Author’s response to reviews

Title: Estimated 8-year cumulative incidence of diabetes mellitus among Sami and non-Sami inhabitants of Northern Norway - The SAMINOR Study

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BEND-D-18-00325
Estimated 8-year cumulative incidence of diabetes mellitus among Sami and non-Sami inhabitants of Northern Norway - The SAMINOR Study Ali Naseribafrouei, M.D.; Bent-Martin Eliassen; Marita Melhus; Johan Svartberg; Ann Ragnhild Broderstad BMC Endocrine Disorders

Dear editor and reviewers,

Thank you very much for reviewing the manuscript and for your valuable comments and suggestions. We have responded to the questions posed by the reviewers and made amendments in the manuscript in accordance with your remarks. All changes to the manuscript have been indicated in the text by track changes.

Editor comments:

1) Please state whether the map in Figure 2 has been taken from other sources. Please acknowledge the source in the figure legend, and if it is under copyright, also state the written permission given to use and adapt it.

Answer: We assume you refer to Figure 1. The map of the study area is used with permission from the Centre for Sami Health Research (CSHR) at UiT The Arctic University of Norway. It is designed by one of the authors, Marita Melhus at CSHR. We have added this phrase to the legend: “Published with permission from Centre for Sami Health Research”.
In the Authors’ contributions section, MM’s contribution is changed to:
“MM designed the map of the study area and assisted in statistical analyses as well as material and
methods’ descriptions.”

Reviewer reports:

Marit Eika Jørgensen (Reviewer 1):
The paper aims to compare the cumulative incidence of type 2 diabetes (T2D) among Sami and non-
Sami in Northern Norway. The topic is of interest, the study is well conducted, and the paper generally
well written. I have however some concerns about the methods applied.

Specific comments:
BACKGROUND:
- The hypothesis is not well stated. Why is it relevant to test a difference in T2D risk according to
Sami status? Is the population suggested to differ genetically, socially, culturally from the Norwegian
population in a way that should affect diabetes risk?

Answer: Sami people are distinct from benchmark (Norwegian) population. Firstly, they may have
their own genetic predisposition/protective factors. Secondly, historically the Sami have had their own
culture, rituals, diet, life style, and so forth, which might affect the risk of diabetes. Several
international studies have shown a striking difference in the prevalence and incidence of diabetes
mellitus between indigenous peoples and majority populations, and previous studies showed (as
mentioned in the introduction) differences in the prevalence of diabetes mellitus between Sami and
non-Sami. To elucidate more the need for such a study and make the hypothesis clearer, we have added
some sentences in the introduction section:

“The Sami are an indigenous people, who have traditionally inhabited northern parts of Norway,
Sweden, and Finland, and the Kola Peninsula of Russia.”
Is changed to:

“The Sami are an indigenous people, who for centuries have inhabited northern parts of Norway,
Sweden, and Finland, and the Kola Peninsula of Russia. Sami people might possess genes that either
predispose them to or protect them against development of diseases like DM. Furthermore, they have
their own culture, diet, and so forth, which might play a role in increasing or decreasing the risk of DM.
Internationally, studies have shown a striking difference in the prevalence and incidence of diabetes
mellitus between indigenous populations and majority populations (3-6). Higher incidence and
prevalence of type 2 DM among indigenous peoples, in comparison to the benchmark populations,
seems to be a shared phenomenon worldwide (2). For example, the age-standardised incidence of type
2 DM of 1814 Australian Aboriginal and Torres Strait Islander adults from 1999 to 2007 was reported
to be 30.5 in 1000 person-years. This incidence rate is nearly four times higher than that for the non-
Indigenous population and 50% higher than the incidence reported 10 years ago in Australian
Aboriginals (7).

Previous research based on data from 24 municipalities in the SAMINOR 1 Survey (2003–2004),
showed no statistically significant difference between Sami and non-Sami in the prevalence of DM,
defined by self-report and/or non-fasting plasma glucose ≥ 11.1 mmol/L.”

“To our knowledge, there are no previous studies investigating the incidence of DM in the Sami
population of rural municipalities in Northern Norway.”
From the introduction we know that baseline diabetes prevalence is not different according to ethnicity, but higher at follow up in SAMINOR 2 among Sami compared to non-Sami. Does this information apply to the total study population at baseline and follow up, or to the population participating in both surveys? While the study shows no difference in cumulative incidence of T2D across ethnic groups, the difference in prevalence at follow up must then necessarily be explained by a higher prevalence of non-incident cases among Sami due to lower mortality, lower migration rates or higher participation rate among Sami with T2D. This should be explained (and discussed) more thoroughly.

