Author’s response to reviews

Title: Socially isolated individuals are more prone to have newly diagnosed and prevalent type 2 diabetes mellitus - The Maastricht Study -

Authors:
Stephanie Brinkhues (stephanie.brinkhues@mumc.nl)
Nicole Dukers-Muijrs (nicole.dukers@ggdzl.nl)
Christian Hoebe (christian.hoebe@ggdzl.nl)
Carla van der Kallen (c.kallen@mumc.nl)
Pieter Dagnelie (dagnelie@maastrichtuniversity.nl)
Annemarie Koster (a.koster@maastrichtuniversity.nl)
Ronald Henry (rma.henry@mumc.nl)
Simone Sep (simone.sep@gmail.com)
Nicolaas Schaper (n.schaper@mumc.nl)
Coen Stehouwer (cda.stehouwer@mumc.nl)
Hans Bosma (hans.bosma@maastrichtuniversity.nl)
Paul Savelkoul (paul.savelkoul@mumc.nl)
Miranda Schram (m.schram@maastrichtuniversity.nl)

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Author’s response to reviews:

Dear Dr. Tamayo,

Thank you for giving us the opportunity to revise our manuscript.

We also thank the reviewers for their useful and helpful comments, which we have addressed in our revised manuscript and in our point-by-point reply below.

We hope that our comments are satisfactory and that the paper is now acceptable for publication in BMC Public Health.
Sincerely,

On behalf of all coauthors,

Miranda Schram and Stephanie Brinkhues

Reviewer reports:

Eirik Abildsnes, M.D, Ph.D. (Reviewer 1):

Dear authors

Thank you for the opportunity to review this paper. I have a few minor suggestions you may consider.

The aim of this study was to assess the associations of a broad range of social network characteristics with diabetes status. This is a well written and important paper of high quality relevant for publication in this journal. I have some suggestions the authors may consider when revising the manuscript.

Thank you for the compliments. We have considered the suggestions by Dr. Abildsnes in the revised version of our manuscript.

Background: This section is well described, and ends up with a justification of the present study and clearly described aims. Line 33, page 5: Consider including examples of psychosocial factors, as this concept may include interpersonal relationships and affiliation to social networks.

Thank you for this suggestion. We included examples of psychosocial factors that have been identified as relevant for the development of T2DM (lines 46-47).

Several environmental and lifestyle factors, as well as psychosocial factors (such as depression and stress), have been identified as relevant for the development of T2DM [3-6].

Methods:

1) According to author guidelines http://bmcpublichealth.biomedcentral.com/submission-guidelines/preparing-your-manuscript/research-article information concerning ethical approval and consent should be included in the Declarations section.

Thank you for this suggestion. We transferred the information concerning ethical approval and consent from the methods section to the Declarations section (lines 510-514).
2) I will suggest a brief explanation of what is meant by 'an extensive phenotyping approach' (page 4, line 68), as this is not obvious to all potential readers without reading reference 21.

Thank you for this suggestion. We added a brief description of the phenotyping approach in this section (lines 83-85).

The study uses state-of-the-art imaging techniques and extensive biobanking to determine both determinants and clinical outcomes of health status.

3) Participants were recruited through mass media campaigns and from the municipal registries and the regional Diabetes Patient Registry via mailings. I miss information about the target group of the mass media campaigns. Individuals at risk of developing diabetes? The measurements used are well described.

Thank you for this suggestion. The target group for the mass media campaigns were people from the general population and individuals with type 2 diabetes aged between 40 and 75 years who live in the southern part of the Netherlands. We added the term “with and without” to the text section (line 87).

Participants with and without diabetes were recruited through mass media campaigns and from the municipal registries and the regional Diabetes Patient Registry via mailings.

4) I miss some information about the development and test properties of the questionnaire mapping social network. Consider to include a reference, reference 21 refers to McCallister L, Fischer CS. A procedure for surveying personal networks. Sociol Methods Res. 1978;7(2):131-48. Otherwise this section is well described.

Thank you for this suggestion. We included two additional references in the section (line 120).

Results and discussion: The results are clearly described in the text. In the discussion section I would consider to include some comments about other negative effects on health associated with poor social network, and include some comments about the total health burden and prevalence of comorbidity in disadvantaged groups with T2DM. Coronary heart disease, chronic pain and depression are very common. Suggested reference: http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(12)60240-2/abstract

Thank you for this suggestion. We included comments about total health burden and other negative health effects of a poor social network in the implications section (lines 462-466).

Moreover, targeting social network characteristics may also have benefits for other chronic conditions, as it has been shown that most of those with a long-term disorder are multimorbid.
[28], and social network characteristics have been found to associate with cardiovascular, endocrine, and immune function [29]. In addition, social isolation and living alone have been found to increase the likelihood of mortality [30].

