Evidence Brief: Virtual Diet Programs for Diabetes

Supplementary Materials

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Department of Veterans Affairs
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U.S. Department of Veterans Affairs
Veterans Health Administration
Health Services Research & Development Service

TABLE OF CONTENTS

SEARCH STRATEGIES

DATABASE: OVID MEDLINE (04-13-2020)

1. Diabetes Mellitus, Type 2/

2. (diabetes adj1 type 2).mp.

3. 1 or 2

4. Self-Management/ or Self Care/ or Disease Management/ or Mentoring/ or Self Report/

5. (monitor* or self?monitor* or manag* or self?manag* or control or self?control* or self?care or coach* or mentor* or (continuous adj1 care)).mp.

6. 4 or 5

7. Mobile Applications/ or exp Cell Phone/ or exp Telemedicine or exp Internet or Smartphone/

8. (tele* or mobile* or mhealth* or m-health* or ehealth* or e-health* or digital* or online* or Internet* or web or web-based or technology* or app or apps or application* or applet* or SMS or text or text-messag* or cellphone* or cell-phone* or phone* or smartphone* or iphone* or ipad* or android* or email* or virtual* or game or game-* or gaming or social media or social network* or Facebook* or Skype* or Twitter* or Snapchat* or Instagram* or LinkedIn*).mp.

9. 7 or 8

10. exp Diet/

11. diet*.mp.

12. 10 or 11

13. 3 and 6 and 9 and 12

14. limit 13 to english language

15. limit 14 to last 5 years

DATABASE: COCHRANE DATABASE OF SYSTEMATIC REVIEWS (04-20-2020)

1. MeSH descriptor: [Diabetes Mellitus, type 2] this term only

2. (diabetes N1 type 2):ti,ab,kw

3. #1 OR #2

4. MeSH descriptor: [Self-Management] this term only

5. MeSH descriptor: [Self Care] this term only

6. MeSH descriptor: [Disease Management] this term only

7. (monitor* or self?monitor* or manag* or self?manag* or control* or self?control* or self?care):ti,ab,kw

8. (OR #4-#7)

9. MeSH descriptor: [Mobile Applications] this term only

10. MeSH descriptor: [Cell Phone] explode all trees

11. MeSH descriptor: [Telemedicine] explode all trees

12. MeSH descriptor: [Internet] explode all trees

13. MeSH descriptor: [Smartphone] this term only

14. (tele* or mobile* or mhealth* or m-health* or ehealth* or e-health* or digital* or online* or Internet* or web or web-based or technology* or app or apps or application* or applet* or SMS or text or text-messag* or cellphone* or cell-phone* or phone* or smartphone* or iphone* or ipad* or android* or email* or virtual* or game or game-* or gaming or social media or social network* or Facebook* or Skype* or Twitter* or Snapchat* or Instagram* or LinkedIn*):ti,ab,kw

15. (OR #9-#14)

16. #3 AND #8 AND #15

DATABASE: CINAHL (04-20-2020)

1. (MH "Diabetes Mellitus, Type 2")

2. TI diabetes N1 type 2 OR AB diabetes N1 type 2

3. S1 OR S2

4. (MH "Self-Management") OR (MH "Self Care") OR (MH "Disease Management") OR (MH "Mentorship") OR (MH "Self Report")

5. TI ((monitor* or self?monitor* or manag* or self?manag* or control or self?control* or self?care or coach* or mentor* or (continuous N1 care))) OR AB ((monitor* or self?monitor* or manag* or self?manag* or control or self?control* or self?care or coach* or mentor* or (continuous N1 care)))

6. S4 OR S5

7. (MH "Mobile Applications") OR (MH "Cellular Phone+") OR (MH "Telemedicine+") OR (MH "Internet+") OR (MH "World Wide Web Applications+") OR (MH "Smartphone")

8. (tele* or mobile* or mhealth* or m-health* or ehealth* or e-health* or digital* or online* or Internet* or web or web-based or technology* or app or apps or application* or applet* or SMS or text or text-messag* or cellphone* or cell-phone* or phone* or smartphone* or iphone* or ipad* or android* or email* or virtual* or game or game-* or gaming or social media or social network* or Facebook* or Skype* or Twitter* or Snapchat* or Instagram* or LinkedIn*)

9. S7 OR S8

10. (MH "Diet+")

11. diet*

12. S10 OR S11

13. S3 AND S6 AND S9 AND S12

14. Narrow by Language - english

15. Narrow by Pubslihed Date: 20150101-20201231

DATABASE: CENTRAL (04-20-2020)

1. Diabetes Mellitus, Type 2/

2. (diabetes adj1 type 2).mp.

3. 1 or 2

4. Self-Management/ or Self Care/ or Disease Management/ or Mentoring/ or Self Report/

5. (monitor* or self?monitor* or manag* or self?manag* or control or self?control* or self?care or coach* or mentor* or (continuous adj1 care)).mp.

6. 4 or 5

7. Mobile Applications/ or exp Cell Phone/ or exp Telemedicine or exp Internet or Smartphone/

8. (tele* or mobile* or mhealth* or m-health* or ehealth* or e-health* or digital* or online* or Internet* or web or web-based or technology* or app or apps or application* or applet* or SMS or text or text-messag* or cellphone* or cell-phone* or phone* or

smartphone* or iphone* or ipad* or android* or email* or virtual* or game or game-* or gaming or social media or social network* or Facebook* or Skype* or Twitter* or Snapchat* or Instagram* or LinkedIn*).mp.

9. 7 or 8

10. exp Diet/

11. diet*.mp.

12. 10 or 11

13. 3 and 6 and 9 and 12

14. limit 13 to last 5 years

15. limit 14 to english language

LIST OF EXCLUDED STUDIES

Exclude reasons: 1=Ineligible population, 2=Ineligible intervention, 3=Ineligible comparator, 4=Ineligible outcome, 5=Ineligible setting, 6=Ineligible study design, 7=Ineligible publication type, 8=Outdated or ineligible systematic review, 9=Non-English language, 10=couldn't find FT

#	Citation	Exclude reason
1	Al-Ozari (2018). "Diabetes and TelecommunicationS (DATES) study to support self-management for people with type 2 diabetes: a randomized controlled trial." BMC Public Health	E7
2	Arambepola, C., et al. (2016). "The Impact of Automated Brief Messages Promoting Lifestyle Changes Delivered Via Mobile Devices to People with Type 2 Diabetes: A Systematic Literature Review and Meta-Analysis of Controlled Trials." Journal of Medical Internet Research 18(4): e86	E7
3	Avedzi HM, et al. (2019). "Healthy Eating and Active Living for Diabetes-Glycemic Index (HEALD-GI): Protocol for a Pragmatic Randomized Controlled Trial." JMIR Res Protoc. 8(3):e11707.	E2
4	Boels, A. M., et al. (2019). "Effectiveness of diabetes self-management education and support via a smartphone application in insulin-treated patients with type 2 diabetes: results of a randomized controlled trial (TRIGGER study)." BMJ open diabetes research and care 7(1).	E2
5	Cassimatis M, Kavanagh DJ, Hills AP, et al. (2015). "The OnTrack Diabetes Web-Based Program for Type 2 Diabetes and Dysphoria Self-Management: A Randomized Controlled Trial Protocol". JMIR Res Protoc. 4(3):e97.	E7
6	Holmen H., et al. (2016). "Stages of change for physical activity and dietary habits in persons with type 2 diabetes included in a mobile health intervention: the Norwegian study in RENEWING HEALTH." BMJ open diabetes res. 4(1):e000193	E4
7	Karduck J., et al. (2018). "Results of the Clinician Apps Survey, How Clinicians Working With Patients With Diabetes and Obesity Use Mobile Health Apps." J Nutr Educ Behav. 50(1):62-69.e61.	E1
8	Kim EK, et al. (2019). "The Effect of a Smartphone-Based, Patient-Centered Diabetes Care System in Patients With Type 2 Diabetes: A Randomized, Controlled Trial for 24 Weeks." Diabetes Care. 42(1):3-9	E2
9	Nelson LA., et al. (2018). "Mobile Phone Support for Diabetes Self-Care Among Diverse Adults: Protocol for a Three-Arm Randomized Controlled Trial." JMIR Res Protoc. 7(4):e92	E7
10	Oka R., et al. (2019). "Study Protocol for the Effects of Artificial Intelligence (AI)-Supported Automated Nutritional Intervention on Glycemic Control in Patients with Type 2 Diabetes Mellitus." Diabetes Ther. 10(3):1151-1161.	E7
11	Porter J., et al. (2016). "Effect of Using Mobile Technology-Based Methods That Record Food or Nutrient Intake on Diabetes Control and Nutrition Outcomes: A Systematic Review." Nutrients. 8(12):815.	E7
13	Ramadas A., et al. (2018) "Randomised-controlled trial of a web-based dietary intervention for patients with type 2 diabetes: changes in health cognitions and glycemic control." BMC Public Health. 18(1):716.	E2
14	Sahin C., et al. (2019). "Tailored mobile text messaging interventions targeting type 2 diabetes self-management: A systematic review and a meta-analysis." Digit Health. 5:2055207619845279	E7

#	Citation	Exclude reason
15	Saslow LR., et al. (2017). "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. 19(2):e36.	E2
16	Thomson H., et al. (2018). "Protocol for a clinical trial of text messaging in addition to standard care versus standard care alone in prevention of type 2 diabetes through lifestyle modification in India and the UK." BMC Endocr Disord.18(1):63	E1
17	Vinitha R., et al. (2019). "Effectiveness of mobile phone text messaging in improving glycaemic control among persons with newly detected type 2 diabetes." Diabetes Res Clin Pract. 158:107919.	E2
18	Vorderstrasse AA., et al. (2015). "Diabetes Learning in Virtual Environments: Testing the Efficacy of Self-Management Training and Support in Virtual Environments (Randomized Controlled Trial Protocol)." Nurs Res. 64(6):485-493.	E2
19	Wu X., et al. (2019). "The Efficacy of Mobile Phone Apps for Lifestyle Modification in Diabetes: Systematic Review and Meta-Analysis." JMIR Mhealth Uhealth. 7(1):e12297.	E7
20	(2019). "The rationale and design of the personal diet study, a randomized clinical trial evaluating a personalized approach to weight loss in individuals with pre-diabetes and early-stage type 2 diabetes." Contemp Clin Trials. 79:80-88	E7
21	Kapostasy, A., et al. (2017). "Effects of a 12-week telenutrition weight loss intervention on diet quality in men." FASEB journal 31(1).	E7
22	Lee, E. S., et al. (2016). "The results of extended study of smart phone based the S-Diabetes Care programme in policyholders with type 2 diabetes." Diabetologia 59(1): S422-S423.	E7
23	Myers, A. K., et al. (2017). "Assessing the feasibility of using an in-home, tablet-based telemonitoring care management program in black (B) and hispanic/latino (H/L) disparity patients with type 2 diabetes mellitus (T2DM)." Endocrine reviews 38(3).	E7
24	Whittemore, R., et al. (2019). "Yo puedo! A self-management group and mHealth program for low-income adults with type 2 diabetes in Mexico City." Diabetes 68.	E7
25	Siegmann, et al. (2019) "Improvement in patient-reported sleep in type 2 diabetes and prediabetes participants receiving a continuous care intervention with nutritional ketosis." Sleep medicine 55 92-99.	E4
26	Vilar-Gomez E., et al. (2019). "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. 9(2):e023597.	E4
27	Zhou W., et al. (2016). "Welltang–A smart phone-based diabetes management application–Improves blood glucose control in Chinese people with diabetes." Diabetes research and clinical practice. 116:105-110.	E2
28	Bao S, Jiang H, Luo Y, Zhang D. Application of diabetes phone recipe software in diet intervention for patients with type 2 diabetes. Chinese Nursing Research 2017;31(11):1407-8. Doi: 10.3969/j.issn.1009-6493.2017.11.042.	E10

Insert table footnotes here, in ESP Figure Notes style.

