PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A Mixed Methods Pilot Study of a Low-Carbohydrate Diabetes Prevention Program Among Adults with Prediabetes in the US
AUTHORS	Griauzde, Dina; Saslow, Laura; Patterson, Kaitlyn; Ansari, Tahoora; Liestenfeltz, Bradley; Tisack, Aaron; Bihn, Patti; Shopinski, Samuel; Richardson, Caroline R

VERSION 1 – REVIEW

REVIEWER	Sarah Hallberg Indiana University Health and Virta Health Employee of Virta Health an online diabetes specialty clinic.
REVIEW RETURNED	22-Aug-2019

GENERAL COMMENTS	This was a single arm pilot study involving 22 individuals to assess the feasibility and acceptability and estimate the weight loss of a Low-Carbohydrate DPP intervention for adults with prediabetes as well. The paper is well written and the design of the study was appropriate for the research questions at hand. Some minor specific comments are as follows: 1.Page 6 line 53 - it may be difficult for the reader to understand the purpose of phasing in dietary changes meal by meal. This could be discussed. 2. Is there a way to assess if increased carbohydrate consumption (as instructed) was associated with the decrease in engagement? ie more carbohydrates reintroduced the less engaged. If that is possible it would be interesting to note.

REVIEWER	Reynaldo Martina University of Liverpool
REVIEW RETURNED	11-Oct-2019

GENERAL COMMENTS	Study design: It is unclear what is meant with mixed methods. This needs clarifying. This terminology can also be misleading as mixed methods can also imply fix and random effect evaluations which is not meant here. How was the prevention program adapted? Where were the subjects selected from? - why that specific clinical? how are patients in this clinic representative for other patient? (generalisability) retention: definition of retention is questionable. Subjects may complete the survey but there is no assessment whether the completion was accurate and or true. Could the subject complete

	the survey yet drop out of the program? - this happens a lot in many clinical programs. were there more definitions of feasibility and acceptability? the variables used to define these parameters should be clearly defined. "e.g." is unacceptable. Secondary objective: changes in weight. I assume decrease is meant. But change can also be an increase. Not unusual in a program like this...Also, change in weight AND achievement of at least 5% weight loss. This definition is also ambiguous. It is unclear how the results described address the objective of feasibility. A little bit more than half attended/maintained sessions . t-test was used but it was not described which variables exactly were analysed using this test and whether it was appropriate to do so. Moreover, it is unclear whether the sample is large enough to investigate the objective of the study so the test seem adhoc and uninformative, even for a pilot study. Perhaps estimates and confidence intervals to understand the variation in the data may be more appropriate.

REVIEWER	Sharon Edelstein George Washington University USA
REVIEW RETURNED	22-Nov-2019

GENERAL COMMENTS	This is a nice, well written manuscript describing a very well done, small pilot study of a very low carbohydrate diet (VLCD) as part of a modified National Diabetes Prevention Program (NDPP) on feasibility, acceptability, and weight loss, with recruitment through primary care. Although this is a small, short term study, the authors have nicely shown that most participants were able to meet the VLCD requirements and lose weight, and those who completed participation lost more weight. The completion rate was high. The participants were largely white and well educated, limiting its representativeness to the national population of patients with prediabetes. However, none of this is new: As the authors note, many studies have shown the ability of patients to lose weight on a VLCD, many with fewer cravings. However this small study adds to the literature nicely, in particular with respect to the NDPP with low-carbohydrate modifications to the 1990's low-fat diet. One specific question: This sentence seems to be written incorrectly: To minimimize side effects (e.g. headache, constipation, muscle cramps, diarrhea, general weakness) participants were instructed to replace one meal a week with a low-carbohydrate alternative, starting with breakfast and snacks.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1 (Sarah Hallberg; Institution and Country: Indiana University Health and Virta Health

1. **This was a single arm pilot study involving 22 individuals to assess the feasibility and acceptability and estimate the weight loss of a Low-Carbohydrate DPP intervention for adults with prediabetes as well. The paper is well written and the design of the study was appropriate for the research questions at hand.**

   We appreciate these comments.