Conclusion: I have no suggestions for changes in this section.

Abstract, tables and figures: I have no suggestions for changes.

Sara Pedron (Reviewer 2): General comments

The article shows the results of a study concerning the association of a large spectrum of social network variables with different stages of diabetes progression, represented by different patient groups in the cross-sectional dataset available.

Results showed significant associations of lower structural and functional support variables with newly diagnosed and previously diagnosed T2DM, albeit with different patterns for men and women, rightly considered in separate analyses by the authors. The authors conclude that social isolation and a lack of participation could contribute to the development of prediabetes into T2DM.

The aim of the study is clearly represented by the authors. Relevant studies in the literature are cited and generally appropriate methods are used. The results are also very interesting and highlight possible further research and intervention possibilities. However in some points they are not carefully interpreted, relevant actual strengths are not highlighted or imprecisely generalized.

Thank you for the compliments. We have considered the suggestions in the revised version of our manuscript.

Major Revisions

1. The authors should avoid any expression which implies causality: they are well aware that they cannot estimate it, nonetheless in some points this is not clear (examples: First sentence of the abstract, hypothesis in the background section).

Thank you for pointing this out. We checked the manuscript and eliminated all expressions that imply causality in our results (see lines 2, 68, 311-314, 317, 348, 356, 363, 373-375, 397-398, 447-448, 458).

2. The authors should consistently rename the group "T2DM" (sometimes also addressed as "prevalent T2DM") as "previously diagnosed T2DM" throughout the whole manuscript (only by
manually adding the number of individuals in each group in Table 1 one can understand that the group T2DM is actually the group "previously diagnosed T2DM" without the newly diagnosed).

Thank you for this suggestion. We renamed the group “T2DM” as “previously diagnosed T2DM” throughout the whole manuscript.

3. The authors should include a more detailed description of the study (when did it start? Is it still ongoing? How many participants involved?) and why did they choose exactly that time period. Reference 21 should be placed at the end of this block as further information for the reader.

Thank you for this suggestion. The Maastricht Study started in November 2010 and is still ongoing. As it is common in such costly and time-intensive cohort studies, we started data cleaning and analysis at the end of 2013 with the data that was collected until then. The time frame was based on inclusion of participants, between November 2010 and October 2013 we have extensively phenotyped 3451 individuals of whom nearly 1000 have type 2 diabetes. With this high number of inclusions we have established an internationally competing data collection in several areas of research, that is suitable for publication.

We extended the description of the study and reference 21 was placed at the end as further information for the reader (lines 81-97).

In brief, the study focuses on the etiology, pathophysiology, complications and comorbidities of type 2 diabetes mellitus (T2DM) and is characterized by an extensive phenotyping approach. The study uses state-of-the-art imaging techniques and extensive biobanking to determine both determinants and clinical outcomes of health status.

Eligible for participation were all individuals aged between 40 and 75 years and living in the southern part of the Netherlands. Participants with and without diabetes were recruited through mass media campaigns and from the municipal registries and the regional Diabetes Patient Registry via mailings. Recruitment was stratified according to known T2DM status, with an oversampling of individuals with T2DM, for reasons of efficiency. Enrollment started in November 2010 and is still ongoing, aiming to include 10,000 participants. The present report includes cross-sectional data from the first 3451 participants, who completed the baseline survey between November 2010 and September 2013. The examinations of each participant were performed within a time window of three months. Further information on The Maastricht study can be found elsewhere [22].

4. The differences between the groups were assessed using appropriate statistical tests. The authors should include the results of these tests in the text or in Table 1. This should be of major concern for the authors: in the discussion section they are often referring to these results as "significant" (text lines: 243, 255, 276-280) but the reader cannot find any confirmation from the data reported.
Thank you for pointing this out. We added these test results to table 2 (p32-33).

5. The main analysis was carried out using a multinomial logistic regression, regressing diabetes status (comparison group for each outcome: NGM) with each social network variable and a set of confounders (age, BMI, educational level, employment status), stratifying by sex. Other typical confounders, which are commonly used are only included in the sensitivity analysis (hypertension, previous CVD, SF36) or reported in the descriptive statistics and in the text, but not included at all (smoking status, alcohol consumption, diabetes duration). Furthermore, income should be also considered as an additional confounder. These variables are essential moderators and should be included, not just in the sensitivity analysis or in the descriptive statistics. This means that further attention must be paid to these variables, either by including them in the main model or by extensively justifying their exclusion in the main model and explaining relevant differences in the results of the sensitivity analysis. I warmly recommend taking all control variables into account also in the main analysis.

