervention participants entered in the type, amount, and timing of food consumed online, which was converted into a pie chart showing a breakdown of calories consumed by food type. Coaching took the form of diet consultations (weekly for first 3 months then monthly for 9 months) and exercise consultations (same frequency). Participants also could track weight and

physical activity and could interact with others in the program through forums, diaries, and chat rooms. Control group participants received usual care from a GP. At baseline, participants had a median BMI between 33.3-34.4 kg/m² (obese). All participants were men. Outcomes were measured at 12 weeks and 1 year.

Results

At 12 weeks, both intervention and control groups lost 2% of their body weight in per-protocol analyses. At 1 year, intervention participants lost 4% of their body weight while the control group maintained a 2% weight loss in per-protocol analyses. None of these changes are clinically significant.

Limitations

This study had major limitations, most notably low rates of adherence (fewer than 50% of participants adhered to the intervention) and high rates of attrition (39% of intervention and 57% of control group dropped out). Researchers also did not conduct intent-to-treat analysis, which could have helped to account for dropouts.

Noom Coach

Study Design

One RCT³⁵ (N = 40) conducted in South Korea evaluated Noom Coach, a 12-week, smartphone-based, diabetes management intervention. Participants were recruited from a single university hospital. Both intervention and control group participants received education from a trained nurse at baseline and were encouraged to exercise, but intervention group participants also received access to an app where they could track their data (diet, physical activity, blood glucose) and receive feedback text messages from a medical team. At baseline, participants had an average BMI between 26.8 kg/m² and 28.9 kg/m² (overweight), had been diagnosed with diabetes for an average of 4-6.6 years, and had an average HbA1c between 8.8% and 9.1%. Outcomes were measured at 12 weeks.

Results

Weight loss was not reported in this study. At 12 weeks, HbA1c levels decreased in both groups (-1.9% [from 8.8% to 6.9%] in intervention group vs -1% [from 9.1% to 8.1%] in control group). A higher proportion of patients in the intervention group (47%) than in the control group (11%) reversed their diabetes (*ie*, lowered HbA1c < 6.5%). Although the percent of participants who stopped taking medication was not reported, 15% of intervention participants and 20% of control patients reduced their dosage of oral antidiabetic agents or insulin. Authors reported no serious adverse events (such as severe hypoglycemia or hospitalization) occurred.

Limitations

This was a small study, so the absolute number of participants who experienced improvements was low (*eg*, the 47% of intervention participants who reversed their diabetes represented 8 people). Other methodological limitations included the fact that participants and outcome assessors were aware of which group participants were in, which could have biased results.

Unnamed Programs

Study Designs

Three RCTs (N =131,³⁸ N =91³⁶, N =115³⁷) evaluated unnamed programs. One RCT³⁸ (n=131) conducted in Canada evaluated a 6-month, mobile phone-based intervention in which both intervention and control groups were coached to increase exercise, modify diet to limit carbohydrate intake, adhere to medications, and engage with PCPs, but intervention group participants had access to an app to help them track health data and either text or schedule phone calls with health coaches as needed. A second RCT³⁶ (N =91) conducted in China evaluated a 6-month, app-based data tracking and counseling intervention compared to usual care. In this study, both groups received instructions to monitor health data (physical activity and diet) and received dietary and exercise guidance, but only the intervention group could use the app and receive continuous feedback from coaches and a medical team. A third RCT³⁷ (N =115) conducted in Germany evaluated a 12-month telemedicine-assisted lifestyle management program compared to usual care. Participants were recruited from outpatient endocrinology clinics, primary care clinics, or based on their enrollment in a private insurance company. Participants tracked their health data (blood glucose, diet, physical activity) on a tablet and discussed progress monthly by phone with a coach who provided support based on stages of change theory. Across the 3 studies, average baseline BMI ranged from 23.3 kg/m² to 37 kg/m² (overweight-obese), HbA1c from 6.9% to 8.9%, and length of time diagnosed with diabetes from 7-12 years. In 1 RCT,³⁷ 94% of participants had >2 chronic diseases, in another³⁶ all participants were >65 years old, and in a third³⁸ participants were recruited from a low-SES community.