Some minor specific comments are as follows:

2. **Page 6 line 53 - it may be difficult for the reader to understand the purpose of phasing in dietary changes meal by meal. This could be discussed.**

   To clarify this point, we have added the following information to the Methods:

   > "While the NDPP curriculum teaches to participants to initiate adherence to a low-fat diet during Session #2, we designed the curriculum to gradually ease individuals into the low-carbohydrate diet for two key reasons. First, we recognized that this dietary change may be drastic for individuals accustomed to consuming high-carbohydrate meals. Accordingly, we desired to increase individuals' competency and self-efficacy through step-by-step introduction of the meal plan, as these constructs have been associated with dietary adherence and favorable changes in health habits in other behavior change studies (35). Second, when transitioning to a very low carbohydrate meal plan, individuals may experience side effects such as headache, constipation, muscle cramps, diarrhea, general weakness (i.e., "keto flu"); a more gradual reduction in carbohydrate intake can reduce the likelihood that individuals experience these symptoms. During session #2, participants were instructed to replace typical breakfast and snack foods with low-carbohydrate options. During sessions #3 and #4, they were instructed to replace lunch and dinner foods, respectively, with low-carbohydrate options. As part of these sessions, participants were also advised about strategies to mitigate potential side effects (e.g., increase water and salt intake if experiencing headache; increase intake of water and non-starchy vegetables if experiencing constipation). Allowable foods included: meats, fish, poultry, eggs, cheese, seeds, nuts, leafy greens, non-starchy vegetables, and some fruits (e.g., berries). Participants were also taught to use low-carbohydrate substitutes when cooking or baking (e.g., almond flour in place of wheat flour)." (Lines 139 to 155)

3. **Is there a way to assess if increased carbohydrate consumption (as instructed) was associated with the decrease in engagement? ie more carbohydrates reintroduced the less engaged. If that is possible it would be interesting to note.**

   This is an interesting question that certainly warrants future investigation, particularly given that one common criticism of low-carbohydrate meal plans is that they are difficult to maintain overtime. Unfortunately, we do not have sufficient data in this small pilot study to meaningfully comment on this topic. However, we intend to explore the relationships between carbohydrate intake, program engagement, and weight loss in a fully-powered randomized controlled trial comparing weight loss among DPP vs. LC-DPP participants.

Reviewer: 2 (Reynaldo Martina; University of Liverpool)

4. **Study design: It is unclear what is meant with mixed methods. This needs clarifying. This terminology can also be misleading as mixed methods can also imply fix and random effect evaluations which is not meant here.**

   We now clarify our use of the term "mixed methods" in both the Abstract and the Methods section of the main text. In the Abstract, we clarify the Research Design:

   > "Single-arm, mixed methods (i.e., integration of quantitative and qualitative data) pilot study." (Lines 31-32)

   In the Methods, we clarify our use of a mixed methods study design:

"We used a mixed methods sequential explanatory study design (29); quantitative data were collected at baseline, 6-months, and 12-months; qualitative data were collected at 6-months and 12-months. Integration(30) of quantitative and qualitative data occurred after the study period when we merged our quantitative and qualitative data. The rationale for this approach is that quantitative data provides a general overview of the intervention's efficacy and limitations, and qualitative data help to explain these findings by exploring participants' experiences and perspectives in more depth (31)." (Lines 98-104)

5. How was the prevention program adapted?

We now provide additional details in the Methods regarding how we adapted the traditional DPP to the LC-DPP:

"We adapted the NDPP's dietary advice to teach participants to follow a VLCD, restricting carbohydrate intake (not including fiber) to 20-35 grams per day during the program's core phase (i.e. weeks 1-16). We did not substantially alter the content of NDPP sessions focused on non-dietary topics such as exercise. While the NDPP curriculum teaches to participants to initiate adherence to a low-fat diet during Session #2, we designed the curriculum to gradually ease individuals into the low-carbohydrate diet for two key reasons. First, we recognized that this dietary change may be drastic for individuals accustomed to consuming high-carbohydrate meals. Accordingly, we desired to increase individuals' competency and self-efficacy through step-by-step introduction of the meal plan, as these constructs have been associated with dietary adherence and favorable changes in health habits in other behavior change studies (35). Second, when transitioning to a very low carbohydrate meal plan, individuals may experience side effects such as headache, constipation, muscle cramps, diarrhea, general weakness (i.e., "keto flu"); a more gradual reduction in carbohydrate intake can reduce the likelihood that individuals experience these symptoms. During session #2, participants were instructed to replace typical breakfast and snack foods with low-carbohydrate options. During sessions #3 and #4, they were instructed to replace lunch and dinner foods, respectively, with low-carbohydrate options. As part of these sessions, participants were also advised about strategies to mitigate potential side effects (e.g., increase water and salt intake if experiencing headache; increase intake of water and non-starchy vegetables if experiencing constipation). Allowable foods included: meats, fish, poultry, eggs, cheese, seeds, nuts, leafy greens, non-starchy vegetables, and some fruits (e.g., berries). Participants were also taught to use low-carbohydrate substitutes when cooking or baking (e.g., almond flour in place of wheat flour)." (Lines 136 to 155)

6. Where were the subjects selected from? - why that specific clinic? how are patients in this clinic representative for other patient? (generalisability)

We now provide additional information in the Methods to provide insight into the generalizability of our data.