EVIDENCE TABLES

DATA ABSTRACTION OF INCLUDED PRIMARY STUDIES

Data Abstraction of RCTs

Author Year N	Patient Characteristics	Intervention	Comparator	HbA1c, weight, medication use outcomes	Harms	Setting
Haste 2017 N= 61 1 year	**Adults with T2D Age:** median 58 years (I) & 61 years (C) **Sex:** All participants were male **Length of time diagnosed with T2D:** NR **Baseline BMI/weight:** median 33.3 kg/m2 (I) & 34.4 kg/m2 (C) / 106.5 kg (I) & 109.3 kg (C) **Baseline HbA1c:** NR **T2D comorbidities:** NR **Other comorbidities:** NR	**Diet:** My Dietician (I) website provided a weight-loss program. Participants used website to record type and amount of food and time consumed. Information could be converted into calories consumed and represented in a pie chart showing percentages for food types consumed. Database of recipes, and non-interactive diet and weight loss advice were available. **Coaching:** Dietitians were expected to provide Web-based consultations on a maximum weekly basis for the first 3 months (n=12) and then monthly for the last 9 months. Exercise experts provided Web-based consultations on a maximum monthly basis for the first 3 months (n=3) and then every 3 months for the last 9 months **Other components:** Participants had the option to record waist and weight measurements and amount of steps taken presented in a graph to display participant's progress as part of the intervention. Users could interact through forums, diaries, and chat rooms.	Control group (C) received usual care for weight loss according to GP's normal processes.	**HbA1c:** NR **Weight/BMI:** In per-protocol analyses, intervention group lost 2.35 kg (compared to 2.2 kg for control) at 3 months. Intervention group lost 4.3 kg (compared to 2.5 kg for control) at 12 months. BMI was reduced by .9 kg/m2 in intervention (vs .7 kg/m2 in control) at 3 months and was reduced by 1.7 kg/m2 (vs .8 kg/m2 in control) at 12 months. **Medication reductions:** NR	NR	Pts recruited through UK primary care research network
Hansel 2017 N=120	**Adults with T2D Age:** mean 57.6 years (I) & 55.5 (C) **Sex (% female):** 66.7% (I&C)	**Diet:** ANODE is a web-based nutritional support tool that is designed to improve lifestyle habits, including both diet and physical activity, and consists of four modules, 3 of which were related to diet: (1) diet and physical activity self-	In control group, participants were asked to continue their usual follow-up with their general practitioner and/or	**HbA1c:** In ITT analysis at 16 weeks, HbA1c had lowered by -.30 (SD .94) in I group and increased by .21 (SD 2.1) in C group.	NR	Two university Hospitals in Paris, France

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Author Year N	Patient Characteristics	Intervention	Comparator	HbA1c, weight, medication use outcomes	Harms	Setting
16 weeks	**Length of time diagnosed with T2D:** NR **Baseline BMI/weight:** 33.4 kg/m2 (I&C)/ 93.3 (I) & 93.5 (C) **Baseline HbA1c:** 7.2% (I&C) **T2D comorbidities:** **Other comorbidities:** 1.9% (I) & 6.7% (C) had microangiopathy; 3.3% (I) & 6.7% (C) had history of CVD	monitoring module, (2) nutritional assessment, (3) balanced diet menu generator. **Coaching:** Based on 24-hour dietary recall, the program informed the patients about the mean level of calories ingested as well as the mean fat, saturated fat, protein, salt, and carbohydrate contents in their diet. Intakes of certain food groups (ie, fish, starchy foods, high-fat foods, dairy products, alcoholic beverages, and water) were also reported. Participants also received advice to ensure a balanced diet according to national guidelines. **Other components:** Human contact limited to hotline support in cases of technical issues. 4th module is a physical activity education and prescription program.	specialist.	**Weight/BMI:** In ITT analysis at 16 weeks, I group lost 2.3 kg (SD 3) of weight vs C group gained .2 kg (SD 2.5). **Medication reductions:** NR		
Kempf 2017 N=202 1 year	**Adults with T2D** **Age (average):** 59 (I) & 60 (C) **Sex (% female):** 45% (I) & 47% (C) **Length of time diagnosed with T2D:** 11 years (I & C) **Baseline BMI/weight:** 35.3 kg/m2 (I) & 37 kg/m2 (C) / 104.3 kg (I) & 110.8 kg (C) **Baseline HbA1c:** 8.4% (I) & 8.2% (C) **T2D comorbidities:** NR **Other comorbidities:** All ppts were overweight or obese	**Diet:** During the first week of the study, the Telemedical Lifestyle Intervention Program (I) group replaced breakfast, lunch, and dinner with 1 g protein-rich meal replacement (PRMR)/kg normal body wt (defined as height in cm 2 100) per meal (dissolved in 250 mL water) and consumed 45 g oil rich in n-3 fatty acids and 750 mL vegetable juice each day. No additional snacks were permitted. During weeks 2–4, breakfast and dinner were replaced by PRMR, and a low-carbohydrate protein-rich lunch was allowed. This lunch included 150–200 g fish or meat, 500 g vegetables, and not more than 50 g carbohydrates from whole grain bread or brown rice. During weeks 5–12, only dinner was replaced with PRMR.	Control subjects remained in routine care (quarterly visits with attending physician for routine health visits as defined by Diabetes Management Programs for T2 diabetes in Germany) (C)	**HbA1c:** HbA1c was reduced more in the TeLiPro group (-1.1% (SD 1.2%)) than the control group (-.2% (SD .8%)) at 12 weeks, which was maintained at 26 weeks and 52 weeks. **Weight/BMI:** Weight was reduced more in TeLiPro group (-6.2 kg) than control group (-1 kg) at 12 weeks, and weight was maintained at 26 weeks and 52 weeks. Similar effects were seen for BMI (2 kg/m2 loss in intervention vs. .3 kg/m2 loss in control).	NR	West-German Centre of Diabetes and Health in Dusseldorf, Germany

Author Year N	Patient Characteristics	Intervention	Comparator	HbA1c, weight, medication use outcomes	Harms	Setting
	and taking at least 2 anti-diabetes medications.	**Coaching:** Weekly care calls (planned duration 20 min) from trained diabetes coaches. Care calls included information about type 2 diabetes, anti-diabetes medication, healthy diet, physical activity, and subjective possibilities for lifestyle changes. Measured data were discussed during these calls. **Other components:** Self-monitoring of blood glucose & mental motivational training		**Medication reductions:** MES was reduced from 3.1 (SD 4.1) to 2.1 (SD 2.2) in intervention group and 3.2 (SD 4.9) to 2.5 (1.5) in control group at 12 weeks which was maintained at 26 and 52 weeks.		
Kim 2015 N=70 6 months	**Adults with T2D Age:** 65.7 (I) & 65.9 (C) Sex (% male): 49% (I) & 51% (C) **Length of time diagnosed with T2D:** 16.6 years (I) & 14.6 years (C) **Baseline BMI/weight:** 25.1 kg/m2 (I) & 25.4 kg/m2 (C)64.9 kg/ 65.2 (I) & 67.4 kg (C) **Baseline HbA1c (%):** 8.6% (I) & 8.7% (C) **T2D comorbidities:** retinopathy (5.7% both groups) **Other comorbidities:** Hypertension (46% (I)/51% (C), dyslipidemia (71% (I)/65.7% (C)), cardiovascular disease (22.9% (I)/14.3% (C)) **Other Comorbidities:** NR	**Diet:** U-health group (I) received a therapeutic lifestyle change program focused on diabetes management according to the recommendations of the American Diabetes Association (ADA) and the Korean Diabetes Association. **Coaching:** Tailored feedback messages by voice or text messages, which are generated automatically through the CDSS rule engine for the data that they entered. **Other components:** Participants were asked to send their health data such as blood glucose level, body weight, exercise, diet, and medication adherence to the u-healthcare center through the auto response system (ARS) or touch pad system (text to speech, TTS) with a mobile phone or a landline.	The control group (C) received standard care (told to monitor blood glucose at same rate as intervention group, average caloric consumption by exercise estimated at the 3- and 6-month visits).	**HbA1c:** 7.51% (U-health group) vs 8.24 % (control) at 6 months. **Weight/BMI:** In the u-healthcare group, body weight and BMI decreased significantly, with no change in the control group at 6 months. The changes in body weight and BMI in the u-healthcare group were significantly greater than those in the standard care group. **Medication reductions:** NR	NR	Seoul National University Bundang Hospital

Author Year N	Patient Characteristics	Intervention	Comparator	HbA1c, weight, medication use outcomes	Harms	Setting
Lim 2016 N=100 6 months	**Adults with T2D** **Age:** 64.3 years (I) & 65.8 (C) **Sex (% male):** 40% (I) & 35% (C) **Length of time diagnosed with T2D:** 14.4 years (I) & 14.6 years (C) **Baseline BMI/weight:** 25.9 kg/m2 (I) & 25.4 kg/m2 (I) /71.2 kg (I) & 70 kg (C) **Baseline HbA1c (%):** 8.1% (I) & 7.9% (C) **T2D comorbidities:** Retinopathy (14% both groups), neuropathy (10% (I)/ 18% (C)) **Other comorbidities**: Cardiovascular disease (26% (I)/16% (C)), stroke (8% (I)/16% (C))	**Diet:** The u-healthcare group (I) received individual assessment of dietary habits over 3 days (two weekdays and 1 day on a weekend), and nutrition education was given to each participant by a dietician. **Coaching:** Diet and exercise counseling was conducted for 1 h at the baseline, 3- and 6-month visits. **Other components:** Education provided on using a public switched telephone network (PSTN)-connected glucometer to measure their blood glucose level at the same frequency as the SMBG group. Daily physical activity of participants was monitored/ transmitted to main server through Bluetooth/PSTN network via a physical activity monitor. Activity information from each participant was evaluated based on his or her recommended activity level set by the exercise physiologist, and a tailored message was transmitted to the mobile phone of the participant	The SMBG group (C) was recommended to measure their blood glucose level at least eight times a week (three or more times fasting, three or more times postprandially, and twice or more at bedtime)	**HbA1c:** The mean HbA1c level of the u-healthcare group had decreased significantly at 3-month follow-up and was maintained for 6 months (8% to 7.3%). HbA1c was unchanged in the SMBG group at 3 and 6 months (8.1% to 7.9%). The number of patients reaching the target HbA1c level after 6 months of follow-up was significantly higher in the u-healthcare group than the SMBG group. **Weight/BMI:** BMI was significantly reduced in the u-healthcare group (26.3 to 25.7 kg/m2) compared with the SMBG group (26.8 to 26.5 kg/m2). Follow-up weight NR. **Medication reductions:** 11.6 % in the u-healthcare group reduced their dose of oral antidiabetic drug or insulin, whereas there was no change in antidiabetic medication in the SMBG group.	NR	Seoul National University Bundang Hospital
Sun 2019 N=91	**Adults with T2D** **Age:** 67.9 years (I) & 68.4 years (C) Sex (% male): 43% (I) & 38% (C)	**Diet:** Patients in the intervention group (I) used the app-based diet management software to input daily dietary intake. The dietitian received the daily dietary record of each patient via the mHealth app.	Control group received usual care (given a free glucometer, instructed to monitor blood glucose regularly, received dietary and exercise	**HbA1c:** Reduction from 6.97% at 3 months to 6.84% at 6 months (intervention group). Control group increased from 7.18% at 3 months to 7.22% at 6	NR	China