Results

In the first RCT,³⁸ both intervention and control group participants lowered HbA1c > 0.5% (-0.7%, from 8.7% to 8% in intervention group; -1%, from 8.9% to 7.9% in control group) at 6 months. In this study, intervention group participants lost 1% of body weight at 6 months – not a clinically significant change – while control group participants had no change, in per-protocol analyses. In the second RCT,³⁶ both intervention and control participants lowered HbA1c > 0.5% at 3 months and maintained changes at 6 months (-0.8%, from 7.8% to 7% in intervention group; -0.7% from 7.9% to 7.2% in control group). In this study, weight was not measured, but neither group lowered their BMI at 3 or 6 months. In the third RCT,³⁷ intervention participants lowered HbA1c by 0.4% (7% to 6.6%) – not a clinically meaningful change – while control group participants remained at baseline levels of HbA1c (6.9%) at 3 months, in per-protocol analyses. BMI was unchanged in both groups. Medication use and diabetes-related harms were not reported by any of these studies, although one RCT³⁸ noted that there were no adverse events related to exercise.

Limitations

Attrition was either high (>26%) or unreported in all 3 studies. Two of the studies^{36,37} had additional methodological issues, including either registering the trial retrospectively³⁶ or not registering the trial at all,³⁷ and there was significantly higher BMI in the intervention than control group at baseline in 1 study.³⁷

DiabMemory + Nutrinaut

Study Design

A pre-post study⁴⁴ (N = 24) conducted in Austria evaluated a 3-month intervention in which participants used 2 apps (DiabMemory and Nutrinaut) to track health data such as blood glucose, weight, and activity (DiabMemory) as well as meals (Nutrinaut). Participants were recruited from a disease management program within a national health insurance program. Coaching consisted of weekly individual counseling from a dietitian. Although the study describes testing the use of these 2 apps in 10 patients with type 2 diabetes, median baseline HbA1c was 5.9% (below the diagnostic threshold for diabetes). Baseline BMI was 34.5 kg/m² (obese).

Results

Weight was not reported, although authors note that participants lowered BMI by 2.7 kg/m². There was no effect on HbA1c at 3 months. Medication use and harms were not reported.

Limitations

Given the small sample size (N = 10 people with diabetes) and low levels of HbA1c at baseline, this study does not provide much useful information on the effect of these apps for people with diabetes. Authors also did not report how they measured outcomes.

SUMMARY AND DISCUSSION

We conducted a rapid evidence review evaluating the last 5 years of research on the effectiveness and harms of virtual diet programs that include a coaching component for people with diabetes. Although systematic reviews are available on the effectiveness and harms of various diets for diabetes¹⁵ as well as systematic reviews on virtual programs (including apps, websites, and patient portals) for diabetes self-management,¹⁹⁻²¹ to our knowledge there have been no systematic reviews specifically evaluating virtual diet programs. By describing the state of the evidence on this topic, this report can help inform the evaluation of the VA and Virta Health's pilot program among Veterans with type 2 diabetes.

Overall, we identified 1 non-randomized, controlled study on Virta Health and 14 studies of 13 other virtual diet programs for diabetes. Though the study of Virta Health had important limitations, it suggests that for selected patients (*ie*, those who are severely obese, interested in an intensive diabetes management program, and willing to adhere to the ketogenic diet), the Virta Health program is associated with improvements in diabetes outcomes such as weight and HbA1c. Some patients who participated in Virta Health also stopped taking medications and reversed their diabetes (*ie*, reduce HbA1c <6.5% with no medications or just metformin). Improvements were maintained for those who continued to participate in the program at 2 years. Three other virtual diet programs for diabetes (TeLiPro, Low Carb Program, and Better Therapeutics), all of which delivered a named diet, were associated with a improvements in 2 diabetes outcomes (*ie*, lowering HbA1c > .5%, weight loss >5%, and/or cessation of any medication). Two of these programs (TeLiPro and Low Carb Program) were associated with maintenance of improvements for a year or longer. In 1 of these programs (TeLiPro) the intervention ended at 12 weeks and in the other (Low Carb Program), participants continued to receive the intervention at 1 year.

