PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A telephone lifestyle intervention to prevent diabetes in women with recent gestational diabetes attending the national health system – The LINDA-Brasil clinical trial
AUTHORS	Schmidt, Maria; Bracco, Paula; Nunes, Maria; Cherubini, Kadhija; Castilhos, Cristina D.; Spagiari, Jainara; Galliano, Leony; Ladwig, Ruben; Del Vecchio, Fabricio; Del Vecchio, Anelita H. M.; Drehmer, Michel; Forti, Adriana; Façanha, Cristina; Zajdenverg, Lenita; de Almeida-Pititto, Bianca; Réa, Rosângela; Dualib, Patrícia; Duncan, Bruce

VERSION 1 - REVIEW

REVIEWER NAME	Cheung, N Wah
REVIEWER AFFILIATION	University of Sydney
REVIEWER CONFLICT OF INTEREST	None
DATE REVIEW RETURNED	19-Feb-2024

GENERAL COMMENTS	This paper reports the results of a randomised controlled trial of a telephone based lifestyle intervention to prevent diabetes after gestational diabetes. It is important that we find means of reducing diabetes risk amongst women who have had GDM. The authors should be congratulated for conducting this large study, which was obviously a huge amount of work, through difficult times. My main concern is that the primary outcome was not significant, and this should be stated, rather than using terms which suggest that there was a treatment effect. Eg, the following in the abstract should be rephrased along these lines: “16% relative lower relative incidence” should be “there was no reduction in diabetes incidence” 29% reduction in diabetes incidence” should be “there was no reduction in diabetes incidence”. Similar statements have been made through the text, and results which are not significant should not include wording which suggests that there was an effect. These all need to be changed. Details of ethics approval should be included in this paper, not just the protocol paper.. For weight gain, did the investigators try adjusting the data for baseline variables? This may also change the p value from 0.09. The investigators suggest that basic education may be a major reason why the trial did not show an effect on diabetes. However basic education really is part of usual care, and our role as researchers is to find interventions which work better than usual care, as opposed to no care. BTW this paragraph used the term

	"modest reduction" which should be "no reduction". Whilst it may make sense to immediately intervene after pregnancy, it may be that this is a particularly difficult group in which to implement an intervention. This could be discussed. Table 2: The lower half and the top half should be formatted similarly if it is to be one table. For weight gain, it would be useful to include the actual weights for the 2 groups. Fig 1: The flowchart should be extended to include boxes for the number of women who dropped out after randomisation or did not complete their evaluations.

REVIEWER NAME	Mercado, Carla
REVIEWER AFFILIATION	CDC Atlanta, Division of Diabetes Translation
REVIEWER CONFLICT OF INTEREST	No competing interests.
DATE REVIEW RETURNED	22-Apr-2024

GENERAL COMMENTS	This is a well-designed clinical trial with potential to have an impact on reducing the development of type 2 diabetes among high-risk women. The main issues were the timing of recruitment which should have been close to the delivery date for all the women, incorporating retention measures, and the lack of recruiting sufficient participants to observe the impact of the intervention. However, there is value in publishing this clinical trial to contribute a reference for a sound study design that could be amended to incorporate lessons learned.

REVIEWER NAME	Crowe, Francesca
REVIEWER AFFILIATION	University of Birmingham, Institute of Applied Health Research
REVIEWER CONFLICT OF INTEREST	None
DATE REVIEW RETURNED	19-May-2024

GENERAL COMMENTS	This randomised controlled trial tested whether a telephone-based lifestyle intervention in women with previous gestational diabetes reduced the risk of type 2 diabetes. The paper is clear and written well. I have some comments. Abstract "Adherence to the telephone intervention was incomplete." It may be better to say that adherence was low or poor? Why did you not show the effect of the intervention in women who were randomised less than a year before the COVI-19 pandemic to show whether there was a differences between the groups rather than just showing this in one subgroup? Please show this together with eth p for heterogeneity if possible. Did the authors explore why women did not adhere to the intervention in terms of completing the sessions? This would be valuable learning. Page 14, line 33: How many women were randomised at the point of ending randomisation? please add this in here. Page 15, line 38: Why did you not involve women with previous