Author Year N	Patient Characteristics	Intervention	Comparator	HbA1c, weight, medication use outcomes	Harms	Setting
6 months	**Length of time diagnosed with T2D:** 11.19 (I) & 11.52 years (C) **Baseline BMI (median)/weight:** 23.6 (I) & 23.3 (C) **Baseline HbA1c (%):** 7.84% (I) & 7.88% (C) **T2D comorbidities:** NR **Other comorbidities:** NR	**Coaching:** The study dietitian offered guidance for blood glucose monitoring and provided dietary advice based on the individual blood glucose levels. The medical teams logged on to the system and sent medical advice and reminders to patients to monitor their glucose levels via the personal messaging app or telephonically every 2 weeks. **Other components:** Physical activity (daily calorie expenditure) was obtained from patients in the intervention group via text message. The patients were instructed on how to text pedometer data to the study personnel. This information was analyzed, and each patient in the intervention group was provided with guidance related to aerobic and resistance-based exercises	guidance during face-to-face meetings at baseline and conclusion of study, although there was no limit on number of visits).	months. At 6 months, the HbA1c level in the intervention group was significantly lower than that at baseline (6.84% vs 7.84%) and lower than control group at 6 months (6.84% vs 7.22%). **Weight/BMI:** Intervention group median BMI increase from 23 at 3 months to 23.8 at 6 months. The control group's median BMI decreased from 23.25 at 3 months to 22.62 at 6 months. **Medication reductions:** NR		
Wayne 2015 N=131 6 months	**Adults with T2D** **Age:** 53.2 years **Sex (% female):** 72% **Length of time diagnosed with T2D:** NR **Baseline BMI (kg/m2)/weight (kg):** 33.74 (I) vs 37 (C) / 93.66 (I) vs 98.76 (C) **Baseline HbA1c (%):** 8.69% (I) & 8.89% (C) **T2D comorbidities:** NR **Other comorbidities:** NR	**Diet:** 6-month intervention where participants were coached to increase exercise, modify diet to limit carbohydrate intake, manage stress, adhere to medications, and engage with PCPs as needed. Food intake was also monitored via photo journaling. **Coaching:** Communication with a health coach took place any time within a 24-hour period through secure messaging, scheduled phone contact, and/or during in-person meetings. All data entered by participants was immediate visible to health coaches. Health coaches provided support when clients diverged from intended health goals and routines. **Other components:** Intervention group was provided with a Samsung Galaxy Ace	Control group received the same intervention but without mobile phone-support.	**HbA1c:** There was a significant between-group difference in HbA1c at the 3-month time point (0.52%, P=.03) favoring the Intervention group, although this difference was not statistically significant at 6 months because the control group's mean HbA1c reduction improved between 3 and 6 months while the intervention group's HbA1c level remained stable. **Weight/BMI:** Significant reductions in body weight (1.22 kg, 95% CI 0.35-2.08; P=.006) and waist	No adverse events resulting from exercise	Two primary care health centers in Toronto, Canada

Author Year N	Patient Characteristics	Intervention	Comparator	HbA1c, weight, medication use outcomes	Harms	Setting
		II mobile phone running Google Android Ice Cream Sandwich (Android 4.0.2) for the study intervention period, a user account with the Connected Wellness Platform (CWP) provided by NexJ Systems, Inc, which supported participants in health-related goal setting and progress monitoring. Key metrics including blood glucose levels, exercise frequency/duration/intensity, and mood were also tracked. Intervention ppts also had access to an exercise education program (exercise classes, resistance training with weights and bands, and cardiovascular exercise.)		circumference (2.23 cm, 95% CI 0.53-3.93; P=.01) in the intervention group. The control group had no change. **Medication reductions:** NR		

NR= Not reported, T2D= Type 2 diabetes, BMI= Body Mass Index, SD= Standard deviation, Pts= Participants

Data Abstraction of Observational Studies

Author Year Study design N Follow-up	Patient Characteristics	Intervention	Comparator	HbA1c, weight, medication use outcomes	Harms	Setting
Althinaravana 2019 Non-randomized clinical trial N=349 2 years	**Adults with T2D Age:** mean 54 (CCI) vs 52 (UC) **Sex** (% female): 67% (CCI) vs 59% (UC) **Length of time diagnosed with T2D**: 8.4 yrs (CCI) vs 7.9 years (UC) **Baseline BMI/weight:** 40.4 kg/m2 (CCI) vs 36.7 (UC)	**Diet:** Education modules (weekly for 12 weeks, bi-weekly for 12 weeks, monthly for 6 months, and then quarterly in the second year) covered core concepts related to the dietary changes for achieving nutritional ketosis, and adaptation to and maintenance of the diet. **Coaching:** Web-based app was used by participants to communicate with their remote care team consisting	UC (usual care) group consisted of care from a PCP or endocrinologist and counseled by RD according to ADA recommendations on nutrition, lifestyles, and diabetes management.	**HbA1c:** HbA1c decreased in CCI group but stayed the same in the UC group at 1 year (mean diff -1.3 [.2]) and at 2 years (mean diff -1.2 [.2]). **Weight/BMI:** Weight decreased in the CCI group, whereas no change was observed in the UC group at 1 year (mean diff -11.4	No treatment-related adverse events occurred between year 1 and 2 in the CCI group including no ketoacidosis or severe hypoglycemia. In year 2, the CCI group experienced 9 adverse events: one breast cancer diagnosis, one mycosis fungoides, one onset of atrial fibrillation (Afib) with	Lafayette, Indiana, USA

Author Year Study design N Follow-up	Patient Characteristics	Intervention	Comparator	HbA1c, weight, medication use outcomes	Harms	Setting
	Baseline HbA1c: 7.6 (CCI) vs 7.6 (UC) **T2D comorbidities:** NR **Other comorbidities:** NR	of a health coach and a medical provider. The remote care team provided education and support regarding dietary changes, behavior modification techniques for maintenance of lifestyle changes, and directed medication changes for diabetes and antihypertensive medications. **Other components:** Continuous care intervention (CCI) participants had access to a web-based software application (app), which was used to provide telemedicine communication, online resources and biomarker tracking tools. The participants used the app to upload and monitor their reportable biomarkers including body weight, blood glucose and beta-hydroxybutyrate (BHB). Biomarkers allowed for daily feedback to the care team and individualization of patient instruction. Participants could also use app to participate in an online peer community for social support.		kg [1.7]) and 2 years (mean diff -9.7 [2.2]). Among CCI patients at 2 years, 74% had >5% weight loss compared to only 14% of UC patients. **Medication reductions:** The mean dose among CCI participants prescribed insulin at baseline decreased by 81% at 2 years (from 81.9 to 15.5 U/day), but not among UC participants (+13%; from 96.6 to 109.3 U/day). Among participants who remained insulin-users at 2 years, mean dose also decreased in the CCI by 61% (from 104.3 to 40.2 U/day, $P = 9.2 \times 10^{-5}$).	heart failure, one onset of migraine, two cases of chest pain (one resulting in stent placement), one pulmonary effusion, and two pulmonary embolisms (one following orthopedic surgery and one with benign ovarian mass/Afib). In the UC group, adverse events occurring in the first year (n = 6) were previously reported (Hallberg 2018), and in the second year, adverse events occurred in six participants: one death from liver cancer, one hospitalization from recurrent seizure, one ureteropelvic junction obstruction from kidney stone, one cerebrovascular accident with left side weakness and sensory disturbances, one chest pain requiring percutaneous coronary intervention,	

Author Year Study design N Follow-up	Patient Characteristics	Intervention	Comparator	HbA1c, weight, medication use outcomes	Harms	Setting
					and one deep vein thrombosis	
Berman 2018 Pre-post N=118 12 weeks	**Adults with T2D** **Age (average):** 50.7 years **Sex (% female):** 81.4% **Length of time diagnosed with T2D:** 2.6 years **Baseline BMI/weight:** 38.1 (SD 8.8) kg/m2 **Baseline HbA1c (%):** 8.1% **T2D comorbidities:** NR **Other comorbidities:** NR	**Diet:** Program promoted plant-based dietary patterns through an app. Included a meal planning feature (5 min/week), educational materials to promote culinary or health literacy (15-20 mins/week), and option to report meals made (1-2 min/day). **Coaching:** Health coaching was provided for 30 mins every 2 weeks by telephone, and a clinical team was available for participants requiring additional support. Health coaching calls were used to set and review personalized behavioral goals. These goals centered on the attainment of dietary skills/repetition for habit formation, and included setting physical activity goals/addressing barriers to these goals **Other components:** An optional, private Facebook community was created to provide additional peer-to-peer and expert peer-to-peer support). App also facilitated self-monitoring of weight daily. Coaches encouraged	None	**HbA1c:** Mean change was –0.8% (SD 1.3) over a mean interval of 3.5 (SD 0.9) months. **Weight/BMI:** Not reported **Medication reductions:** Participants took on average 1.4 diabetic medications at baseline. 4% of participants (4/97) changed medications or dosages within the 12-week study. 17% reported decreasing or stopping 1 or more diabetic medications and 8% (8/97) increased or added 1 or more diabetic medications.	One participant reported suicidal ideations to a coach, and another participant was hospitalized briefly for dehydration after a flu-like illness. Both participants recovered fully from their events and were able to continue participating in the study.	Participants from 38 states recruited online

Author Year Study design N Follow-up	Patient Characteristics	Intervention	Comparator	HbA1c, weight, medication use outcomes	Harms	Setting
		participants to increase physical exercise to 30 mins/day. Health coaches could escalate care to nurse practitioner, internist, psychiatrist, chef-educator, and RD as needed. Participants were told to manage medications with their primary care team or endocrinologist.				
Buhanpuri 2018 Non-randomized control trial N=349 1 year	**Adults with T2D Age(average):** mean 54 (CCI) & 52 (UC) **Sex (% female):** 67% (CCI) & 59 (UC) **Length of time diagnosed with T2D:** NR **Baseline BMI/weight:** BMI 40.4 kg/m2 (CCI) & 36.7 (UC)/ weight 116.5 kg (CCI) & 105.6 (UC) **Baseline HbA1c (%):** 7.6 (CCI) & 7.6 (UC) **T2D comorbidities:** NR **Other comorbidities:**	**Diet:** CCI participants self-selected to receive education via either an onsite group setting (CCI-onsite) or via the app (CCI-web). There were no instructions given to the CCI group on counting or restricting calories. The CCI participants were instructed to restrict carbohydrate, eat protein in moderation, and consume fat to satiety. **Coaching:** The remote care team (health coach and physician or nurse practitioner) provided nutritional advice and medication management. Participants were guided by individualized nutrition recommendations to achieve and sustain nutritional ketosis. CCI participants were instructed to restrict carbohydrate, eat protein in moderation, and consume fat	UC (usual care) group was referred to RD providing dietary advice according to ADA	**HbA1c:** From ITT analysis, 1-year HbA1c was lower in CCI group (6.29 (.07) vs UC group (7.84 (.19)), with a mean diff of diff = -1.5(.17). **Weight/BMI:** From ITT analysis, 1-year weight was lower in CCI group (102.7 kg (1.5)) vs. UC group (107.3 kg (2.6)), with a mean diff of diff= -13.7 **Medication reductions:** From ITT analysis, significant reductions were observed in overall use of antihypertensive medication in CCI group (− 11.4% (2.8%)) vs no change	No evidence of vascular harm or benefit from 1 year of nutritional ketosis in patients with T2D	Lafayette, Indiana, USA