"Michigan Medicine has 14 adult primary care clinics throughout Southeast Michigan that serve approximately 240,000 patients with racial/ethnic characteristics similar to 2016 U.S. Census Data estimates for the state of Michigan (80% White, 14% African-American, 5% Latino, 3% Asian) (32). Approximately 70% of Michigan Medicine patients have commercial insurance and approximately 30% have federal insurance (e.g., Medicare, Medicaid). We conducted this study at one outpatient clinic with a demographic and payor mix similar to that of the health system." (Lines 108 to 113)

We further comment on the issue of generalisability in the Limitations:

"First, we recruited individuals from one primary care clinic within a US academic medical center and our results may not be generalizable to other populations. Because the prevalence of prediabetes is increasing worldwide (49), there is a critical need to develop and test novel interventions for T2DM prevention among diverse

populations and concomitantly explore what works for whom and under what circumstances (50,51)." (Lines 392 to 396)

7. **Retention: definition of retention is questionable. Subjects may complete the survey but there is no assessment whether the completion was accurate and or true. Could the subject complete the survey yet drop out of the program? - this happens a lot in many clinical programs.**

We have two measures of program engagement: (1) session attendance and (2) survey completion. We know from anecdotal cases in this small pilot study that some participants remained engaged in the program, but could not attend sessions due to personal and/or professional circumstances. Despite non-attendance, these individuals remained in periodic communication with the lifestyle coach, received course materials by e-mail, and completed assessments at 6 and 12 months. Accordingly, we felt that survey completion was the most accurate representation of study retention in this small sample. Notably, this reviewer raises the important concern that participants in behavioral health interventions may complete study assessments (e.g., surveys) despite non-adherence to the lifestyle change recommendations. In the fully-powered trial, we will explore the relationships between clinical outcomes (e.g., weight, HbA1c), session attendance, and completion of study assessments.

We have aimed to clarify this point in the Methods:

> "LC-DPP retention rate was determined by calculating the rate of completion of the 6-month and 12-month surveys. Although session attendance is commonly used as a measure of intervention retention in larger trials, we observed that several participants in this small pilot study could not attend sessions due to personal and/or professional circumstances. However, they remained in periodic communication with the lifestyle coach, received course materials by e-mail, and completed assessments at 6 and 12 months. Accordingly, we felt that survey completion was the most accurate representation of study retention in this small sample." (Lines 195 to 201)

8. **Were there more definitions of feasibility and acceptability? the variables used to define these parameters should be clearly defined. "e.g." is unacceptable.**

We have added a more detailed explanation of our feasibility and acceptability measures to the Methods:

> *"Secondary Measures:*
> Intervention feasibility and acceptability: Measures of feasibility and acceptability were uptake, session attendance, and study retention rates. LC-DPP uptake rate was defined as the number of participants who enrolled in the intervention divided by the total number of individuals invited to participate.
>
> Session attendance was determined by calculating the rate of attendance at core and maintenance sessions. Rates of session attendance were compared with the CDC's Diabetes Prevention Recognition Program (DPRP) standards (28). The DPRP monitors the fidelity and quality of community-based DPPs, and requires that at least 60% of program participants attend ≥9 core sessions and ≥3 maintenance sessions. We aimed to achieve these session attendance metrics to demonstrate LC-DPP feasibility.
>
> LC-DPP retention rate was determined by calculating the rate of completion of the 6-month and 12-month surveys. Although session attendance is commonly used as a measure of intervention retention in larger trials, we observed that several participants in this small pilot study could not attend sessions due to personal and/or professional circumstances. However, they remained in periodic communication with the lifestyle coach, received course materials by e-mail, and completed assessments at 6 and 12 months. Accordingly, we felt that survey completion was the most accurate representation of study retention in this small sample.
>
> To further understand the program's acceptability, we conducted semi-structured interviews at 6 and 12 months. During interviews, we explored participants'

general experiences with the intervention as well as specific facilitators of and barriers to VLCD adherence." (Lines 186 to 204)

9. **Secondary objective: changes in weight. I assume decrease is meant. But change can also be an increase. Not unusual in a program like this...Also, change in weight AND achievement of at least 5% weight loss. This definition is also ambiguous.**

We have aimed to clarify this important point. As this reviewer notes, it was possible that we may have observed an increase in participants' weight. Accordingly, we use the term "weight change" rather than "weight loss."

We have revised our Methods to more clearly define our weight outcome measures:

"Primary Measures: Weight change

(1) Change in body weight at 6 months and 12 months: Body weight was measured and recorded at each attended session. Among session non-attendees, we attempted to schedule 6- and 12-month weigh-ins at participants' convenience. We calculated average body weight change and percent body weight change at 6 months and 12 months compared to baseline. All weights were obtained using a calibrated scale.