Although benefits were more limited, 6 other virtual diet programs (u-Healthcare, Our Path, GlycoLeap, Noom Coach, and unnamed programs from Wayne 2015 and Sun 2019) were associated with a clinically meaningful improvement in 1 diabetes-related outcome (either lowering HbA1c >.5% or weight loss > 5%). In the Noom Coach study, more people reversed diabetes (*ie*, reduced HbA1c <6.5%) in the intervention group than the control group. Perhaps not surprisingly, in studies evaluating these 6 programs, participants that were in more active control groups (*ie*, those that received some but not all of the program) were more likely to experience improvements in diabetes outcomes than those that were in more passive control groups (*ie*, those who received usual care alone). Results from studies of uHealthcare and Noom Coach are especially interesting, as control group participants who received diet counseling from a coach experienced clinically meaningful improvements in HbA1c, but intervention group participants who received the diet counseling *and* had access to virtual tools experienced *greater* improvements. As a whole, studies in this review illustrate 2 important ideas: 1) most people who receive usual care for diabetes do not experience clinically meaningful improvements in outcomes such as HbA1c, weight, or medication reductions, and 2) diet counseling from a health coach may be associated with clinically meaningful improvements in diabetes-related outcomes, but the use of technology to facilitate tracking of health data or increase the number of touchpoints with a health coach may be associated with *additional* improvements.

LIMITATIONS

There were limitations to both our rapid review methods and methodological limitations of the included studies.

Rapid Review Limitations

One limitation of our review was that we only searched for the past 5 years of research on virtual diabetes diet programs, and as a result we may have missed older studies. However, we likely identified most of the relevant, recent literature on virtual diet programs that are currently available to patients. A second limitation is that we had 1 reviewer include studies and abstract data with second reviewer checking, which could have resulted in missing eligible studies or data. However, we made attempts to reduce this risk by establishing explicit inclusion criteria for studies and developing and using a piloted data abstraction tool. A third limitation is that we did not examine outcomes other than HbA1c, weight loss, medications reductions, and harms. Future reviews should examine other patient-important outcomes associated with these programs, such as patient satisfaction and quality of life.

Primary Study Limitations

A major methodological limitation of these studies is that a third (5/15) did not include a separate control group. As a result, for these studies, it is impossible to rule out the possibility that effects were due to either residual confounding or co-interventions that happened at the same time as the intervention. Studies also generally relied on volunteers who were interested in an intensive diabetes management program and had been screened out through various steps and therefore may not be representative of the typical patient with diabetes.

Of the 10 studies that used control groups, 5^{11,30,31,34,37,39-41} compared an intensive intervention to a more passive control group (usual care, typically from a GP or specialist). This is problematic for a few reasons. First, from a methodological standpoint, usual care often requires “minimal time and effort for the health care provider and/or participant and may be accompanied by low levels of interest or belief in its effectiveness”,⁵⁵ which can threaten the internal validity of the study. As discussed previously, studies in this review indeed found that participants who received usual care experienced no improvements in outcomes. This may at least partially be because participants did not believe usual care would be effective for them. Second, comparing an intensive, multi-component intervention to usual care makes it difficult to determine what is driving differences in outcomes. For example, in the 2 controlled studies of programs that showed a significant improvement in multiple diabetes outcomes compared to usual care (TeLiPro & Virta Health), we could not determine if it was the diet, the coaching, the tracking of health information, or the fact that patients had access to providers on a much more frequent basis (in some cases, every day) that caused the outcomes. Only 1 program (Virta Health) involved practitioners who were able to make adjustments to medications and 1 other (Low Carb Program) encouraged participants to regularly contact their providers regarding medication adjustments. It is not clear whether this capability is critical, especially if a goal of the coaching is to be able to wean some patients off of their diabetes medications. Importantly, we do not know to what extent the ketogenic diet was responsible for the improvements that patients experienced in the Virta Health study, and whether delivering the same intervention with a different diet (such as the Mediterranean diet) would have the same effects.

Additional limitations seen across studies include high attrition (>20%) or differential attrition between intervention and control groups, as well as inconsistent use of and reporting of results from intent-to-treat analyses.

GAPS AND FUTURE RESEARCH

We provide 2 sets of recommendations. The first set of recommendations is for the retrospective evaluation of the first group of Veterans enrolled in the pilot project involving Virta. The second set of recommendations is for a prospective evaluation of any additional Veterans that may enroll in a planned expansion of virtual diet programs being contemplated by the VA.