Author Year Study design N Follow-up	Patient Characteristics	Intervention	Comparator	HbA1c, weight, medication use outcomes	Harms	Setting
	- % smokers (3.8% CCI & 14.9% UC)	to satiety from the start of the study. **Other components:** Web-based software application (app) for biomarker reporting and monitoring including body weight, blood glucose and blood betahydroxybutyrate (BHB; a marker of ketosis). If participants reported headaches, constipation or lightheadedness, remote care team recommended individualized adjustments to sodium and fluid intake. Social support was provided via an online peer community.		(+8.3% (4.8%)) in UC group (diff-in-diff -19.7% (5.6%)) at 1 year. Significant reductions were also observed with diuretics in CCI group (− 9.7% (2.75%)) vs. no change (+3.2% (4.1%)) in UC group (diff-in-diff -12.8% (4.9%)). There was difference in ACE or ARB and statin use between groups at 1-year.		
Hallberg 2018 Non-randomized control trial N=349 1 year	**Adults with T2D Age (average):** 54 (CCI) & 52 (UC) **Sex (% female):** 67% (CCI) 59% (UC) **Length of time diagnosed with T2D:** 8.4 years (CCI) & 7.9 (UC) **Baseline BMI/weight:** BMI 40.4 kg/m2 (CCI) 36.7 (US)/ weight 116.5 kg (CCI) & 105.6 (UC) **Baseline HbA1c:** 7.6% (CCI) & 7.6 (UC)	**Diet:** Participants received individualized nutrition recommendations that allowed them to achieve and sustain nutritional ketosis with a goal of 0.5–3.0 mmol L-1 blood BHB. Participants were encouraged to report daily hunger, cravings, energy, and mood on a four-point Likert scale. Daily protein intake was initially targeted to a level of 1.5 g kg-1 of reference body weight and adjusted as necessary. Participants coached to incorporate dietary fats to satiety. Participants advised to consume adequate intake of omega-3 and	UC (usual care) group received care from PCP or endocrinologist and were counseled by RD on diabetes self-management, nutrition and lifestyle.	**HbA1c:** In the CCI group, HbA1c was significantly reduced from 7.6% to 6.3% after 1 year, the UC group had no changes in HbA1c. **Weight/BMI:** In the CCI group, weight was reduced from 116.5 kg to 102.7 kg (-13.8 kg), the UC group had no changes in weight. **Medication reductions:** In the CCI group, usage of diabetes medications	No cases of metabolic acidosis. One CCI patient had a clinically significant rise in serum creatinine, but group mean declined at 1 year. Adverse events occurred in 6/262 CCI participants including one non-ST-segment myocardial infarction, one inferior myocardial ischemia by electrocardiogram, one metastatic neuroendocrine carcinoma, one malignant cancer with	Lafayette, Indiana, USA

Author Year Study design N Follow-up	Patient Characteristics	Intervention	Comparator	HbA1c, weight, medication use outcomes	Harms	Setting
	T2D comorbidities: NR **Other comorbidities:** NR	omega-6 polyunsaturated fats, while it was recommended that the remainder of their intake from fat come from both monounsaturated and saturated sources. Other aspects of the diet were individually prescribed, including consumption of 3–5 servings of non-starchy vegetables and adequate mineral and fluid intake for the ketogenic state. Patients also took a multivitamin. **Coaching:** Health coach and medical provider (physician or nurse practitioner) provided advice and medication management. **Other components:** Used a software application to track biomarkers. Social support was provided via an online peer community. Care coordination between CCI and PCP as needed. Participants also received education on behavior change strategies, and could choose whether they received education classes in person or online (met weekly for 12 weeks, bi-weekly for 12 weeks, monthly for 6 months)		(excluding metformin) was reduced significantly (56.9 ± 3.1% to 29.7 ± 3.0%). Prescription for DPP-4 (9.9–6.3%), insulin (29.8–16.7%), SGLT-2 inhibitors (10.3–0.9%), sulfonylureas (23.7–0%), and thiazolidinediones (1.5–0.4%) decreased in the CCI group. GLP-1 prescriptions were statistically unchanged (13.4% at baseline to 14.4% at 1 year, P = 0.67), and metformin decreased slightly (71.4–65.0%, P = 0.04) for CCI participants. 40% of CCI participants who began the study with insulin prescriptions (average dose of 64.2 units) eliminated the medication, while the remaining 60% (47/78) of insulin users reduced daily dosage from 105.2 to 53.8 units. Patients enrolled in UC for 1 year showed no significant change for prescription of	multiple brain lesions and lung tumor, and death from renal hemorrhage and failure and hyperkalemia. Adverse events occurred in 6/87 UC pts: one percutaneous coronary intervention (PCI) to left anterior descending stenosis, one PCI to right coronary artery, two carotid endarterectomies (one of which was successful), multifactorial encephalopathy, and diabetic ketoacidosis with pulmonary emboli.	

Author Year Study design N Follow-up	Patient Characteristics	Intervention	Comparator	HbA1c, weight, medication use outcomes	Harms	Setting
				medication for the 34 UC participants that continued using insulin, the average daily dose increased from 96.0 to 111.9 units.		
Idris 2020 Single-arm, longitudinal study N=896 12 months	**Adults with T2D Age (average):** 49.4 years **Sex (% female):** 70% **Length of time diagnosed with T2D:** NR **Baseline BMI/weight:** 33.7 kg/m2 / 94.7 kg **Baseline HbA1c:** NR **T2D comorbidities:** NR **Other comorbidities:** NR	**Diet:** OurPath program was designed to help participants make behavioral changes while also increasing their knowledge of nutrition and other self-management behaviors. Ppts could access educational articles with multimedia components (10-15 min to read/article) that addressed nutrition topics in addition to physical activity, stress, mental well-being, and sleep. Pts also received a recipe group. The program was divided into 2 periods: the initial phase of the program: Core phase (3 months) and sustain phase (9 months). **Coaching:** Registered dietitians or nutritionists delivered one-to-one health coaching via a private, text-based instant messaging function within the app. Coaching based on NICE guidelines. **Other components:** In addition to nutrition, the	None	**HbA1c:** NR **Weight/BMI:** In per-protocol analyses, intervention group lost 2.35 kg (compared to 2.2 kg for control) at 3 months. Intervention group lost 4.3 kg (compared to 2.5 kg for control) at 12 months. BMI was reduced by .9 kg/m2 in intervention (vs .7 kg/m2 in control) at 3 months and was reduced by 1.7 kg/m2 (vs .8 kg/m2 in control) at 12 months. **Medication reductions:** NR	NR	UK

Author Year Study design N Follow-up	Patient Characteristics	Intervention	Comparator	HbA1c, weight, medication use outcomes	Harms	Setting
		program aimed to increase knowledge of physical activity, adequate sleep, and general physical and mental well-being, which were addressed in multi-media articles. Ppts also received an activity tracker and a scale. There was a group chat option where up to 10 ppts could ask a health coach questions.				
Koot 2019 Pre-post study N=100 6 months	**Adults with T2D Age:** 54 years **Sex (% male):** 50% **Length of time diagnosed with T2D:** 9.3 years **Baseline BMI/weight:** 29.8 (kg/m2) / 79.7 kg **Baseline HbA1c (%):** 8.8% **T2D comorbidities:** NR **Other comorbidities:** NR	**Diet:** Meal photos taken by participants uploaded onto the app for health coach evaluation. Health coaches rate meals using a 1 to 5 linear scale. Meal scores awarded based on the balance of nutrients, food quality, and nutritional content. Meal scores based on Singapore Health Promotion Board's national dietary guidelines. A total of 24 educational lessons on diabetes and self-management were delivered online. This curriculum was adapted for the local population and covers topics from the 7 healthy self-care behaviors as described by the American Association of Diabetes Educators. Quizzes tested knowledge on diabetes, obtained information about participants' lifestyle habits, and were designed to	None	**HbA1c:** HbA1c levels were 1.1 percentage points lower at follow-up compared to baseline in ITT analyses. 49 of 100 participants (49%) achieved a ≥1 percentage point reduction in HbA1c levels. The average duration between intervention start and follow-up HbA1c tests was 24.2 weeks. **Weight/BMI:** Participants achieved a weight loss of 2 kg at follow-up compared to baseline. 17 out of 100 participants (17%) lost ≥5% of their initial body weight at baseline	NR	A single community health care facility in Singapore

Author Year Study design N Follow-up	Patient Characteristics	Intervention	Comparator	HbA1c, weight, medication use outcomes	Harms	Setting
		keep participants engaged throughout each lesson. **Coaching:** Health coaches' rate and respond to all meal logs and regularly send messages to participants to provide recommendations, encouragement, and personalized feedback on progress and answer participants' questions. **Other components:** Blood glucose and weight monitoring, and physical activity tracking.		**Medication reductions:** NR		
Ku 2020 Pilot study N=40 12 weeks	**Adults with T2D** **Age:** 46.6 years (I) & 53.4 (C) **Sex (% male):** 45% (I) & 25% (C) **Length of time diagnosed with T2D:** 4 years (I) &6.6 years (C) **Baseline BMI/weight:** 28.9 kg/m2 (I) & 26.8 kg/m2 (C) **Baseline HbA1c (%):** 8.8% (I) & 9.1% (C) **T2D comorbidities:** NR	**Diet:** Subjects in the smartphone-based care group (I) were asked to log their dietary data using this application. This tool enables the user to calculate their dietary intake easily using a well-established database of local foods. When a meal is recorded in the application, a color code (red, yellow, and green) is presented to help patients choose healthier foods within the allotted calories per day (green, "It's a good choice!"; yellow, "Please eat only moderate amounts."; red, "Sometimes, just a little.") **Coaching:** Both groups of patients received conventional	The conventional care group (C) did not receive feedback after baseline consultation	**HbA1c:** A1C levels in both groups decreased significantly relative to the baseline [smartphone-based care group, −1.9 ± 1.6%; conventional care group, −1.0 ± 1.0%]. **Weight/BMI:** NR **Medication reductions:** 5.0% (n = 3) and 20.0% (n = 4) of patients reduced the dose of oral antidiabetic agents or insulin in the smartphone-based	No serious adverse events, such as severe hypoglycemia or hospitalization, were reported	Chungbuk National University Hospital (CBNUH)

Author Year Study design N Follow-up	Patient Characteristics	Intervention	Comparator	HbA1c, weight, medication use outcomes	Harms	Setting
	Other comorbidities: Hypertension (25% (I)/40% (C)), dyslipidemia (40% (I)/50% (C)), cardiovascular diseases (5% (I)/15% (C), cerebrovascular diseases (0% (I)/5% (C))	diabetes care education from a trained nurse at baseline. Feedback text messages were sent to the intervention group after baseline consultation by the medical team within a day after a comprehensive assessment of daily blood glucose profile, food intake, and physical activity information registered at the website. **Other components:** All patients were taught to test and record their blood glucose levels and were asked to exercise. All patients were recommended the following exercise programs; strategies to avoid hypoglycemia, adequate types of exercise (aerobic/resistant/flexible), intensity (at a moderate level), frequency (at least 3 times per week), and duration (at least 150 minutes per week).		care group and the conventional care group.		
McKenzie 2017 Pre-post study N=262 11 weeks	**Adults with T2D Age:** mean 54 **Sex:** 67% were female **Length of time diagnosed with T2D:** NR **Baseline BMI/weight:** BMI 40.8 kg/m2 (8.9)/	**Diet:** Intervention that incorporated education on principles of ketogenic diet and role of ketones as a biofeedback mechanism during weekly 90-min classes online or in-person. Pts also received individualized nutritional recommendations to sustain nutritional ketosis based on ketogenic diet	None	**All measurements taken at 10-11 weeks** **HbA1c:** Reduction from 7.6% (1.5%) to 6.6% (1.1%). **Weight/BMI:** BMI reduced from 40.8(8.9) kgm2 to	1 subject withdrew due to side effects (diarrhea due to fat intolerance). No serious adverse events in this time period including no serious symptomatic hypoglycemic events requiring medical intervention.	West Lafayette, IN. IRB was at Ciscan Health Lafayette East, Lafayette, Indiana.