	GDM in the design of the intervention. Do you think this could have helped develop an intevention that was more effective? In the analysis, Page 15, line 28: "alfa" should be alpha

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 Prof. N Wah Cheung, University of Sydney		
This paper reports the results of a randomised controlled trial of a telephone-based lifestyle intervention to prevent diabetes after gestational diabetes. It is important that we find means of reducing diabetes risk amongst women who have had GDM. The authors should be congratulated for conducting this large study, which was obviously a huge amount of work, through difficult times.	We thank the reviewer for the kind words and for the insightful comments and helpful suggestions. We have made the changes recommended and believe they have improved the manuscript.	
My main concern is that the primary outcome was not significant, and this should be stated, rather than using terms which suggest that there was a treatment effect. Eg, the following in the abstract should be rephrased along these lines: "16% relative lower relative incidence" should be "there was no reduction in diabetes incidence" 29% reduction in diabetes incidence" should be "there was no reduction in diabetes incidence". Similar statements have been made through the text, and results which are not significant should not include wording which suggests that there was an effect. These all need to be changed.	We have made these changes in the Abstract.	Abstract "There was no reduction in the incidence of diabetes (HR=0.84; 0.60-1.19) and only a non-significant 0.97 kg less weight gain (p=0.09). Among the 305 women randomized more than one year before the COVID-19 pandemic, the intervention did not reduce the incidence of diabetes (HR=0.71; 0.48-1.04), despite a 2.09 kg (p=0.002) lesser weight gain."

	We made similar changes throughout the text as can be seen in the track changes marked up version of the manuscript.	
Details of ethics approval should be included in this paper, not just the protocol paper.	The ethics approval details were provided at the end of the manuscript. We have now added the names of the remaining Ethics Committees.	Ethics approval “The ethics committee of the Hospital de Clínicas de Porto Alegre (Project 120097, May 4, 2012) and of each additional clinical center(Centro de Estudos em Diabetes e Hipertensão, Maternidade-Escola da UFRJ, Universidade Federal de São Paulo, Escola Superior de Educação Física da Universidade Federal de Pelotas, and Empresa Brasileira de Serviços Hospitalares) approved the protocol. Written consent was obtained at initial recruitment during pregnancy and again before randomization.”
For weight gain, did the investigators try adjusting the data for baseline variables? This may also change the p value from 0.09.	Good point. Consistent with the findings in Table 1, indicating generally similar characteristics between groups, adjustments of the overall weight difference did not materially change this result. We added this at the end of the section Effects on the secondary outcome: weight change.	Effects on the secondary outcome: weight change “Adjustment for baseline factors did not materially change the overall results, the adjusted difference being 0.99 kg (p=0.08).”
The investigators suggest that basic education may be a major reason why the trial did not show an effect on diabetes. However basic education really is part of usual care, and our role as researchers is to find interventions	We agree and have removed this text and the term “modest reduction”.	

which work better than usual care, as opposed to no care. BTW this paragraph used the term “modest reduction” which should be “no reduction”.	We have now focused the section Interpretation of the Main Study Findings on the problem of low adherence.	
Whilst it may make sense to immediately intervene after pregnancy, it may be that this is a particularly difficult group in which to implement an intervention. This could be discussed.	Good suggestion. We added text on this while reorganizing the sections Interpretation of the Main Findings and Applicability and Future Research.	Interpretation of the Main Findings “Although the main reason for this probably relates to the inherent difficulties of recent motherhood, …” Applicability and future research “Stimulating busy new mothers, especially those with limited resources can be challenging.”
Table 2: The lower half and the top half should be formatted similarly if it is to be one table. For weight gain, it would be useful to include the actual weights for the 2 groups.	Due to space limits (5 tables/figures) we presented the main results in a single table. We followed your suggestions to reorganize the Table formatting and have included the absolute weights as requested.	See new Table 2.
Fig 1: The flowchart should be extended to include boxes for the number of women who dropped out after randomisation or did not complete their evaluations.	We have done this.	Figure 1 See the bottom of the flowchart.
Reviewer 2 Dr. Carla Mercado, CDC Atlanta		
This is a well-designed clinical trial with potential to have an impact on reducing the development of type 2 diabetes among high-risk women.	Thank you for this comment. We believe that postpartum support for these women is essential and hope that the accumulating evidence will make this clear.	
The main issues were the timing of recruitment which should have been close to the delivery date for all the women, incorporating retention	Thank you for this comment. We agree that these three issues are the basic ones We revised the	Study limitations “First, our intervention to increase and sustain

