PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A systematic review and meta-analysis of trials of social network interventions in type 2 diabetes
AUTHORS	Spencer-Bonilla, Gabriela; Ponce, Oscar; Rodriguez-Gutierrez, R; Alvarez-Villalobos, Neri; Erwin, Patricia; Larrea-Mantilla, Laura; Rogers, Anne; Montori, Victor

VERSION 1 - REVIEW

REVIEWER	Lise L Gluud Gastrounit, Copenhagen University Hospital Denmark
REVIEW RETURNED	13-Mar-2017

GENERAL COMMENTS	I enjoyed reading the submitted paper, which describes a systematic review with meta-analyses of trial evaluating social networks in the management of people with type 2 diabetes. The paper is easy to read and the topic interesting. I do, however, have several concerns. The review includes data from 15 trials. However, none of the pairwise meta-analyses include all trials. One meta-analysis includes 13 RCTs, but the remaining pairwise meta-analyses include a much smaller number. In addition, the meta-analysis including the 13 RCTs have pooled all trials regardless of the duration of follow up. This analysis is not described in the methods section (or the published protocol). In the protocol, the authors have suggested that RCTs with short-term, intermediate and 'long-term' follow should be analysed separately. I agree and am convinced that many clinicians as well as researchers would believe that this would make clinical sense. Unfortunately, the reported analysis does not show the effect of the intervention at different time points although text explains that there was a possible short term effect which disappeared. I would recommend keeping the original analysis. I am not convinced that it is clinically reasonable to combine outcomes with such different follow up The publication does not clearly describe the primary outcomes, but defines the following outcomes as being those considered in the review: quality of life, social support, treatment burden, metabolic control, and diabetes-related morbidity and mortality. The paper reports HbA1c after 3 months, six months and more than 6 months. In the registration of the review, the primary outcomes were Quality of life, perceived social support, and HbA1c assessed early (2, 3 or 4 months), intermediate (after 5, 6 or 7) and late (after at least 8 months). In an abstract presentation of the results, 'Social Networks in Type 2 Diabetes Management: Systematic Review and Meta-analysis of Randomized Trials' (American Diabetes Association, 72-LB), the authors presented the following analyses: 'Pooled estimates of effect for HbA1c showed a statistically significant improvement when measured at 2-4 months after baseline (5 trials, 477 participants; MD -0.23 [95% CI, -0.35 to -0.12], I2=0%) but not at

	longest follow-up, which ranged from 3-24 months (12 trials, 1507 participants; MD -0.03 [95% CI, -0.38 to 0.33], I2=93%). I understand that it is sometimes not possible to conduct the planned analyses when performing systematic reviews. Lack of the necessary data can be a limitation in several situations. On the other hand, outcome reporting bias can occur and affect the results of meta-analyses in systematic reviews. Based on the observational nature of the review, it is essential that primary and secondary outcomes are defined a priory and reported based on the original plan. If it was not possible to conduct the analyses exactly as planned, then the changes should be made clear in the methods section and accounted for in the evaluation of the results. In addition, the use of multiple primary outcomes increases the risk of generating spurious results. Accordingly, the level of significance should be adjusted accordingly. In addition, analyses that evaluate the risk of spurious findings due to repeated/cumulative testing should be considered (e.g., sequential analysis). One of the main analyses have an I-square value of >90%. This means that the heterogeneity was considerable. The combination of RCTs in a meta-analysis with such high heterogeneity should be avoided. The analyses, conclusions and interpretation of the results should account for the quality of bias control in the included trials. In addition, the evaluation made based on the GRADE assessment should be clarified.

REVIEWER	Luis Fernandez-Luque Qatar Computing Research Institute Doha, Qatar
REVIEW RETURNED	18-Apr-2017

GENERAL COMMENTS	This paper provides an interesting review on the role of social network support for interventions aiming at supporting patients with diabetes type II. It is very well known that social support is crucial, and to the best of my knowledge very few studies have been looking how social support can be done in this particular area. 1) The title strongly focus on social network support. I think nowadays people would have expected to address online social networks. To reduce ambiguity I suggest the authors mention they focused on offline social networks. As I explained in the following point I think the exclusion criteria has reduce drastically the potential studies focused on online peer support. 2) The authors do mention as exclusion criteria "we excluded RCTs involving social relationships created for the trial", which most likely will result in the exclusion of many online interventions where the participants interact with their peers. Further, the authors only have one "peer" intervention in their review (Shaya FT, 2014). Paradoxically, in that paper the peers in social network were formed after the intervention "Patients in the intervention group (n=68) were asked to recruit peers, form small groups, and attend monthly diabetes education sessions, emphasising peer support". Regarding this point I have two concerns. 2.1) Why there was such exclusion criteria stablished, and how it did affect the study (potential limitations) knowing that online social