Thank you for this suggestion. We revised our main analysis and included age, BMI, educational level, employment status, hypertension, previous CVD, SF36, alcohol consumption and smoking status as potential confounders in the main analysis. We have chosen not to include diabetes duration as potential confounder as we do not consider this variable of sufficient quality for further analysis, as it has been shown that onset of type 2 diabetes occurs at least 4-7 years before diagnosis (Harris et al., 1992). In addition, duration of diabetes was only available in 587 diabetes participants. Educational level as well as employment status were included in the main analysis as indicators of income. We performed additional analyses where we replaced educational level or employment status with income, and additionally adjusted for income. The additional analyses showed that the risk estimates were robust, no severe deviations from the main analysis were observed. However, 25% of the participants did not provide information on income, therefore, we have chosen to include educational level and employment status in the main analysis.

6. The results of the analysis are very interesting. Nonetheless the most interesting results are not always fully highlighted or they are sometimes unnecessarily generalized. Authors should also add some degree of uncertainty and should be more cautious with the results interpretation. Furthermore, "socially isolated individuals" and "lack of social participation" are general terms (discussion section): what do the authors exactly mean with these terms? Where can I spot the results at a glance? The authors should either name the variables they are looking at or define these terms here or in a previous paragraph. Furthermore, if with "lack of participation" the authors are looking at the variables for contact frequency, proximity and type of relationship, the results are rather unclear, with some significant associations different for men/women and not always backed by the sensitivity analysis. In light of these and previous considerations, authors should revise their implications and conclusions. The main result is not that "the promotion of social integration and participation is a promising target in T2DM" (already known from previous literature cited in the background section) but the association with the single aspects they found, especially the type of relationship in women, the emotional support for important decisions and the practical support for sickness in both sexes.
Thank you for this suggestion. According to Major Revisions Nr. 5 and 6, we have rewritten the results and discussion section, and revised our implications and conclusions (lines 443-484).

Moreover, according to Minor Revisions Nr. 2, we included a table (table 1, p. 31-31) with variable definitions, introducing all variables and terms used in the manuscript. The revised results at a glance were summarized at lines 282-300.

Minor Essential Revisions

1. The authors should position their study in a more accurate way in the previously available literature: several good key studies (refs. 6-13, 8 studies) are cited in the background section, described in the following paragraph and are extensively cited in the discussion section in order to corroborate almost all of the results. Reporting that “the role of social network characteristics in the development of T2DM has hardly been studied” is in my opinion not fully accurate. The authors should consider a reformulation of this point, in the background and in the discussion sections, by highlighting the rising interest in the last years and the relevance of this topic. Given the results of previous literature a more detailed and conjoint investigation of a larger spectrum of social factors is essential, and that is exactly what has been done in this study.

   Thank you for this suggestion. We reformulated this point as suggested by the reviewer (lines 48-55).

   Recently, there is raising interest for the role of social network characteristics in the development of T2DM [6-13]. Prevention strategies that promote social integration and participation may prove promising [14-17]. Among individuals with T2DM, beneficial effects of social support have been reported on diabetes care [18], activation for self-management [19], and health/health-related behaviors [20].

   Given the results of previous research, a more detailed and conjoint investigation of a broad range of social network characteristics is essential.

2. The authors should include a detailed account of how the different variables were computed, for example in an additional table. For example the division in levels of education is not fully understandable for the international reader: is the categorization similar to the ISCED education categorization? What is the difference between family and household? Including the variables definitions in an additional table would also help to make the text reading more fluid in paragraph 2.2.5, where authors should avoid using double parenthesis in the text.

   Thank you for this suggestion. We included an additional table (table 1) including the variables definitions (p.31-31).

3. An interesting point in the article is the division in different stages of the disease. The authors often highlight this point interpreting also differences between the groups as possible
mechanisms with which the variables affect the "development" of the illness. In order to assess this, the correct control group for previously diagnosed/newly diagnosed T2DM should be prediabetes, and not the NGM group. Be careful in interpreting your results or add this point in the analysis.

Thank you for this suggestion. We carefully checked the interpretation of the results as suggested by the reviewer and eliminated interpretations that were not appropriate (lines 310-314, 321-324).

4. The authors should include in the text a reference to the scale in which the functional support variables are computed (only available in the footnotes of the tables). Authors should also complete the results description of the same variables by adding "one additional unit of emotional support" "...was associated with 32% higher odds...", they should quantify this "less".

Thank you for this suggestion. We added the scale in the text (line 144) and in table 1, and completed the results description by quantifying it “less” (lines 256-270).

5. Figure 2: authors should add proper labeling of the axis and of the graphs described. "Less emotional support(...)" should be quantified also in this case (see previous point).

Thank you for this suggestion. We adjusted figure 2 according to the results of the new main analysis and added labelling of the axis and graphs described.