Answer: The mentioned studies in the introduction are based upon the total study populations in each of the surveys. Lack of difference in the prevalence of DM (all types of DM) in SAMINOR 1, applies to the total study population of this survey (n=16208). Higher prevalence of type 2 DM in SAMINOR 2 applies to the total population participated in SAMINOR 2 (n=5878). We emphasize that SAMINOR 1 covered a much larger geographical area (24 municipalities) compared to SAMINOR 2 (10 municipalities), so the targeted populations differed in the two surveys. Another explanation for different results is the use of different methodologies in SAMINOR 1 and 2 to ascertain DM. We used non-fasting plasma glucose and/or self-report in SAMINOR 1, but HbA1c and/or self-report in SAMINOR 2 to categorize diabetics. The reason for this is that HbA1c was not measured in SAMINOR 1. As there is not a high concordance between glucose-based measures and HbA1, it is quite likely that if we had used HbA1c in the SAMINOR 1 study, the estimated prevalence and the individuals categorized as diabetics would have been different.

Lack of statistically significantly different cumulative incidence of DM (all types of DM, not only type 2 DM) might (as also explained in the discussion section) be due to a small number of participants in the present study (those who participated in both SAMINOR 1 and 2) (n=3303). However, we cannot exclude the possibility of different mortality, migration or participation rates among Sami with type 2 DM.

METHODS

How is the study population selected from the general population in the 10 municipalities? From households? A random geographic sample? And what is the population size in these municipalities? Have any efforts been done to ensure representation of both Sami and non-Sami? Is it likely that the name of the survey (SAMINOR) influences the motivation to participate for the non-Sami population?

Answer: Based on previous knowledge, the 10 included municipalities were selected due to a high proportion of inhabitants with Sami background. This was done to maximize the number of Sami in the sample. All these municipalities are rural municipalities with populations less than 5000 inhabitants. In both SAMINOR 1 and SAMINOR 2, everyone in the predefined age span living in these municipalities were invited to participate, regardless of their ethnic background. That is, the whole population in the selected age groups was invited. The surveys were promoted as surveys on health and living conditions, and invitees were encouraged to participate to provide information about the health situation in their own municipality, in addition to get personal feedback of their own health status. The name “SAMINOR” was not used at the time of invitation to SAMINOR 1, and was not emphasized when conducting SAMINOR 2. However, the fact that the surveys were conducted by the Centre for Sami Health Research and that some questions (especially in SAMINOR 1) were directed to Sami participants, may have influenced participation. Both ethnic groups might have had their own concerns regarding the study and the net effect of such potential non-participation bias is unknown to us as there
is no ethnic registry in Norway. Regarding this, we have added a section in the Methods section:

“The included municipalities were chosen due to a high number of Sami inhabitants. The invitees were informed that the study aimed primarily at collecting knowledge about health, diseases, and living conditions in regions with Sami and Norwegian populations and provide a health profile for their county/municipality, in addition to getting personal feedback of their own health status.”

- Study sample: A bit of information on the SAMINOR 1 would be useful. How many participated, how many were invited? It seems that 11,558 invited from SAMINOR 1 might have been invited for SAMINOR 2. Is it correctly understood that non-participants in SAMINOR 1 potentially could have participated in SAMINOR 2? Would you be able to track such information? And would it be possible to connect to Norwegian registers for information on death, diagnosis of T2D?

Answer: For both SAMINOR 1 and 2, we have referred to the original paper, which have described in detail all aspects of the survey. In SAMINOR 1, 24 municipalities were included, but in the present study, the data are based on inhabitants from the 10 municipalities that were included in both SAMINOR 1 and 2. We were concerned that if we described more in detail about SAMINOR 1, the text would be extensive and the reader would get bewildered. We have, however, added some new information about SAMINOR 1 in the beginning of the Study sample section.

Inhabitants of the 10 municipalities included in SAMINOR2, were invited regardless of having been invited or participated in SAMINOR 1. It is therefore correct that non-participants in SAMINOR 1 may have participated in SAMINOR 2. In fact, out of the 6004 participants in SAMINOR 2, only 3872 had previously participated in SAMINOR 1. After exclusions (see Figure 2), 3303 of these persons were included in our analyses.

It would have been possible to obtain data from the cause of death registry (the entire follow-up, but diabetes is not often registered as the cause of death), the prescription database (from 2004) and specialist health care (from 2008), but due to limited resources and time constraints, this was not prioritized. We acknowledge, however, that this is a weakness of our study.