	networks interventions with an RCT design will normally requiere the creation of a new social network for the participants. in fact only one paper is addressing peer support despite the popularity of eHealth peer support platform for people with chronic conditions. 2.2.) Why the exclusion criteria was not applied to (Shaya FT, 2014)?, if the peers were recruited after randomization (so they might have not been part of their social network prior the intervention. 3) The value of this study heavily depend on its potential applicability for people designing interventions. As such I would have expected a table describing how the interventions were delivered (face-2-face sessions, groups, online, etc.)

VERSION 1 – AUTHOR RESPONSE

Reviewer #1

Comment 1: “The review includes data from 15 trials. However, none of the pairwise meta-analyses include all trials. One meta-analysis includes 13 RCTs, but the remaining pairwise meta-analyses include a much smaller number. In addition, the meta-analysis including the 13 RCTs have pooled all trials regardless of the duration of follow up. This analysis is not described in the methods section (or the published protocol). In the protocol, the authors have suggested that RCTs with short-term, intermediate and ‘long-term’ follow should be analysed separately. I agree and am convinced that many clinicians as well as researchers would believe that this would make clinical sense. Unfortunately, the reported analysis does not show the effect of the intervention at different time points although text explains that there was a possible short term effect which disappeared. I would recommend keeping the original analysis.

I am not convinced that it is clinically reasonable to combine outcomes with such different follow up. The publication does not clearly describe the primary outcomes, but defines the following outcomes as being those considered in the review: quality of life, social support, treatment burden, metabolic control, and diabetes-related morbidity and mortality. The paper reports HbA1c after 3 months, six months and more than 6 months.

In the registration of the review, the primary outcomes were Quality of life, perceived social support, and HbA1c assessed early (2, 3 or 4 months), intermediate (after 5, 6 or 7) and late (after at least 8 months). In an abstract presentation of the results, ‘Social Networks in Type 2 Diabetes Management: Systematic Review and Meta-analysis of Randomized Trials’ (American Diabetes Association, 72-LB), the authors presented the following analyses: ‘Pooled estimates of effect for HbA1c showed a statistically significant improvement when measured at 2-4 months after baseline (5 trials, 477 participants; MD -0.23 [95% CI, -0.35 to -0.12], I2=0%) but not at longest follow-up, which ranged from 3-24 months (12 trials, 1507 participants; MD -0.03 [95% CI, -0.38 to 0.33], I2=93%). I understand that it is sometimes not possible to conduct the planned analyses when performing systematic reviews. Lack of the necessary data can be a limitation in several situations. On the other hand, outcome reporting bias can occur and affect the results of meta-analyses in systematic reviews. Based on the observational nature of the review, it is essential that primary and secondary outcomes are defined a priory and reported based on the original plan. If it was not possible to conduct the analyses exactly as planned, then the changes should be made clear in the methods section and accounted for in the evaluation of the results.”

Response:

Thank you for your comments. Because trials assessing any of the outcomes of interest were eligible for inclusion, but not all trials reported on all of the outcomes of interest, not all pairwise meta-analyses include all trials. This eligibility criterion is a strength rather than a limitation, as it reduces the risk the review will end up amplifying reporting bias. We have added the following statement to section 2.5 (page 8, paragraph 2) after the description of outcomes of interest:

“Eligible trials reporting on at least one of these outcomes were included.”

In addition, two trials, (Haltiwanger 2012 and McEwen 2017) assessed outcomes of interest but did not provide enough quantitative data to be analyzed in any of the pair-wise meta-analyses. This is reflected in our PRISMA flow chart in which we note that though 19 trials are included, only 17 provide quantitative data that could be pooled in meta-analyses.

We agree that clinicians and researchers will be interested in the follow-up specific estimates of the effects of the intervention on HbA1c. Therefore, we have included the forest plots (HbA1c at 6 and >7 months) we had omitted from our original submission in the supplementary material.