Author Year Study design N Follow-up	Patient Characteristics	Intervention	Comparator	HbA1c, weight, medication use outcomes	Harms	Setting
	weight 117 kg (26.3) **Baseline HbA1c:** average 7.6% **T2D comorbidities:** NR **Other comorbidities:** NR	principles. (typically, <30 g/day carb, 1.5 g/kg protein, dietary fats to satiety, consumption of 3-5 servings of nonstarchy vegetables, adequate mineral and fluid intake). **Coaching:** Personal health coach available for advice and problem solving daily via 1-on-1 texting. **Other components:** Education also covered pathophysiology of diabetes and appropriate behavior change techniques. Peer support community available as well as physician supervision/medication management. Pt also tracked data such as glucose level 1-3x/day and sent this to physician, who could titrate medication.		37.9(8.5) kgm2. Weight reduced from 117(26.3) kg to 109 (24.9) kg. **Medication reductions:** 13 (5%) had medication increase, 88 (34%) had no change, 112 (42%) had medication decrease, and 28 (11%) had no medications at baseline or follow-up.		
Saslow 2018 Single-arm longitudinal study N=1,000 1 year	**Adults with T2D Age:** 56.1 years **Sex (% female):** 59.3% **Length of time diagnosed with T2D:** NR **Baseline BMI/weight:** 89.6 kg **Baseline HbA1c (%):** 7.8%	**Diet:** Low Carb Program is a 10-week, automated, structured health intervention for adults with type 2 diabetes. Program modules explored strategies to reduce dietary sources of sugar high-starch foods, such as bread, pasta, and rice. Participants were encouraged to make portion control and carbohydrate restriction	None	**HbA1c:** Overall, everyone who participated lowered HbA1c by -.76% at 1 year. Participants who completed the Low-Carb Program lowered HbA1c by –1.17%. Partial completers lowered HbA1c by -.6% which was significantly	NR	United Kingdom

Author Year Study design N Follow-up	Patient Characteristics	Intervention	Comparator	HbA1c, weight, medication use outcomes	Harms	Setting
	T2D comorbidities: NR **Other comorbidities:** Hypertension (39.7%), high cholesterol (35%)	decisions based on visual plate representations. In place of carbohydrate-rich foods, an increased intake of green vegetables, low-glycemic index fruits and fats are advocated. **Coaching:** Weekly automated feedback was provided to users based on their use of the program through email notifications. **Other components**: The program stresses the importance of regular contact with the participants' health care providers for adjustments in medications in weeks 1, 2, and 10. The program further reinforces behavior change through integrated tracking whereby program users are encouraged to track their health data including mood, food intake, blood glucose levels, weight, sleep, and HbA1c. Participants were also encouraged to set goals (ie, to lose weight, reduce medication dependency, or make healthier choices).		different from baseline. Noncompleters lowered HbA1c by -.16% which was not statistically different from baseline. **Weight/BMI:** Overall, everyone who participated lost on average 3.31 kg. Program completers lost 7.45 kg of weight. Partial completers lost 2.13 kg but was not significantly different from baseline. Non-completers lost -.35 kg which was also not statistically significant. **Medication reductions:** At 1 year, of those originally prescribed medications, 289/714 (40.4%) individuals were able to stop one or more hypoglycemic medications. Of the 743 participants who started with an HbA1c, equal to or above the type 2		

Author Year Study design N Follow-up	Patient Characteristics	Intervention	Comparator	HbA1c, weight, medication use outcomes	Harms	Setting
				diabetes threshold of 6.5%, 195 (26.2%) reduced their HbA1c to below the threshold while taking no glucose-lowering medications or just metformin.		
Schusterbauer 2018 Pre-post study N=10 3 months	**Adults with T2D** **Age:** 53 years **Sex (% female):** 20% **Length of time diagnosed with T2D:** NR **Baseline BMI/weight**: 34.45 kg/m2 **Baseline HbA1c (%)**: 5.9% **T2D comorbidities:** NR **Other comorbidities:** NR	**Diet:** The follow-up period lasted for three months, starting after the stationary treatment. For the first month, the transmission of images of three main meals daily was obligatory. **Coaching:** The patients received a weekly individual feedback from their dietitian as well as general motivational messages. **Other components**: The therapy plan included the weekly recording of blood pressure, weight and blood sugar (3 values on one day).	None	**HbA1c:** Increased from 5.9 % at baseline to 6.05% at 3-month follow-up (not a significant increase). **Weight/BMI:** The median BMI was reduced by 2.74 kg/m2 which was a significant reduction. **Medication reductions:** NR	NR	Austria
Von Storch 2019 Prospective study N=115 3 months	**Adults with T2D** **Age:** 59.4 years (I) & 58.4 (C) **Sex (% male):** 78% (I) & 85% (C) **Length of time diagnosed with T2D:** 7 years (I&C)	**Diet:** 12-month intervention (I) where participants received a tablet computer where they collected dietary information. **Coaching:** Coach and participant discussed and interpreted the submitted data concerning the participant's health behavior. Coaching was based on the	Usual care group (C) received routine care by their physician without additional treatment.	**HbA1c:** Intervention group had average HbA1c values of 6.6% (from 7.05%) after 3 months, whereas controls remained at their baseline level of 6.9%.	NR	Participants were recruited if they were covered by the health insurance Central Krankenversicherung AG (Central), Germany.

Author Year Study design N Follow-up	Patient Characteristics	Intervention	Comparator	HbA1c, weight, medication use outcomes	Harms	Setting
	Baseline BMI/weight: 31.9 kg/m2 (I) & 29.3 kg/m2 (C) **Baseline HbA1c:** 7% (I) & 6.9% (C) **T2D comorbidities:** mean of 3 (I&C) **Other comorbidities:** multimorbidity (>2 chronic diseases): 98.3% (I) & 94.5% (C)	Transtheoretical Model of Prochaska. It consisted of a stage-matched personalized assessment, including different modules representing major problem areas with emphasis on diet, physical activity, self-control, emergency, clinical, and stress management. It also involves a mental motivational training and development of daily life routines. **Other components**: Participants also received a glucometer and a step counter and tracked these via table.		**Weight/BMI:** Both groups had unchanged BMI (32.3 to 31.8 kg/m2 [I] vs. 29.3 to 29.4 [C]) at 3 months, although intervention group had higher BMI at both baseline and follow-up. **Medication reductions:** NR		

NR= Not reported, T2D= Type 2 diabetes, BMI= Body Mass Index, SD= Standard deviation, Pts= Participants

QUESTIONS FOR QUALITY ASSESSMENT (RCTS)

Risk of bias from randomization process	• Was allocation sequence random? • Was the allocation sequence concealed until participants were enrolled and assigned to interventions? • Did baseline differences between intervention groups suggest a problem with the randomization process?
Deviation from intended interventions - assignment to interventions	• Were participants aware of their assigned intervention during the trial? • Were carers and people delivering the interventions aware of participants' assigned intervention during the trial? • Were there deviations from the intended intervention that arose because of the trial context? • Were these deviations likely to have affected the outcome? • Were these deviations from intended intervention balanced between groups? • Was an appropriate analysis used to estimate the effect of assignment to intervention? • Was there potential for a substantial impact of the failure to analyze participants in the group to which they were randomized? • Was an appropriate analysis used to estimate the effect of adhering to the intervention?
Risk of bias due to missing outcome data	• Were data for this outcome available for all, or nearly all, participants randomized? • Is there evidence that the result was not biased by missing outcome data? • Could missingness in the outcome depend on its true value? • Is it likely that missingness in the outcome depended on its true value?
Risk of bias in measurement of the outcome	• Was the method of measuring the outcome appropriate? • Could measurement or ascertainment of the outcome have differed between intervention groups? • Were outcome assessors aware of the intervention received by the study participants? • Could assessment of the outcome have been influenced by knowledge of the intervention received?
Risk of bias in selection of the reported result	• Were the data that produced these results analyzed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis? • Is the numerical result being assessed likely to have been selected on the basis of the results from: multiple eligible measurements or analyses of the data?

QUESTIONS FOR QUALITY ASSESSMENT OF COHORT STUDIES

Selection Bias	• Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? • Do start of follow-up and start of intervention coincide for most participants? • Were adjustment techniques used that are likely to correct for the presence of selection biases?
Bias in Classification of Interventions	• Were intervention groups clearly defined? • Was the information used to define intervention groups recorded at the start of the intervention? • Could classification of intervention status have been affected by knowledge of outcome or risk of the outcome?
Bias due to Departures from Intended Interventions	• Were the deviations from the intended intervention beyond what would be expected in usual practice? • Were important co-interventions balanced across intervention groups? • Was the intervention implemented successfully for most participants?

	• Did study participants adhere to the assigned intervention regimen?
Bias in Measurement of Outcomes	• Could the outcome measure have been influenced by knowledge of the intervention received? • Were the outcome assessors aware of the intervention received by study participants? • Were the methods of outcome assessment comparable across intervention groups? • Were any systematic errors in measurement of the outcome related to intervention received
Bias due to Confounding	• Is there potential for confounding of the effect of intervention in this study? • Did the authors use an appropriate analysis method that controlled for all the important confounding domains? • Did the authors control for any postintervention variables that could have been affected by the intervention?
Bias due to Missing Data	• Were outcome data available for all, or nearly all, participants? • Were participants excluded due to missing data on intervention status? • Were participants excluded due to missing data on other variables needed for the analysis
Bias in the Selection of Reported Results	• Were results likely to be selected and reported based on results from multiple analyses, multiple outcome measurements or different subgroups?

QUESTIONS FOR QUALITY ASSESSMENT OF PRE-POST STUDIES

Selection Bias	• Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? • Do start of follow-up and start of intervention coincide for most participants? • Were adjustment techniques used that are likely to correct for the presence of selection biases?
Pre-post considerations	The issues are similar to those for follow-up studies. For studies that prospectively follow a specific group of units from pre-intervention to post-intervention, selection bias is unlikely. For repeated cross-sectional surveys of a population, there is the potential for selection bias even if the study is prospective
Bias in Classification of Interventions	• Were intervention groups clearly defined? • Was the information used to define intervention groups recorded at the start of the intervention? • Could classification of intervention status have been affected by knowledge of outcome or risk of the outcome?
Pre-post considerations	Whether specification of the distinction between pre-intervention time points and post-intervention time points could have been influenced by the outcome data
Bias due to Departures from Intended Interventions	• Were the deviations from the intended intervention beyond what would be expected in usual practice? • Were important co-interventions balanced across intervention groups? • Was the intervention implemented successfully for most participants? • Did study participants adhere to the assigned intervention regimen?
Pre-post considerations	Whether the effects of any preparatory (pre-interruption) phases of the intervention were appropriately accounted for.