Recommendations for the retrospective evaluation of originally enrolled Veterans

Given the effects of Virta Health have only been evaluated in 262 participants that were on average severely obese (40.4 kg/m²), it is important to evaluate whether Veterans who may have different baseline characteristics and comorbidities can experience similar benefits as those in the Virta Health study. We therefore recommend that the pilot project capture as much information as is possible on Veteran participants' baseline characteristics (including BMI, HbA1c, lipid levels, diabetes duration, and any comorbidities) as well as outcomes (HbA1c, weight loss, medication cessation, and harms) at time points as close as possible to the time points used in the Virta Health study (baseline, 3 months, 1 year, 2 years). Given that many Veterans have multiple chronic diseases,⁵⁶ it is also important to capture whether Veterans participating in Virta Health experience any exacerbation of existing conditions or develop any other conditions such as coronary artery disease, chronic kidney disease, or diverticulitis. By matching the assessment of Virta Health among Veterans to the previous assessment of Virta Health in the general population, researchers can determine whether the potential impact of the Virta Health program appears to be comparable in Veterans and in the general population. This may help in understanding how patient characteristics such as baseline BMI and comorbidities affect the overall effectiveness of the program. To minimize the potential for attrition bias, outcomes of patients who dropped out of the program should be compared to those who stay in the program. Researchers could consider stratifying by engagement in the program to determine the minimum level of engagement needed for a clinically meaningful change in outcomes. Finally, if researchers compare those who participated in Virta to those who expressed interest in Virta but were not selected for participation, results are likely to be valid for adverse events but not necessarily diabetes outcomes. This is because those who are interested in but not selected for Virta may have low levels of belief in the effectiveness of usual care, which could theoretically affect their diabetes outcomes, but is unlikely to affect the occurrence of adverse events.

Recommendations for a prospective evaluation of Veterans that may enroll in the future

Our primary recommendation for the prospective evaluation of an expanded virtual diet program is to use a separate control group that is matched in terms of intensity to the selected program. If a program based on a ketogenic diet is chosen by VA, 1 based on an alternate diet (*e.g.*, low-carb, plant based, Mediterranean or general diabetes guidelines) could be used as a comparator. This could help clarify what is driving outcomes and whether any components of the program can be modified based on patient preference or need.

A recent RCT⁵⁶ (n=25) evaluated a virtual ketogenic diet program compared to the ADA's "Create Your Plate" diet (neither group received coaching) and found that those in the ketogenic group experienced greater improvements in HbA1c, weight loss, and diabetes reversal – although the ketogenic group also received additional behavioral help that the control group did not receive. Similar to the other studies in this report, this means it is impossible to tell whether it was the diet that drove outcome differences, or something else. Therefore, a study that delivers the same intervention in both groups *with the exception of the diet* would help to isolate the effect of the diet on outcomes. This is a critically important question in VA, as the ketogenic diet may be unappealing or contraindicated in some Veterans with type 2 diabetes, and other diets – such as the Mediterranean diet – have more evidence supporting their long-term cardiovascular benefits.⁵⁷

In addition to Virta, 3 options of commercially available programs available in English include the Low Carb Program (developed in the UK), Better Therapeutics (developed in the US), and Our Path (also developed in the UK), all of which showed that participants' experienced improvement in either weight or HbA1c. Using a different virtual diabetes diet program as a control group would have the added benefit of helping to determine whether different programs are acceptable alternatives should a Veteran decline to use a specific diet such as ketogenic diet or plant-based diet. A third alternative would be to compare a commercial program to continuous care provided by a diabetes educator within the context of an interdisciplinary care team,⁵⁸ an intervention that is similar in intensity to Virta and other commercial programs but is not delivered virtually. The VA's National Center for Health Promotion and Disease Prevention has expanded a program of Telephone Life Coaches who may be able to deliver a comparably intensive program.⁵⁹

While randomizing patients to either the selected program or a comparator would be the most straightforward way to reduce the risk of selection and confounding bias, this might be difficult to do outside of a specifically funded research study. It also would not replicate the real-life effectiveness of Veterans choosing which diet or program they want to participate in. Therefore, one approach researchers could take is to let participants select their preferred program. A second approach would be to use an alternative program as a "back-up" in the event participants could not tolerate the selected diet. This option should only be used if it is not feasible to let participants select their preferred program. If participants are not randomized to different groups, it would be important to measure, report, and control for baseline factors that can potentially confound the results.

Similar to our recommendations for the retrospective evaluation, we recommend that the prospective evaluation capture detailed information on participants' baseline characteristics (including BMI, HbA1c, diabetes duration, and any comorbidities) and measure outcomes at similar time points as seen in the Virta Health study. Researchers may also consider measuring other baseline characteristics such as motivation or comfortability with technology, as this may provide additional information on mediators or moderators of treatment effect. We also recommend that researchers look for a wide range of data on harms as well as other patient-important outcomes such as quality of life.