(2) Percentage of participants who achieved ≥5% body weight loss: At 6 months and 12 months, we determined the percentage of participants who achieved goal weight loss by dividing the number of individuals who achieved ≥5% body weight loss by the number of study enrollees with baseline weight data (n=21). We similarly calculated the percentage of participants who achieved 10% body weight loss at each time point." (Lines 174 to 184)

10. **It is unclear how the results described address the objective of feasibility. A little bit more than half attended/maintained sessions.**

High rates of non-attendance are a common problem among behavioral health interventions, including traditional DPPs. Accordingly, the Centers for Disease Control and Prevention's Diabetes Prevention Recognition Program requires DPPs to achieve a session attendance threshold. We used this threshold as our measure of feasibility, which we clarify in the Methods:

> "Session attendance was determined by calculating the rate of attendance at core and maintenance sessions. Rates of session attendance were compared with the CDC's Diabetes Prevention Recognition Program (DPRP) standards (28). The DPRP monitors the fidelity and quality of community-based DPPs, and requires that at least 60% of program participants attend ≥9 core sessions and ≥3 maintenance sessions. We aimed to achieve these session attendance metrics to demonstrate LC-DPP feasibility." (Lines 190 to 194)

We have also expanded our discussion of the results to include a comparison with reported attrition rates in traditional DPPs:

> "Similarly, attendance at LC-DPP core sessions was high, meeting CDC DPRP standards (28) with 67% (n=14) attending at least 9 core sessions; attendance decreased during the program's maintenance phase with only 52% (n=11) attending at least 3 maintenance sessions. Notably, rates of attrition are often high in real-world behavioral health interventions, including traditional DPPs where approximately half of participants remain engaged with the intervention at 6 months (4,42). Accordingly, by CDC DPRP standards and in comparison to real-world DPPs, our findings suggest that an LC-DPP is feasible. Additional strategies (e.g., incentives, varied class times) could be explored to augment participants' session attendance." (Lines 357 to 365)

11. **t-test was used but it was not described which variables exactly were analysed using this test and whether it was appropriate to do so. Moreover, it is unclear whether the sample is large enough to investigate the objective of the study so the test seem adhoc and uninformative, even for a pilot study. Perhaps estimates and confidence intervals to understand the variation in the data may be more appropriate.**

Thank you for this comment. We agree with this reviewer that paired t-test was not the appropriate test to use when comparing pre-post changes in the frequencies of participants' physical symptoms. Given our small sample and non-normal distribution of the data, we used a nonparametric statistical test, the Wilcoxon matched-pairs sign-rank test, to compare pre-post changes in the frequencies of participants' physical symptoms. Through use of this more appropriate statistical test, we were able to discern statistically significant changes in participants' physical symptoms from baseline to 6 and 12 months, which we now comment on in the Results.

We have added the following information to the Methods:

> "Given our small sample and non-normal distribution of the data, we used a nonparametric statistical test, the Wilcoxon matched-pairs sign-rank test, to compare pre-post changes in the frequencies of participants' self-reported physical symptoms at 6 and 12 months compared to baseline. All analyses were conducted using Stata 14." (Lines 233 to 236)

We have added the following information to the Results:

"Change in self-reported physical symptoms: Change in self-reported physical symptoms: There was an increase in self-reported constipation from baseline to 6 months (p=0.006). There was a decrease in muscle cramps from baseline to 6 months (p=0.005) and a decrease in physical weakness from baseline to 6 months (p=0.05) and 12 months (p=0.05). There were no other statistically significant differences in self-reported side effects at 6 or 12 months compared to baseline." (Lines 274 to 278)

Reviewer: 3 (Sharon Edelstein; George Washington University, USA)

12. **This is a nice, well written manuscript describing a very well done, small pilot study of a very low carbohydrate diet (VLCD) as part of a modified National Diabetes Prevention Program (NDPP) on feasibility, acceptability, and weight loss, with recruitment through primary care. However, none of this is new: As the authors note, many studies have shown the ability of patients to lose weight on a VLCD, many with fewer cravings. However, this small study adds to the literature nicely, in particular with respect to the NDPP with low-carbohydrate modifications to the 1990's low-fat diet.**

    We appreciate these comments

13. **Although this is a small, short term study, the authors have nicely shown that most participants were able to meet the VLCD requirements and lose weight, and those who completed participation lost more weight. The completion rate was high. The participants were largely white and well educated, limiting its representativeness to the national population of patients with prediabetes.**

    Please see Response #14 for our further discussion of this study limitation.

14. **This sentence seems to be written incorrectly: To minimize side effects (e.g. headache, constipation, muscle cramps, diarrhea, general weakness) participants were instructed to replace one meal a week with a low-carbohydrate alternative, starting with breakfast and snacks.**

    We hope that we have clarified this important point in Response #10.

We thank you for these comments and feel that they have strengthened the manuscript. We hope that we have addressed this concern in our responses above and look forward to your further feedback.