Bias in Measurement of Outcomes	- Could the outcome measure have been influenced by knowledge of the intervention received? - Were the outcome assessors aware of the intervention received by study participants? - Were the methods of outcome assessment comparable across intervention groups? - Were any systematic errors in measurement of the outcome related to intervention received?
Pre-post considerations	Whether methods of outcome assessment were comparable before and after the intervention; and Whether there were changes in systematic errors in measurement of the outcome coincident with implementation of the intervention.
Bias due to Confounding	- Is there potential for confounding of the effect of intervention in this study? - Did the authors use an appropriate analysis method that controlled for all the important confounding domains? - Did the authors control for any postintervention variables that could have been affected by the intervention?
Pre-post considerations	Whether measurements of outcomes were made at sufficient pre-intervention time points to permit characterization of pre-intervention trends and patterns; whether there are extraneous events or changes in context around the time of the intervention that could have influenced the outcome; and whether the study authors used an appropriate analysis method that accounts for time trends and patterns, and controls for all the important confounding domains.
Bias due to Missing Data	- Were outcome data available for all, or nearly all, participants? - Were participants excluded due to missing data on intervention status? - Were participants excluded due to missing data on other variables needed for the analysis
Pre-post considerations	Whether outcome data were missing for whole clusters (units of multiple individuals) as well as for individual participants.
Bias in the Selection of Reported Results	Were results likely to be selected and reported based on results from multiple analyses, multiple outcome measurements or different subgroups?
Pre-post considerations	The issues are the same as for follow-up studies

QUALITY ASSESSMENT OF INCLUDED PRIMARY STUDIES

Quality Assessment of RCTs

Author, Year	Risk of bias from randomization process (high, some concerns, low)	Risk of bias from deviation from intended interventions (assignment) (high, some concerns, low)	Risk of bias from missing outcome data (high, some concerns, low)	Risk of bias in measurement of the outcome (high, some concerns, low)	Risk of bias in selection of the reported result (high, some concerns, low)	Quality Rating (Good, Fair, Poor)
Hansel 2017	Low Randomized by means of computer program; Allocation concealed until assigned to interventions; Baseline characteristics similar between groups	Fair Participants and coaches aware of assigned intervention during trial; ITT and PP analysis performed	Fair Missing primary endpoint data for 9 participants from intervention and 5 from control; more ppts lost to follow up in intervention vs control [11 vs 5] due to lack of interest.	Fair Diet assessor blinded, unclear if other study staff measuring HbA1c or weight were blinded. Other assessments were self-administered.	Low All outcomes from registry were reported	Fair
Haste 2017	Low Researchers used Sealed Envelope Web-based System with stratification to balance diabetes medication variable; Allocation concealed until enrollment in intervention; Baseline characteristics similar between groups	High Participants and coaches aware of assigned intervention during trial; Fewer than half of participants adhered to intervention; No ITT analysis	High 57% of control and 39% of intervention group had dropped out by 12 months	Fair Outcome assessors aware of assignment; Measurement of outcomes conducted in GP offices and was appropriate.	Low All outcomes from registry were reported	Poor

Author, Year	Risk of bias from randomization process (high, some concerns, low)	Risk of bias from deviation from intended interventions (assignment) (high, some concerns, low)	Risk of bias from missing outcome data (high, some concerns, low)	Risk of bias in measurement of the outcome (high, some concerns, low)	Risk of bias in selection of the reported result (high, some concerns, low)	Quality Rating (Good, Fair, Poor)
Kempf 2017	Low	Fair	Fair	Fair	Low	Fair
	Electronically generated random list created by trial statistician; Allocation concealed until assigned to interventions; baseline characteristics similar between groups	Participants not aware of assignment; study nurse; Drop-out rate in control group higher than in intervention group (26% vs. 9% drop-out rate); ITT analysis.	No significant differences between those who completed and those who dropped out; Follow-up data being low in both groups (56/100 control pts and 77/102 intervention pts had data collected at 52 weeks)	Assessor blinded, and data analyst blinded after assignment to intervention; Multiple adjustment models used to assess treatment difference in HbA1c reduction	All outcomes from registry were reported	
Kim 2015	Fair	Fair	Low	Fair	Low	Fair
	Block randomization; Not clear if allocation sequence concealed; baseline characteristics similar between groups	High levels of adherence - only 2 dropouts per group; Not clear if participants aware of assignment; doctors aware of assignment. PP analysis.	No missing data indicated in text or figures; Equal dropouts between intervention and control, overall low rates.	Most outcomes self-measured but unclear how HbA1c, BMI measured, not clear if participants or outcome assessors blinded	All outcomes from registry were reported	

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Author, Year	Risk of bias from randomization process (high, some concerns, low)	Risk of bias from deviation from intended interventions (assignment) (high, some concerns, low)	Risk of bias from missing outcome data (high, some concerns, low)	Risk of bias in measurement of the outcome (high, some concerns, low)	Risk of bias in selection of the reported result (high, some concerns, low)	Quality Rating (Good, Fair, Poor)
Ku 2020	Fair	Fair	Low	Some concerns	Low	Fair
	Randomized with freely available online automated random number generator program; Not stated if allocation sequence concealed; Baseline characteristics similar between groups although number of blood glucose measurements were higher in smartphone group than control.	Participants and providers not blinded. Full analysis set approach (ie, ITT) used to analyze data. Low drop out-rate.	Low drop-out rate, even between groups	Outcome assessors aware of assignment. Outcomes measured in laboratory setting.	All outcomes from registry were reported	
Lim 2016	Fair	Fair	Low	Fair	Fair	Fair
	Block randomization; Not clear if allocation was concealed; baseline characteristics similar between groups.	Not clear if blinded; 14% of intervention and 16% of control withdrew for similar reasons; ITT and PP analysis performed.	Table 2 indicates data is available for all ppts who completed the study.	It's unclear if outcomes were measured by participants or in clinic, and it was unclear if clinical outcome assessors were blinded.	Quality of life outcome from registry not reported	
Sun 2019	Fair	High	High	Some concerns	Fair	Poor
	Random number sequence generated by SPSS in batches of 6 patients at a time; not clear if patients were blinded to allocation; baseline characteristics similar between groups	No information about dropouts at follow-up points; No information about adherence; Not clear if blinded; No information on whether ITT was conducted.	No information about dropouts or about missing data	Measurements were assessed via laboratory; Not clear if outcome assessors blinded	Registration was retrospective and there's no indication results were from multiple analyses.	

Author, Year	Risk of bias from randomization process (high, some concerns, low)	Risk of bias from deviation from intended interventions (assignment) (high, some concerns, low)	Risk of bias from missing outcome data (high, some concerns, low)	Risk of bias in measurement of the outcome (high, some concerns, low)	Risk of bias in selection of the reported result (high, some concerns, low)	Quality Rating (Good, Fair, Poor)
Von Storch 2019	High Randomization method not stated; allocation concealment not clear; baselines mostly similar except for BMI (higher in intervention); Also, more participants in intervention than control	High High attrition rate (82/219 (37%) completed baseline questionnaire in intervention group, 64/219 (29%) at follow-up; 68/79 (86%) completed in control, 55/79 (70%) at follow-up); only those that completed at follow-up were analyzed	Fair Listwise deletion for missing data - deleted 4 from intervention group	High Measurements appropriate, HbA1c measured in laboratory but BMI was self-reported	Fair No trial registration reported or connected to PubMed page	Poor
Wayne 2015	Low Random number sequence generated from random number-generating program; allocation concealed until assignment to intervention; baselines similar except for SF-12 Mental Health Composite Scores	Fair No blinding of participants or coaches; high overall attrition (26%) but similar rates between intervention (28%) and control (23%). ITT analysis.	Fair >20% attrition rate in both groups, no other indication of missing data	Fair HbA1c and weight measured by physician or research staff, unclear if they were aware of participant allocation	Low All outcomes from registry are represented and no signs of multiple analyses	Fair

Quality Assessment of Observational Cohort Studies

Author Year	Selection bias (High, Some Concerns, Low)	Bias in classification of interventions (High, Some Concerns, Low)	Bias due to departures from intended interventions (High, Some Concerns, Low)	Bias due to measurement of outcomes (High, Some Concerns, Low)	Bias due to confounding (High, Some Concerns, Low)	Bias due to missing data? (High, Some Concerns, Low)	Bias in the selection of reported results (High, Some Concerns, Low)	Overall quality (Good, Fair, Poor)
Althinaravanan 2019	See Hallberg 2018	See Hallberg 2018	Some concerns 2-year attrition was 26% for intervention vs. 22% for control for reasons like intervening life events, difficulty attending visits, and insufficient motivation.	Some concerns Body composition not measured in control participants. Study doesn't comment on whether outcome assessors were blinded to treatment group.	See Hallberg 2018	High At least 22% of control and 26% intervention data at 2 years missing based on drop-out, study doesn't report whether additional data was missing.	See Hallberg 2018	Fair
Buhanpuri 2017	See Hallberg 2018	See Hallberg 2018	See Hallberg 2018	Some concerns No outcomes collected for control group at 70 days. Investigator performing carotid ultrasonography was blinded to treatment group, but not clear if clinicians collecting other measurements were blinded.	See Hallberg 2018	High At least 22% of control and 26% intervention data at 2 years missing based on drop-out, study doesn't report whether additional data was missing.	See Hallberg 2018	Fair
Hallberg 2018	High Overall, intervention group was	Low Pts prospectively consented to	Some concerns 17% of intervention and 10% of control dropped out, but	Some concerns No outcomes collected for control group at 70 days.	Some concerns Study doesn't provide much information	High 4% of baseline and 24% of 1-year	Low Outcomes from protocol are	Fair

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older and had higher BMI/weight than control group. More people were taking diabetes medication (excluding metformin) in control than intervention. No propensity-matching or other analyses to control for baseline differences. 3x as many people in intervention as control.	take part in the study and could choose either the intervention or control treatment.	reasons for drop out not reported. ITT analysis used.	Study doesn't comment on whether outcome assessors were blinded to treatment group. .	about usual care, such as what other interventions they might have received from providers, to determine if there was a potential for confounding. .	values were missing.	reported across articles.