CONCLUSIONS

While they have important limitations, studies of Virta Health and other virtual diet programs suggest that selected populations with type 2 diabetes may lower HbA1c, lose weight, reduce medication use, or reverse diabetes after participating in an intensive program based on a ketogenic diet or other diets. Due to limitations in study designs, we could not determine whether these outcomes were driven by the remote continuous care interventions or by the diets. Additionally, because studies enrolled participants who were interested in intensive diabetes management programs and met other study eligibility criteria, findings may not apply to the wider, unselected Veteran population. As Veterans' preferences for the type of diet they follow are likely to vary, a practical solution to improving diabetes care should include testing a variety of diet options if the particular diet is not the critical component of the intervention. This type of evaluation could inform how Virta Health and other virtual diabetes programs might be adapted to meet the needs of a variety of Veterans with type 2 diabetes.

ACKNOWLEDGMENTS

This topic was developed in response to a nomination by Steve Pizer, PhD and David Atkins, MD MPH for the purpose of informing the ongoing VA and Virta Health pilot project evaluation. The scope was further developed with input from the topic nominators (*ie*, Operational Partners) and the ESP Coordinating Center.

In designing the study questions and methodology at the outset of this report, the ESP consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

The authors gratefully acknowledge Payten Sonnen for her help with data extraction and Julia Haskin, MA for her editorial review. The authors also acknowledge the following individuals for their contributions to this project:

Operational Partners

Operational partners are system-level stakeholders who have requested the report to inform decision-making. They recommend Technical Expert Panel (TEP) participants; assure VA relevance; help develop and approve final project scope and timeframe for completion; provide feedback on draft report; and provide consultation on strategies for dissemination of the report to field and relevant groups.

David Atkins, MD, MPH
Director
Health Services Research and Development

Steve Pizer, PhD
Chief Economist
Partnered Evidence-based Policy Resource Center
VA Boston Healthcare System

Key Informants

The ESP sought input from 2 Key Informants with expertise in delivering diet education and counseling among patients with type 2 diabetes in clinical settings.

Shannon Hughes, RD CDE
VA Portland Health Care System, Nutrition and Food Service
Portland, OR

Dawn Barnachea, RD CDE
VA Portland Health Care System, Nutrition and Food Service
Portland, OR

REFERENCES

1. Liu Y, Sayam S, Shao X, et al. Prevalence of and Trends in Diabetes Among Veterans, United States, 2005-2014. *Prev Chronic Dis*. 2017;14:E135-E135.
2. National Diabetes Statistics Report 2020; Estimates of Diabetes and Its Burden in the United States. Centers for Disease Control and Prevention. <https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf>. Published 2020. Accessed May 26, 2020, 2020.
3. *VA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF TYPE 2 DIABETES MELLITUS IN PRIMARY CARE*. Department of Veteran Affairs Department of Defense;2017.
4. Evert AB DM, Gardner CD, Garvey WT, Lau K, MacLeod, Mitri J, Pereira RF, Rawlings K, Shamera Robinson, Saslow K, Uelmen S, Urbanski PB, Yancy W. Nutrition Therapy for Adults With Diabetes or Prediabetes: A Consensus Report. *Diabetes Care*. 2019;42.
5. MacLeod J, Franz MJ, Handu D, et al. Academy of Nutrition and Dietetics Nutrition Practice Guideline for Type 1 and Type 2 Diabetes in Adults: Nutrition Intervention Evidence Reviews and Recommendations. *Journal of the Academy of Nutrition and Dietetics*. 2017;117(10):1637-1658.
6. MacKeen D. What Is the Keto Diet and Does It Work? The New York Times <https://www.nytimes.com/2020/01/02/style/self-care/keto-diet-explained-benefits.html>. Published 2020. Updated January 6, 2020. Accessed May 26, 2020.
7. Diet Review: Ketogenic Diet for Weight Loss. Harvard University. <https://www.hsph.harvard.edu/nutritionsource/healthy-weight/diet-reviews/ketogenic-diet/>. Published 2020. Accessed May 25, 2020.
8. Westman EC, Tondt J, Maguire E, Yancy WS. Implementing a low-carbohydrate, ketogenic diet to manage type 2 diabetes mellitus. *Expert Review of Endocrinology & Metabolism*. 2018;13(5):263-272.
9. Muscogiuri G, Barrea L, Laudisio D, et al. The management of very low-calorie ketogenic diet in obesity outpatient clinic: a practical guide. *Journal of Translational Medicine*. 2019;17(1):356.
10. Gershuni VM, Yan SL, Medici V. Nutritional Ketosis for Weight Management and Reversal of Metabolic Syndrome. *Curr Nutr Rep*. 2018;7(3):97-106.
11. Hallberg SJ, McKenzie AL, Williams PT, et al. Effectiveness and safety of a novel care model for the management of type 2 diabetes at 1 year: an open-label, non-randomized, controlled study. *Diabetes Therapy*. 2018;9(2):583-612.
12. Bueno NB, de Melo IS, de Oliveira SL, da Rocha Ataide T. Very-low-carbohydrate ketogenic diet v. low-fat diet for long-term weight loss: a meta-analysis of randomised controlled trials. *Br J Nutr*. 2013;110(7):1178-1187.
13. Joshi S, Ostfeld RJ, McMacken M. The Ketogenic Diet for Obesity and Diabetes—Enthusiasm Outpaces Evidence. *JAMA Intern Med*. 2019;179(9):1163-1164.
14. Kirkpatrick CF, Bolick JP, Kris-Etherton PM, et al. Review of current evidence and clinical recommendations on the effects of low-carbohydrate and very-low-carbohydrate (including ketogenic) diets for the management of body weight and other cardiometabolic risk factors: A scientific statement from the National Lipid Association Nutrition and Lifestyle Task Force. *Journal of Clinical Lipidology*. 2019;13(5):689-711.e681.