measures, and the lack of recruiting sufficient participants to observe the impact of the intervention.	Study Limitations section to address them more directly.	breastfeeding was hampered by trial entry occurring more distant from delivery (56.3% ≥6 months after pregnancy). Second, an attrition bias is possible as we had no follow-up for 43 (9.2%) women. However, these losses were similar in the intervention and control groups (19 and 24, respectively). Moreover, since most (72%) women not returning were randomized closer to the pandemic, this key reason for losses was likely non-differential with respect to outcomes. Third, recruitment shortfall, much due to the pandemic-induced premature closure of the trail, led to insufficient statistical power to affirm that the 16% lower incidence found was real."
Reviewer 3 Dr. Francesca Crowe, University of Birmingham		
This randomised controlled trial tested whether a telephone-based lifestyle intervention in women with previous gestational diabetes reduced the risk of type 2 diabetes. The paper is clear and written well. I have some comments.	Thank you for your kind comment.	
Abstract "Adherence to the telephone intervention was incomplete." It may be better to say that adherence was low or poor?	Thank you for bringing this point to our attention. In the Abstract, we now state more directly what we considered a low attendance. We also made slight changes throughout text.	Abstract "….although only 75% attended the minimum number of telephone sessions"
Why did you not show the effect of the intervention in women who were randomised less than a year before the COVI-19 pandemic to show whether	Our intention with this figure was only to describe the incidence of diabetes overall and before the	

there was a difference between the groups rather than just showing this in one subgroup? Please show this together with the p for heterogeneity if possible.	COVID-19 began impacting the trial. Although this comparison was not based on an a priori hypothesis, we presented results for both strata in Figure 3 (including p-value for the heterogeneity test), Table 2 and Supplementary Table 3.	
Did the authors explore why women did not adhere to the intervention in terms of completing the sessions? This would be valuable learning.	We lost contact with them and cannot characterize the reasons precisely. However, we agree that this information could aid the design of future studies. We added text based on our subjective observations throughout the trial.	Interpretation of the Main Findings “Although it is difficult to ascertain the reasons for this, we believe that moving to another city, frequent change in prepaid phone numbers, dealing with challenging new responsibilities and priorities, and the lack of motivation contributed, particularly when close to the COVID-19 pandemic."
Page 14, line 33: How many women were randomised at the point of ending randomisation? please add this in here.	We added “466 women”.	Statistical Analyses, 3d paragraph “With the onset of the COVID-19 pandemic, we ended randomization on 13 March 2020, with 466 women randomized and eligible to the trial.”
Page 15, line 38: Why did you not involve women with previous GDM in the design of the intervention. Do you think this could have helped develop an intevention that was more effective?	Actually, we did get some involvement during the pilot studies. We added this information in the specific section, at the end of Methods.	Patient and public involvement “However, during pilot studies we had two focal group discussions with women with recent gestational diabetes who gave meaningful suggestions for the telephone sessions.”
In the analysis, Page 15, line 28: "alfa" should be alpha	Thank you for letting us know. We have corrected it.	

VERSION 2 – REVIEW

REVIEWER NAME	Crowe, Francesca
REVIEWER AFFILIATION	University of Birmingham, Institute of Applied Health Research
REVIEWER CONFLICT OF INTEREST	None
DATE REVIEW RETURNED	24-Jul-2024

GENERAL COMMENTS	Thank you for addressing all the comments.

VERSION 2 – AUTHOR RESPONSE