Quality Assessment of Observational Pre-post Studies

Author Year	Selection bias (High, Some Concerns, Low)	Bias in classification of interventions (High, Some Concerns, Low)	Bias due to departures from intended interventions (High, Some Concerns, Low)	Bias due to measurement of outcomes (High, Some Concerns, Low)	Bias due to confounding (High, Some Concerns, Low)	Bias due to missing data (High, Some Concerns, Low)	Bias in the selection of reported results (High, Some Concerns, Low)	Overall quality (Good, Fair, Poor)
Berman 2018	Low Selection bias in intervention arm only unlikely.	Low Intervention group clearly defined.	Some concerns Some features of the app were added 1 month before the end of the intervention (AI conversational bot, ability to enter home finger-stick readings). Attrition rate was 9%, reasons for attrition reported.	High HbA1c & medication use were self-reported.	High Secular trends or other confounders could have influenced results- there was no control group to rule this out.	Low 93% provided some or all post-intervention data. Last-value-carried-forward approach for missing data.	Low ITT analysis used and unlikely to be the result of multiple analyses.	Poor
Idris 2020	Low Selection bias in intervention arm only unlikely. .	Low Intervention group clearly defined.	Some concerns No data on attrition or adherence provided.	Some concerns Lowest weight during 8-week time period used as measurement of weight, which is a large measurement period for a 3-month intervention. Weight collected through in-	High Secular trends or other confounders could have influenced results- there was no control group to rule this out.	High Only 896/3649 (about 25%) of participants that took part in the program took 6 and 12-month weight readings.	Some concerns Unclear why researchers didn't measure outcomes at 3 months after core intervention.	Poor

			home scales that automatically transferred readings. Self-reported data at baseline.					
Koot 2019	Low	Low	Some concerns	Some concerns	High	Low	Low	Poor
	Selection bias in intervention arm only unlikely.	Intervention group clearly defined.	Attrition was 13%, reasons for attrition reported although not in great detail. Adherence decreased over time (Fig 2).	Weight could be captured 2 months before baseline assessment, and 12-38 weeks after intervention, which is a large measurement period. Unclear which measurement was used if multiple were taken during the time period. Measurements taken in clinic but unclear if outcome assessors were blinded.	Secular trends or other confounders could have influenced results- there was no control group to rule this out.	Dropouts + missing data = 17%	Outcomes match protocol.	
Saslow 2018	Low	Low	Some concerns	High	High	Some concerns	Low	Poor
	Patients who were followed up were a random sample of	Intervention group clearly defined.	Attrition not reported but only 70% reported outcomes at 12 months. 52% completed all	Participants self-reported HbA1c, weight, medications at baseline and follow-up.	Secular trends or other confounders could have influenced results- there was	70% of participants reported outcomes at 12 months. Last observation carried forward for participants who did	Unlikely to be the result of multiple analyses.	

	1000 out of 7809 eligible. Used GraphPad Random Generator Software.		lessons. ITT analysis used.		no control group to rule this out.	not report outcomes at 12 months (no change). With high attrition rate, could have skewed results.		
Schusterbauer 2018	Low Selection bias in intervention arm only unlikely.	Low Fact that participants were part of 2 programs is clear, information about interventions is limited.	Some concerns All 10 ppts had follow-up data. Study only reports on use of the nutrition app.	Some concerns Unclear how BMI was measured (ie, self-report, via in-home scale, or in clinic). Also unclear how other patient data was collected (weight, body fat, HbA1c).	High Secular trends or other confounders could have influenced results- there was no control group to rule this out.	Low All 10 patients had follow-up data (Table 1)	Low Outcomes unlikely to be result of multiple analyses.	Poor

PEER REVIEW COMMENTS TABLE

Comment #	Reviewer #	Comment	Author Response
Are the objectives, scope, and methods for this review clearly described?			
1	2	Yes	None
2	3	Yes	None
3	4	Yes	None
4	5	Yes	None
5	6	Yes	None
6	7	Yes	None
Is there any indication of bias in our synthesis of the evidence?			
7	2	No	None
8	3	No	None
9	4	No	None
10	5	No	None
11	6	No	None
12	7	Yes - Heavily focused on Virta and comparing it to other interventions, and making recommendations for VA studies with Virta. The scope and questions don't match much of the Recommendations and Conclusions.	We broadened the discussion and conclusion sections to discuss all the virtual diabetes programs identified in the report.
Are there any published or unpublished studies that we may have overlooked?			
13	2	No	None
14	3	No	None
15	4	No	None
16	5	No	None
17	6	No	None
18	7	No	None
Additional suggestions or comments can be provided below. If applicable, please indicate the page and line numbers from the draft report.			
19	2	This is exceptionally useful and timely information for VHA's ongoing evaluation of the Virta program. The results are clearly and accessibly presented and the recommendations are well grounded in the evidence.	Thank you.
20	3	This well-written and engaging report describes the results of a nicely-conducted rapid review of virtual diet programs for patients with type 2 diabetes (DM2), which has a special focus on the Virta Health program. Overall, the findings appear valid and the interpretations reasonable. I have the following comments, organized by section.	Thank you.
21	3	Intro 1) Page 8, line 36 – Change "replace insulin or modify how	We made this change.

		insulin is used by the body" to "augment insulin levels, increase sensitivity to insulin, or impart other glucose-lowering effects."	
22	3	Intro 2) Page 9, line 15 – consider changing "limits body's production of glucose" to "limits body's access to glucose" to account for decreased enteric absorption of glucose as well as 'production' (implies gluconeogenesis).	We made this change.
23	3	Intro 3) Page 9, line 21 – Comment on calorie restriction. Some ketogenic diets do not require aggressive calorie restriction, which can also make them easier to follow for some.	We added: "and there are no restrictions on the amount of calories consumed."
24	3	Intro 4) Page 9, line 24 – Consider noting potential for acutely worsening LDL with ketogenic diet under 'skeptics' points. This may be idiosyncratic, in that certain patients can experience dramatic worsening of LDL. See: Kirkpatrick CF, 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. J Clin Lipidol. 2019 Sep-Oct;13(5):689-711.e1. doi: 10.1016/j.jacl.2019.08.003. Epub 2019 Sep 13.	We added "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"** and added Kirkpatrick 2019 as an additional citation.
25	3	Intro 5) Page 9, line 26 – With appropriate medication management, hypoglycemia risk may actually be lower with ketogenic diet – see: Yancy WS, et al. Comparison of Group Medical Visits Combined With Intensive Weight Management vs Group Medical Visits Alone for Glycemia in Patients With Type 2 Diabetes: A Noninferiority Randomized Clinical Trial. JAMA Intern Med. 2019 Nov 4;180(1):70-9. doi: 10.1001/jamainternmed.2019.4802. Online ahead of print. Consider mentioning with potential benefits.	Thank you for your comment. We decided not to include reduced risk of hypoglycemic events as a potential benefit of the ketogenic diet. Although the Yancy 2019 study you cite did indeed find a reduced risk of hypoglycemia in the intervention arm among those that consumed a low carbohydrate diet, that arm also attended more frequent group visits and received other co-interventions such as physical activity and weight management counseling, so we cannot conclude that it was the diet that caused the reduction in hypoglycemic events. The Kirkpatrick 2019 review you cite above also notes that the ketogenic diet may be associated with an increased risk of hypoglycemic events (and thus patients should be monitored closely

			and have medications adjusted as needed, as you point out).
26	3	Intro 6) Page 10, line 11 – Additional info on the approach to "physician management of medications" would be helpful.	We added "(ie, titration of medications based on biomarker tracking)" to give a brief overview of the physicians' approach to medication management in this study.
27	3	Intro 7) Page 10, line 16-21 – Include info on how patients were identified for Virta pilot. Was this a voluntary, opt-in design, and what would that suggest about selection bias and generalizability of findings from this open-label, uncontrolled study?	For brevity's sake, in the executive summary we comment that the study has "important limitations" and then provide more detail on these limitations (including the fact that participants chose which intervention they wanted to participate in) on p. 20-21 of the report.
28	3	Methods 1) Inclusion criteria – Only included last 5 years, but given evolution in technology, reasonable to assume that relevant studies would be captured in this window. Limitation further mitigated by scanning reference lists and consulting with experts as a quality check to assure no missed articles within or prior to window.	No comment.
29	3	Methods 2) Reviews at title/abstract and full text level were by one reviewer with overreading from another for this rapid review. Customary for 2 investigators to independently review each citation at these levels, with citations moving to the next level when included by either reviewer. Though reasonable for a rapid review approach used for this project may have reduced sensitivity.	No comment.
30	3	Methods 3) Data abstraction completed by one reviewer with overreading from another – no concerns.	No comment.
31	3	Methods 4) Quality assessment performed using a validated tool by one reviewer with overreading from another – often QA is done by two independent reviewers, but utilized approach likely adequate for rapid review.	No comment.
32	3	Methods 5) SOE assessment appropriate	No comment.
33	3	Methods 6) Given conceptual heterogeneity in included studies, qualitative synthesis appropriate.	No comment.

34	3	Methods 7) Included outcomes appropriate, as were definitions of clinically meaningful changes. Might have also considered ascertainment for other patient-centered outcomes such as QOL, Diabetes Distress, etc.	We agree that these are important outcomes and have included quality of life as an additional outcome that studies should evaluate in the future (p. 35). We also added language to the "limitations" section (p. 34) to indicate that examining these 4 outcomes alone was a limit of our review and future reviews should examine "other patient-important outcomes associated with these programs, such as patient satisfaction and quality of life."
35	3	Results 1) Page 19, line 51 – Allowing patients to self-sort into Virta group vs. control is a MAJOR weakness of the approach in this study. Not only does this design feature likely underlie the measured differences between the intervention and control groups (baseline differences in BMI and insulin use), but it is likely to have introduced innumerable between-group differences in unmeasured factors like motivation, comfort with technology, medical complexity, and others. In essence, this study appears to have allocated people who wanted to lose weight to Virta and those that didn't to control. In light of this selection bias, I would hesitate to treat this study as truly controlled, and instead would consider it as a pre-post examination of Virta in a highly selected population (meaning that the generalizability of the findings to the wider Veteran population is likely very limited). I see that these and other issues are noted in the 'Limitations' section on page 20, line 52; the criticisms in the first paragraph of this section are appropriate, and if anything, could be even stronger. The concerns articulated re: changes to the clinicaltrials.gov protocol and data fragmentation are also highly concerning.	We agree that the non-randomization of patients into intervention and control groups and data fragmentation are major limitations of this study. We did not make any changes to the report based on this comment.
36	3	Results 2) Page 20, line 41 – Would clarify "Overall, these results indicate the benefits of the program are maintained long-term" by adding "Overall, these results indicate the benefits of the program are maintained long-term in this selected population."	We made this change.
37	3	Results 3) Limitations for other studies appropriately noted. If possible, would be helpful to have additional data on how populations were recruited for the other studies (TeLiPro, Low Carb Program, Better Therapeutics, etc.), as this information	We added information on participant recruitment processes for each study.