6. Paragraph 4.2: the authors should consider adding a reference to a possible reverse causality also in this paragraph: it is very likely that patients suffering from a chronic disease need a higher/broader functional support from their social network. By looking at the cross section, lower self-reported levels of functional support do not necessarily imply that their social network offers them a generally and absolutely lower functional support, but rather that they perceive it as less adequate to their needs (that means relatively lower). Also in this case a longitudinal analysis could help to shed some light on this very interesting point. Furthermore, Jones et al. (2015) use cross sectional data: no causal effect is shown (line 329).

Thank you for this suggestion. We rephrased this paragraph as suggested by the reviewer (lines 400-414).

Both Norberg et al. (2007) and Jones et al. (2015) showed that low emotional support was associated with T2DM in women [7] and older adults [8], although their methods used to assess functional support were less detailed. The longitudinal results from Norberg et al. (2007) suggest that low functional support increases the risk of T2DM [7].

To our knowledge, this study is the first to assess the association of a broad range of functional support measures with prediabetes, newly diagnosed T2DM and previously diagnosed T2DM. Our results indicate that emotional support in important decisions, and practical support with
small jobs and in sickness were important characteristics that should be addressed in T2DM prevention strategies. However, in this cross-sectional study, we cannot assess whether participants received an absolutely lower level of functional support, or whether they perceive it as less adequate to their needs (that means relatively lower), and therefore, their satisfaction with functional support is lower. Recently, it has been shown that low social network satisfaction is associated with increased risk of T2DM [27].

7. Table 2: given the possibility of reverse causality, it would be helpful for the reader to include titles in the table to distinguish outcome variables/explanatory variables. Also explicitly state (in the text or in the table) that you are controlling for each of the social support variables separately and not in the same regression.

Thank you for this suggestion. We included titles in the table (table 3) and the following statement in the text (lines 179-181):

Every network variable was assessed separately, risk estimates were adjusted for age, BMI, educational level, employment status, alcohol consumption, smoking status, Hypertension, prior CVD and general health status (SF36).

Discretionary Revisions

1. An additional contribution of the paper could have been the joint evaluation of some of the included aspects (structural AND functional support). The authors should also consider the inclusion of some interactions between the social inclusion/participation/support variables.

Thank you for this suggestion. We have chosen for the separate evaluation of the social network characteristics as such a broad range of variables has not yet been assessed in one study. The joint evaluation or inclusion of interactions between social network characteristics would exceed the aim of the present report.

2. Concerning the main analysis, the division in "newly diagnosed" and "previously diagnosed" T2DM should be used as further sub-analysis, while the outcome "overall T2DM" (newly diagnosed + previously diagnosed cases) should be included in the main analysis for completeness (see ref. 12).

Thank you for this suggestion. The division of newly diagnosed and previously diagnosed T2DM is of added value to the current literature, as the associations of social network characteristics have hardly been studied in newly diagnosed T2DM. Therefore, we would like to maintain the division in ‘newly diagnosed’ and ‘previously diagnosed’ in the main analysis.

3. Figure 1 is in my opinion not necessary since it does not add any information nor does it facilitate the understanding. What about substituting this figure with a detailed account of the
results of the chi-squared/ANOVA/Kruskal-Wallis tests for the significance of differences among the considered groups? (see Major Revisions nr. 4)

Thank you for this suggestion. We added the results of the unadjusted analysis to table 2. Figure 1 visualizes the differences in network size and composition between men and women, and the NGM, prediabetes, newly diagnosed T2DM and previously diagnosed T2DM groups. Therefore, we think that figure 1 facilitates the understanding of the social network characteristics used in the present study and we therefore would like to maintain Figure 1 in the Manuscript.

4. Paragraph 2.2.4.: please consider writing in italics/in quotation marks the single variables (e.g.: emotional support(discomfort), emotional support(important decisions)…). Not differentiating these elements from the text causes some problems in the text fluency.

Thank you for this suggestion. We eliminated the description of the variables in the text and included them in table 1 (as suggested in Major Revision Nr. 2).

5. Table 1: please consider restructuring of the first part of the table, adding italics titles (like the subsequent parts) for lines with multiple values.

Thank you for this suggestion. We restructured the first part of the table as suggested by the reviewer (table 2).

6. Please check the list of references according to the requirements of the journal (e.g. proper citation of books; ref. 19 and ref. 22 wrongly cited).

Thank you for pointing this out. We checked the references and adjusted it according to the requirements of the journal when applicable.

7. Please avoid using semicolon in the text body. In the conclusion section a full stop is missing (line 380).

Thank you for this suggestion. We eliminated semicolons in the text body and added the full stop that was missing in the conclusion section.