We have also included a section to the methods section that reads as follows (page 10, paragraph 3):

2.8 Modifications to the registered protocol

The included trials were heterogeneous in terms of length of follow-up. In addition to performing pooled analyses for HbA1c at 3, 6, and >7 months of follow-up, to increase the power and applicability of our analyses, we also pooled all measures of HbA1c at the longest follow-up reported.

There are two schools of thoughts in relation to pooling heterogeneous results. Those who pool conditional on heterogeneity (a data-driven approach) and those who pool by protocol and then explore a priori explanations for heterogeneity in the form of subgroup effect hypothesis using interaction testing or meta-regression. We adhere to the latter school and find that it leaves readers with best estimates of high value either of the overall effect or of subgroup effects or with best estimates of low value, but still the best estimates to apply, with very low confidence, to resolving patient problems. That this is not a whim motivated by this project alone, reviewers can consider not only our protocol, but also previous reviews our group has published in the last decade.

Comment 3: “In addition, the use of multiple primary outcomes increases the risk of generating spurious results. Accordingly, the level of significance should be adjusted accordingly. In addition, analyses that evaluate the risk of spurious findings due to repeated/cumulative testing should be considered (e.g., sequential analysis).”

Response: There is considerable debate about the value of adjusting p values or 95% confidence intervals for multiple comparisons at the individual study level, yet alone at the evidence synthesis level. [Cochrane handbook for systematic review, version 5.0.2, section 16.7.2]

If one were to believe that adjustment is necessary, then it would not matter whether the comparisons are deemed primary or secondary. The possibility of chance findings at the individual study level (random error) is in fact reduced by pooling across trials. Furthermore, the comparisons were not driven by the comparisons available in the studies but were set a priori. This allowed us to report what data was not available and where there are gaps in knowledge. As the reviewer has asked above, we should stick to our planned analysis in the protocol, and there was no adjustment planned. We have considered major sources of error and trustworthiness in the evidence by assessing for risk of bias and other limitations (indirectness, inconsistency, imprecision) using the GRADE approach. Finally, the main results are expressed with considerable uncertainty such that no definitive claim of causality

is made. Given the quality of the evidence summarized, even if adjustment had affected p-values, we doubt the conclusions could be made any weaker or could be strengthened. This review, in essence, does most of its work in setting a research agenda, rather than producing strong inferences to guide clinical practice or policy.

Comment 4: “One of the main analyses have an I-square value of >90%. This means that the heterogeneity was considerable. The combination of RCTs in a meta-analysis with such high heterogeneity should be avoided.”

Response: We have responded to this concern above (response to comment 1, last paragraph). We agree that the social support analysis has high inconsistency. We expected this outcome given the heterogeneity in patients, intervention, comparators, and scales used to measure the construct of social support and planned a random effects meta-analysis of it. Rather than omit the results of a pre-specified analysis, we found it superior to explore potential explanations for the observed inconsistency through planned subgroup analyses presented in supplementary table S4. [Cochrane handbook for systematic review, version 5.0.2, section 9.5.4; Users’ Guide to the Medical Literature, 3rd Edition, Ch 23]. To help readers consider this limitation, we highlight this inconsistency in the GRADE assessment and noted this limitation in the results section of the manuscript which reads as follows (page 12, paragraph 2).

When considering the body of evidence, unexplained inconsistency in results across RCTs further reduced confidence in the overall results, particularly for the social support outcome.

Comment 5: “The analyses, conclusions and interpretation of the results should account for the quality of bias control in the included trials. In addition, the evaluation made based on the GRADE assessment should be clarified.”

Response: We thank the reviewer for their recommendation. Of course using the GRADE approach to describe the evaluation is considered state-of-the-art. Yet, the reviewer is correct that not many readers would be immediately familiar with its structure and content. On the other hand, we cite the major papers in which GRADE is discussed and explained to a better extent than what is pertinent in the body of topical review. Thus, we have added the following text section 2.5 of the methods with regard to the GRADE approach (page 9, paragraph 1):

“This approach assesses the confidence merited by the body of evidence based on the risk of bias of the individual studies, inconsistency in the results, indirectness, imprecision and other considerations.”

We have also added the following text to the conclusion (page 13, paragraph 2, section 4.3)

“The body of evidence to date is limited at moderate risk of bias, heterogeneous, with inconsistent results, and based on individualistic theories. The results, however, are promising.”

Reviewer #2

Comment 1: “The title strongly focus on social network support. I think nowadays people would have expected to address online social networks. To reduce ambiguity I suggest the authors mention they focused on offline social networks. As I explained in the following point I think the exclusion criteria has reduce drastically the potential studies focused on online peer support.”