		would help in considering the external validity of these approaches.	
38	3	Summary/Discussion 1) Page 32, line 18 – This is a rather generous interpretation of the Virta study, given the concerns about selection bias and lack of causality raised by the investigators in the Limitations section associated with that study (page 20, line 52). Might consider rephrasing as: "The study of Virta Health had critical limitations, but does suggest that for selected patients, participation in Virta Health is associated with improvements in important diabetes outcomes (weight, HbA1c, medication cessation, and diabetes reversal)." The authors indicated that benefits "were associated" with participation in the other named diets (page 32, line 25), so would certainly use the same cautious language for the Virta study.	We agree that it is important to use the same cautious language in describing the Virta study given its limitations, and have revised this sentence to say: "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 participate in Virta Health also stop taking medications and reverse their diabetes (ie, reduce HbA1c <6.5% with no medications or just metformin)." We also revised a similar sentence in the executive summary.
39	3	Summary/Discussion 2) Given that most of the relevant studies of technology-facilitated named interventions were not RCTs, there is a similar concern re: page 32, line 51. Rather than "2) diet counseling from a health coach can lead to 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 can lead to additional improvements," would say "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."	We agree and changed the language from "can lead" to "may be associated with."
40	3	Summary/Discussion 3) Agree with discussion of limitations of comparing multi-component interventions to UC (page 33, line 32). This suggests that a truly convincing study of Virta (or other named diet) would either use a similar virtual platform to compare two different diets (e.g., LCD vs. Mediterranean, given VA/DOD initial recommendation for Mediterranean diet) or use different	Agreed that a factorial design would be an ideal study design to address both questions on diet type and delivery model. However, given the short time frame in which the prospective evaluation would need to start, we have focused our research recommendations on what we believe is the most important question to

		approaches (e.g., virtual vs. in-person) to compare the same diet. A factorial design could examine both the diet type and delivery model, but would require a larger, more expensive study.	address (ie, whether ketogenic diet is necessary, or if another diet can be used instead).
41	3	Summary/Discussion 4) Page 34, line 1 – In addition to suggested covariates, would also suggest that validated scales be used to capture baseline and longitudinal information on key factors like motivation, diabetes distress, quality of life, as these may represent important moderators of intervention effect.	We added a sentence: "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" to the "Recommendations for prospective evaluation" section.
42		Summary/Discussion 1) Page 35, line 8 – Unless VA has expressed that it is committed to Virta to the exclusion of other options, would hesitate to make the following recommendation: "A second approach would be to use a non-Virta program as a "back-up" in the event participants could not tolerate the ketogenic diet or otherwise did not like the Virta program." Even with appropriate measurement of and adjustment for baseline factors, comparing front-line Virta users to users of another program who did not like or tolerate Virta would fundamentally be an apples-to-oranges comparison, and would not answer the question of which program works better for Veterans. Would only use such a design as a last resort.	Agreed and we added the sentence: "This option should only be used if it is not feasible to let participants select their preferred program." to clarify this should be a last resort.
43	3	Conclusions 1) Page 35, line 24 – Concerned about the validity of this statement as per above comments on Page 32, line 18. Would instead couch this statement in terms of "select populations" and "association" (rather than language that even cautiously implies causation). Existing data on Virta does not clearly establish causation, and the magnitude of the findings should not be generalized to the wider, unselected Veteran population.	We revised the conclusion to discuss all virtual diabetes programs in response to another reviewer's comments. However, we removed any causal language and instead used language that describes that **selected** participates may lower diabetes outcomes **after participating** in intensive diabetes management program based on the ketogenic diet or other diets.
44	3	Conclusions 2) The fact that the findings from the existing Virta study should not be generalized to the wider, unselected Veteran population (particularly in terms of that magnitude of effect) means that these data have major limitations in determining the cost-effectiveness of the Virta approach for VA overall. May consider mentioning this.	Agreed and we added the sentence: "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."

45	3	Conclusions 3) In order to assure applicability of future findings re: Virta to wider Veteran population, studies are needed in representative populations attained via proactive sampling (not simply those choosing Virta, as this will bias sample toward individuals likely to benefit), active comparators (including non-LCD options) or other appropriate control groups, randomized designs, longer timeframes, and a wide range of clinical and patient-centered outcomes and harms. Could consider broader statements to this effect in Conclusions (recognizing the real-world fact that RCTs may not be feasible prior to adoption – however, there are major concerns about the current level of evidence supporting Virta).	We disagree that to assure applicability to Veteran populations, patients must be randomized to interventions. We believe the most appropriate strategy to determining the real-life effectiveness of Veterans choosing which diet or program they want to participate in is to use a non-randomized study design. In the "future research needs" section, we comment on the need for non-randomized study designs that evaluate active comparators and a wide range of clinical and patient-important outcomes and harms. We therefore have not made any revisions to the conclusions to address this comment, as the most important points are covered in the "future research needs" section.
46	4	This is a high-quality well-written review. I agree strongly with the recommendations made for evaluating Virta in both the retrospective and prospective group of Veterans. Having comparators will be quite useful and make the study findings much more useful.	Thank you.
47	4	It was not fully clear to me from a quick read how much of the data was from what was sent by the companies themselves since there was a note that data were requested from companies. I may have missed this in a quick read of the report. There are clear potential biases in companies reporting their own data and in studies published by companies. Please make sure to mention potential reporting bias in the executive summary and summary of limitations. This was already mentioned under specific studies but it was not clear how much this might impact study findings overall in the summary of findings. Apologize if I just missed seeing this.	We agree that there is the potential for reporting bias in describing data from literature that has not been peer reviewed. We have therefore revised the sentence on p. 14 to now state: "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."** We also previously stated in the Virta Health section on p. 20: "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. 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."

48	5	Appreciate this review offering future suggestions and ideas for research and data gathering for Virta and VA data collection. Suggestion I would offer includes: if possible, please be certain to make clear the direction ADA and VA/DoD suggest in regards to diet. They both support individualization of diet/nutrition per each person's preferences and needs. Along with individualization for diabetes self-management. The Mediterranean diet was referenced as another option for patients to try, but bottom line it needs to be made clear that their recommendations include ongoing individualization.	We added the sentence to the description of the VA/DOD recommendations: "These recommendations emphasize that the chosen diet be tailored to patient preferences and needs."
49	5	The reviewers may also consider risks such as CAD and CKD in addition to diverticulitis as mentioned towards end of this review. CAD and CKD as a whole may have a much deeper impact and create risks for these diabetic patients in the long term if following something like the ketogenic diet. Perhaps a study showing this evidence may need to be included or considered.	We added coronary artery disease and chronic kidney disease as additional conditions that should be monitored in future studies.
50	5	Greatly appreciate being a part of this project! An excellent review by the ESP team! Thank you.	No comment.
51	6	First, I really appreciated being an informant and reviewer for this report. Thanks for the opportunity! Second, this report is excellent. It is very informative and well written. I'm so happy you guys looked into this data. I especially like the recommendation regarding further research to figure out if it's the diet that's helping or the program itself. As an educator, I'm really excited to get an answer to this, so thank you!	No comment.
52	6	Only 1 edit found: Dietitian is spelled wrong in 2 places (page 24, line 23 and page 28 line 39)	Thank you, we have corrected these.
53	6	Other comments (all subjective and from an educator's standpoint, so feel free to take them or leave them): 1. Page 7, states "we recommend that researchers capture a wide range of information on harms, including exacerbations or development of conditions such as diverticulitis". Completely agree with this statement but there are more severe and common diseases we worry about and see with the Keto diet. So I think a better example would be something like kidney failure. Your line isn't wrong, just a suggestion.	Per comment #49, we added chronic kidney disease as an additional condition that should be monitored in future studies.
54	6	Other comments (all subjective and from an educator's standpoint, so feel free to take them or leave them):	Per comment #38, we have changed this sentence to say: "Though the study of Virta Health had important limitations, it suggests that

		2. Page 32 under Summary and Discussion: words such as "convincingly" and "rapid", how are they defined? Without a definition it almost sounds biased.	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 participate in Virta Health also stop taking medications and reverse their diabetes (ie, reduce HbA1c <6.5% with no medications or just metformin)."
55	6	Other comments (all subjective and from an educator's standpoint, so feel free to take them or leave them): 3. Page 32: The paper says several times "patients who are unlikely to improve in usual care". How is this defined? From an educators standpoint those that sign up for Virta seem to me to be the kind of patient that would benefit from usual care, so I'm curious.	We agree this phrase is confusing. Throughout the report, we removed "patients who are unlikely to improve in usual care" and replaced it with "for selected patients (*ie*, those who are severely obese, interested in an intensive diabetes management program, and willing to adhere to the ketogenic diet) to make it clear who might benefit from this program based on the existing evidence. We have also added a sentence to the "future research needs section" to indicate that: 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, 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."
56	6	Other comments (all subjective and from an educator's standpoint, so feel free to take them or leave them): 4. The report says the Virta program results in decreased weight, HbAlc, medication cessation, and diabetes reversal. You define "diabetes reversal" as and HbAlc <6.5. I would add HbAlc <6.5 without medications because diabetics on meds/insulin can achieve an HbAlc <6.5 without reversing diabetes. Also, not all T2 diabetics can reverse diabetes or get off of their meds. If their diabetes has progressed to the	We agree and added "without medications" to the "definitions of clinically meaningful change by outcome." We also comment in the report on how each study defined diabetes reversal. In terms of the language on the Virta study specifically, we agree it's important to clarify that only some patients experienced diabetes reversal. We have revised to say: "Some

		point that they no longer produce enough insulin, medication cessation and diabetes reversal is not possible. Only those that still produce their own insulin can achieve this. I worry it gives a false hope. I would think a statement more like- Virta leads to weight loss and decreased HbAlc and can potentially lead to medication cessation and diabetes reversal in some, is more accurate. Again, that's just an educators point of view.	patients also stop using diabetes medications and reverse their diabetes."
57	6	Other comments (all subjective and from an educator's standpoint, so feel free to take them or leave them): 5. Last subjective comment: Bottom of page 34 it talks about the potential of other diets if a Veteran prefers. I agree some Veterans may prefer another diet, but the Keto diet is also contraindicated in some pts. I think that should be pointed out too.	We revised this sentence to say: "…the ketogenic diet may **be unappealing or contraindicated in some** Veterans with type 2 diabetes…"
58	7	Page 4 line 56: The ketogenic diet is not necessarily </=10% kcal from carbohydrate, and can be less than this if needed for the patient to achieve ketosis.	We revised to say "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."
59	7	Page 5 line 14: The VA - Virta relationship in 2019 was a non-research Strategic Partnership, so you must remove the word "study" here and elsewhere when referring to the partnership. In this line and line 15, it is also unclear whether you are referring to the VA partnership or another non randomized study (add the reference # for the study to which you are referring).	We have changed "study" to "project" on line 14. We revised line 15 to indicate that a "separate" non-randomized study provides evidence on the Virta Health program. We do not include references in the executive summaries of ESP reports; however, we do include the references to the pilot project and study in the introduction section where these are discussed in more detail.
60	7	Page 8 line 43: The Academy of Nutrition and Dietetics does not abbreviate their name "AND" but rather The Academy. I couldn't find another use of "AND" but it should be referred to as The Academy	We have changed "AND" to "The Academy."
61	7	Page 9 line 6: The ketogenic diet is not necessarily </=10% kcal from carbohydrate, and can be less than this if needed for the patient to achieve ketosis.	We made the same revision here as in the executive summary: "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."
62	7	Page 10 line 21: The VA - Virta partnership is not a research study; please remove any reference of this partnership as a	We have changed "study" to "project" where applicable in this paragraph.

		"study." https://www.blogs.va.gov/VAntage/58037/innovative-treatment-vets-type-2-diabetes/	
63	7	Page 10 line 30: This sentence seems at odds with the stated scope of the ESP. While perhaps true and very valuable, it doesn't fit with the stated questions of the ESP. Recommend remove this sentence: "This rapid evidence review was commissioned by the VA's Health Services Research & Development (HSR&D) program to help inform evaluation of the VA and Virta Health pilot program."	We believe this sentence is aligned with the stated scope and questions of the review. The scope of an ESP review is informed not only by the key questions and PICOs, but also the purpose and audience of the review. We have therefore left in the sentence in the report, but revised it for clarity.
64	7	Page 33: Gaps and Future Research section. Remove or rewrite to connect this section with your ESP questions and scope.	We revised the gaps and future research section to be more generally applicable to research of all virtual diabetes diet programs.
65	7	Page 35 Conclusions section. Revise to connect this section with your ESP questions and scope. Or delete the first sentence would suffice.	We revised the conclusion to discuss findings of all virtual diabetes programs.

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