15. Low Carbohydrate Diets for Diabetes: A Review of the Clinical Effectiveness and Guidelines. Ottawa: CADTH. Published 2019. Updated October 2019. Accessed May 26, 2020, 2020.
16. Neuenschwander M HG, Schwingshackl L, Schlesinger S. Impact of different dietary approaches on blood lipid control in patients with type 2 diabetes mellitus: a systematic review and network meta-analysis. *Eur J Epidemiol.* 2019;39:837-852.
17. Pan B WY, Yang Q, et al. The impact of major dietary patterns on glycemic control, cardiovascular risk factors, and weight loss in patients with type 2 diabetes: a network meta-analysis. *J Evid Based Med.* 2019;12:29-39.
18. Schwingshackl L CA, Hoffmann G, Schwedhelm C, Boeing H. A network meta-analysis on the comparative efficacy of different dietary approaches on glycaemic control in patients with type 2 diabetes mellitus. *Eur J Epidemiol.* 2018;33:157-170.
19. Veazie S, Winchell K, Gilbert J, et al. Rapid Evidence Review of Mobile Applications for Self-management of Diabetes. *J Gen Intern Med.* 2018;33(7):1167-1176.
20. Wu X, Guo X, Zhang Z. The Efficacy of Mobile Phone Apps for Lifestyle Modification in Diabetes: Systematic Review and Meta-Analysis. *JMIR Mhealth Uhealth.* 2019;7(1):e12297.
21. Sahin C, Courtney KL, Naylor PJ, R ER. Tailored mobile text messaging interventions targeting type 2 diabetes self-management: A systematic review and a meta-analysis. *Digit Health.* 2019;5:2055207619845279.
22. Vita Health: Clinically Proven Treatment for Diabetes Reversal <https://www.virtahealth.com/>. Accessed May 26, 2020, 2020.
23. Veterans Living with Type 2 Diabetes Achieve Rapid Health Improvements in Virta Health Partnership with VA. Virta Health <https://www.virtahealth.com/blog/veterans-type-2-diabetes-rapid-health-improvement-virta-treatment>. Updated February 4, 2020. Accessed 2020, May 26.
24. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ.* 2011;343:d5928.
25. Sterne J HM, McAleenan, Reeves B, Higgins J. Chapter 25: Assessing risk of bias in a non-randomized study. Cochrane Training <https://training.cochrane.org/handbook/current/chapter-25>. Accessed May 26, 2020.
26. Berkman ND, Lohr KN, Ansari M, et al. *Grading the Strength of a Body of Evidence When Assessing Health Care Interventions for the Effective Health Care Program of the Agency for Healthcare Research and Quality: An Update Methods Guide for Effectiveness and Comparative Effectiveness Reviews.* Rockville MD2013.
27. Sherwani SI, Khan HA, Ekhzaimy A, Masood A, Sakharkar MK. Significance of HbA1c Test in Diagnosis and Prognosis of Diabetic Patients. *Biomark Insights.* 2016;11:95-104.
28. Donnelly JE, Blair SN, Jakicic JM, Manore MM, Rankin JW, Smith BK. American College of Sports Medicine Position Stand. Appropriate physical activity intervention strategies for weight loss and prevention of weight regain for adults. *Med Sci Sports Exerc.* 2009;41(2):459-471.
29. Defining Adult Overweight and Obesity. Centers for Disease Control and Prevention. <https://www.cdc.gov/obesity/adult/defining.html>. Updated April 3, 2020. Accessed May 26, 2020.
30. Kempf K, Altpeter B, Berger J, et al. Efficacy of the Telemedical Lifestyle intervention Program TeLiPro in Advanced Stages of Type 2 Diabetes: A Randomized Controlled Trial. *Diabetes Care.* 2017;40(7):863-871.