Response:

We have modified the description of the eligibility criteria to explicitly mention online social networks. It now read as follows (page 6, paragraph 3):

“Thus, we excluded RCTs involving social relationships created for the trial, e.g., RCTs testing interventions enrolling and training patients with type 2 diabetes to provide peer support to other participants or using online communities.”

Our exclusion decision does not rest on the inference that online communities are not relevant or even increasingly relevant. Rather, we are interested in the enduring ties, weak or strong, that patients with diabetes present with when receiving diabetes care. The literature about online communities tend to introduce these communities to patients as an intervention and thus represent another mechanism, not less valuable, for social network support.

Comment 2: “The authors do mention as exclusion criteria "we excluded RCTs involving social relationships created for the trial", which most likely will result in the exclusion of many online interventions where the participants interact with their peers. Further, the authors only have one "peer" intervention in their review (Shaya FT, 2014). Paradoxically, in that paper the peers in social network were formed after the intervention "Patients in the intervention group (n=68) were asked to recruit peers, form small groups, and attend monthly diabetes education sessions, emphasising peer support". Regarding this point I have two concerns.

Why there was such exclusion criteria stablished, and how it did affect the study (potential limitations) knowing that online social networks interventions with an RCT design will normally requiere the creation of a new social network for the participants. in fact only one paper is addressing peer support despite the popularity of eHealth peer support platform for people with chronic conditions.”

Response:

Observational data has repeatedly shown an association between social support and positive health outcomes. This support is often provided by enduring relationships in patients’ social networks. We sought to explore whether this kind of support could be bolstered for patients and their consistent and enduring social ties.

In the case of Shaya 2014, the peers that were included were required to be “neighbours, friends, or family members” of the index patient who also had diabetes. Our judgment, made transparent in our report, is that these represent enduring relations and not strangers that will become networked only through the trial protocol. As with any classification, grey zones will exist which is why it is customary to make decisions about eligibility independently, in duplicate, and with adequate inter-rater reliability; all these, strengths of our review.

Comment 3: “The value of this study heavily depend on its potential applicability for people designing interventions. As such I would have expected a table describing how the interventions were delivered (face-2-face sessions, groups, online, etc.)”

Response:

We appreciate this suggestion by the reviewers and the editorial office. We have enhanced our trial characteristics table by adding an “intervention description” column. We have also moved it from the supplement to the main text. We hope that this table, in conjunction with figure 3 (a summary of the

strategies used in the intervention and control arms of each trial) provide a comprehensive practical and theoretical description of the interventions in each trial. The column titled “Setting where intervention was delivered” describes whether the interventions were delivered in person or not.

We are very grateful for all the observations and suggestions from both the editor and the reviewers who have no doubt strengthened the report, which we now hope you will consider worth publishing in your journal.

VERSION 2 – REVIEW

REVIEWER	Lise L Gluud Copenhagen University Hospital Hvidovre Denmark
REVIEW RETURNED	31-May-2017

GENERAL COMMENTS	Overall, I believe that the revisions improved the paper and I enjoyed reading it again. I only have a one additional comment/suggestion which is that the text in the abstract indicates that 19 RCTs were included in the meta-analyses. I suggest including the number of RCTs in the text, e.g., (0.88 standard deviations [95% CI: 0.40, 1.36], I2=90%, 7 RCTs).

VERSION 2 – AUTHOR RESPONSE

Reviewer #1

Comment: “Overall, I believe that the revisions improved the paper and I enjoyed reading it again. I only have a one additional comment/suggestion which is that the text in
the abstract indicates that 19 RCTs were included in the meta-analyses. I suggest including the number of RCTs in the text, e.g., (0.88 standard deviations [95%CI: 0.40, 1.36], 12=90%, 7 RCTs) .”

Response:
We thank the editorial office and reviewer for their suggestion to indicate the number of trails pooled for each outcome in the abstract. We have made the requested change and the results section of the abstract (page 3, paragraph 3) now reads as follows:

Interventions improved social support (0.88 standard deviations [95% CI: 0.40, 1.36], I2=90%, 8 RCTs), and HbA1c at 3 months (-0.23 percentage points [95% CI: -0.38, -0.08], I2=12%, 9 RCTs), but not quality of life.

We are very grateful for all the observations and suggestions from both the editor and the reviewers who have no doubt strengthened the report, which we now hope you will consider worth publishing in your journal.