31. Hansel B, Giral P, Gambotti L, et al. A Fully Automated Web-Based Program Improves Lifestyle Habits and HbA1c in Patients With Type 2 Diabetes and Abdominal Obesity: Randomized Trial of Patient E-Coaching Nutritional Support (The ANODE Study). *J Med Internet Res*. 2017;19(11):e360.
32. Lim S, Kang SM, Kim KM, et al. Multifactorial intervention in diabetes care using real-time monitoring and tailored feedback in type 2 diabetes. *Acta Diabetol*. 2016;53(2):189-198.
33. Kim KM, Park KS, Lee HJ, et al. Efficacy of a New Medical Information system, Ubiquitous Healthcare Service with Voice Inception Technique in Elderly Diabetic Patients. *Sci*. 2015;5:18214.
34. Haste A, Adamson AJ, McColl E, Araujo-Soares V, Bell R. Web-Based Weight Loss Intervention for Men With Type 2 Diabetes: Pilot Randomized Controlled Trial. *JMIR Diabetes*. 2017;2(2):e14.
35. Ku EJ, Park JI, Jeon HJ, Oh TK, Choi HJ. Clinical Efficacy and Plausibility of a Smartphone-based Integrated Online Real-time Diabetes Care System via Glucose and Diet Data Management: A Pilot Study. *Intern Med J*. 2020;06:06.
36. Sun C, Sun L, Xi S, et al. Mobile Phone-Based Telemedicine Practice in Older Chinese Patients with Type 2 Diabetes Mellitus: Randomized Controlled Trial. *JMIR Mhealth Uhealth*. 2019;7(1):e10664.
37. Von Storch K, Graaf E, Wunderlich M, Rietz C, Polidori MC, Woopen C. Telemedicine-Assisted Self-Management Program for Type 2 Diabetes Patients. *Diabetes Technol Ther*. 2019;21(9):514-521.
38. Wayne N, Perez DF, Kaplan DM, Ritvo P. Health Coaching Reduces HbA1c in Type 2 Diabetic Patients From a Lower-Socioeconomic Status Community: A Randomized Controlled Trial. *J Med Internet Res*. 2015;17(10):e224.
39. McKenzie AL, Hallberg SJ, Creighton BC, et al. A Novel Intervention Including Individualized Nutritional Recommendations Reduces Hemoglobin A1c Level, Medication Use, and Weight in Type 2 Diabetes. *JMIR Diabetes*. 2017;2(1):e5.
40. Bhanpuri NH, Hallberg SJ, Williams PT, et al. Cardiovascular disease risk factor responses to a type 2 diabetes care model including nutritional ketosis induced by sustained carbohydrate restriction at 1 year: an open label, non-randomized, controlled study. *Cardiovascular diabetology*. 2018;17(1):56.
41. Athinarayanan SJ, Adams RN, Hallberg SJ, et al. Long-term effects of a novel continuous remote care intervention including nutritional ketosis for the management of type 2 diabetes: a 2-year non-randomized clinical trial. *Front Endocrinol (Lausanne)*. 2019;10:348.
42. Saslow LR, Summers C, Aikens JE, Unwin DJ. Outcomes of a Digitally Delivered Low-Carbohydrate Type 2 Diabetes Self-Management Program: 1-Year Results of a Single-Arm Longitudinal Study. *JMIR Diabetes*. 2018;3(3):e12.
43. Idris I, Hampton J, Moncrieff F, Whitman M. Effectiveness of a Digital Lifestyle Change Program in Obese and Type 2 Diabetes Populations: Service Evaluation of Real-World Data. *JMIR Diabetes*. 2020;5(1):e15189.
44. Schusterbauer V, Feitek D, Kastner P, Toplak H. Two-Stage Evaluation of a Telehealth Nutrition Management Service in Support of Diabetes Therapy. *Stud Health Technol Inform*. 2018;248:314-321.

45. Berman MA, Guthrie NL, Edwards KL, et al. Change in Glycemic Control With Use of a Digital Therapeutic in Adults With Type 2 Diabetes: Cohort Study. *JMIR Diabetes*. 2018;3(1):e4.
46. Koot D, Goh PSC, Lim RSM, et al. A Mobile Lifestyle Management Program (GlycoLeap) for People With Type 2 Diabetes: Single-Arm Feasibility Study. *JMIR Mhealth Uhealth*. 2019;7(5):e12965.
47. Saslow LR, Mason AE, Kim S, et al. An Online Intervention Comparing a Very Low-Carbohydrate Ketogenic Diet and Lifestyle Recommendations Versus a Plate Method Diet in Overweight Individuals With Type 2 Diabetes: A Randomized Controlled Trial. *J Med Internet Res*. 2017;19(2):e36.
48. McKenzie A, Athinarayanan S, Adams R, Volek J, Phinney S, Hallberg S. SUN-LB113 A Continuous Remote Care Intervention Utilizing Carbohydrate Restriction Including Nutritional Ketosis Improves Markers of Metabolic Risk and Reduces Diabetes Medication Use in Patients With Type 2 Diabetes Over 3.5 Years. *Journal of the Endocrine Society*. 2020;4(Supplement_1).
49. ADAMS RN, MCKENZIE A, ATHINARAYANAN SJ, HALLBERG S, MCCARTER JP, PHINNEY S. 889-P: Early Engagement in a Continuous Care Intervention Predicts One-Year Improvements in Weight and HbA1c among Adults with T2D. *Diabetes*. 2019;68(Supplement 1):889-P.
50. ATHINARAYANAN SJ, MCKENZIE A, ADAMS RN, HALLBERG S, MCCARTER JP, PHINNEY S. 759-P: Analysis of a Two-Year Continuous Care Intervention Including Nutritional Ketosis—Exploring Baseline Predictors of Diabetes Reversal and Remission. *Diabetes*. 2019;68(Supplement 1):759-P.
51. Vilar-Gomez E, Athinarayanan SJ, Adams RN, et al. Post hoc analyses of surrogate markers of non-alcoholic fatty liver disease (NAFLD) and liver fibrosis in patients with type 2 diabetes in a digitally supported continuous care intervention: an open-label, non-randomised controlled study. *BMJ Open*. 2019;9(2):e023597.
52. Siegmann MJ, Athinarayanan SJ, Hallberg SJ, et al. Improvement in patient-reported sleep in type 2 diabetes and prediabetes participants receiving a continuous care intervention with nutritional ketosis. *Sleep medicine*. 2019;55:92-99.
53. Watson R, Pickler R, Noyes J, et al. How many papers can be published from one study? *Journal of Advanced Nursing*. 2015;71(11):2457-2460.
54. Jackson D, Walter G, Daly J, Cleary M. Editorial: Multiple outputs from single studies: acceptable division of findings vs. ‘salami’ slicing. *J Clin Nurs*. 2014;23(1-2):1-2.
55. Aycock DM, Hayat MJ, Helvig A, Dunbar SB, Clark PC. Essential considerations in developing attention control groups in behavioral research. *Research in Nursing & Health*. 2018;41(3):320-328.
56. Balbale SN, Etingen B, Malhiot A, Miskevics S, LaVela SL. Perceptions of Chronic Illness Care Among Veterans With Multiple Chronic Conditions. *Mil Med*. 2016;181(5):439-444.
57. Martínez-González MA, Gea A, Ruiz-Canela M. The Mediterranean Diet and Cardiovascular Health. *Circulation Research*. 2019;124(5):779-798.
58. McGill M, Blonde L, Chan JCN, et al. The interdisciplinary team in type 2 diabetes management: Challenges and best practice solutions from real-world scenarios. *J Clin Transl Endocrinol*. 2016;7:21-27.
59. Telephone Lifestyle Coaching (TLC) Program. <https://www.prevention.va.gov/TLC/>. Published 2020. Updated April 29, 2020. Accessed August 19, 2020.