The following changes has been done:

“The present analyses are based on longitudinal data of those participating in both SAMINOR 1 and SAMINOR 2 from the above-mentioned ten municipalities. In SAMINOR 2, 12,455 subjects, aged 40–79 years, were invited to take part, and 6004 participated (48.2%).”

was changed to:

“In SAMINOR 1, a total of 27,987 subjects, aged 30 or 36–79 years were invited, and 16,865 participated (60.6%). In SAMINOR 2, 12,455 subjects, aged 40–79 years, were invited to take part, and 6004 participated (48.2%), whereof 3872 persons had previously participated in SAMINOR 1. The present analyses are based on longitudinal data including individuals participating in both SAMINOR 1 and SAMINOR 2 who did not fill the exclusion criteria detailed below.”

- It is stated that the participant rate was 56.2% (3303 of 5875). However, usually, the participant rate is calculated from the eligible population (those still alive, still living in the relevant municipalities). Thus, I assume, the correct participant rate is actually higher than 56.2%?
Answer: We acknowledge that the term “participation rate” is not correct in this regard, so we change it to “follow-up rate” in the Methods section, study sample.

- **Covariates:** It seems that some of the covariates (e.g. income, SCL-10, marital status) may affect diabetes risk through other risk factors (e.g. obesity, physical activity). If the primary purpose is to adjust for confounders that may mask potential ethnic differences, I suggest that you include primarily covariates with an independent and biologically plausible influence on diabetes risk.

Answer: We have assessed the effect of covariates which either directly influence development of the DM (e.g. obesity, inactivity) or indirectly affect the risk of developing DM (e.g. income, marital status, and mental health). In the last model (table 4), we have included all relevant covariates that were shown to have significant effect on the risk of DM (WHtR and education). We also refer to the answer to the next, related, question from the reviewer.

- **Statistical analysis:** The long list of separate analyses for each diabetes risk factor (beyond age and gender) seems inappropriate. Again, if the purpose is to adjust for confounders to un-mask an association between ethnicity and incident T2D, the relevant analytical approach should be a multivariable regression including all relevant confounders.

Answer: The applied approach consisted of two steps. In the first step, some possible risk factors for DM were assessed (in combination with age and ethnic group and separately for each sex). In the second step (the last line in table 4), only covariates that had significant effect (“all relevant confounders”) were included. Education (in women) and several variables related to body composition/obesity were statistically significantly associated with diabetes risk, even after adjustments for age and ethnic group. As the obesity-related variables (WC, WHtR and BMI) are highly correlation with each other, we chose to include one of them (WHtR) in the multivariate model together with age and ethnic group.

- Why is the SCL score categorized instead of using the continuous information?

Answer: As the applied cut-off (1.85) for categorizing individuals with symptoms of anxiety and depression has been validated and used in several studies, we believe dichotomization makes it easier to compare with other studies. Regardless of including SCL as a continuous or dichotomized score, the odds ratio is not statistically significant (results not shown).

- It seems inadequate to stratify for sex unless a significant interaction is observed (no indication of this in the data). The current approach assumes an interaction between sex and all covariates. It would be more correct to simply adjust for sex.

Answer: Generally speaking, we prefer to do sex-specific analyses if the data allow so. As results from SAMINOR 1 showed a higher obesity prevalence and a more sedentary lifestyle among women (particularly Sami women) than among men, we expected that women had a higher risk of developing type 2 DM. Therefore, we wanted to do our analyses separately for each sex. We did also examine a combined model adjusting for sex, but neither in this model a statistically significant difference was found between Sami and non-Sami in the 8-year cumulative incidence of DM (results not shown).
RESULTS:
- Para 2: Differences in risk factor levels for Sami and non-Sami (men and women) are described with Table 2 as reference. Table 2 however, only describes differences between participants and non-participants.

Answer: Yes. Table 2 was unfortunately omitted from the original version and Table 1 was repeated. We have rectified this in the new version.

- Table 3: The age-groups are VERY broad, and as mentioned before, I find no good argument for sex-stratification. For presentation, I suggest instead a figure showing the cumulative T2D incidence as a function of age with a line for each ethnic group (men and women together). Alternatively that the estimated cumulative incidence is predicted for a specific age, sex, smoking status, BMI level etc.

Answer: In Table 3, we have presented the cumulative incidence of DM both in two age groups and in total. The broad age-groups were chosen to avoid groups with a very low number of diabetes cases.

DISCUSSION
- The discussion is very long and could easily be shortened by one third. E.g. the discussion about misclassification of diabetes with HbA1c is not really relevant here. Although the discussion about non-participation is important, this section could also be much shorter.

Answer: Some parts of the Discussion section which seemed less important are now shortened. These parts are now deleted:

“The HbA1c reflects average plasma glucose concentration during the preceding two to three months (27). The test has high levels of pre-analytical stability and reproducibility, fewer day-to-day perturbations during periods of stress and illness, and convenience (no need for fasting state or glucose overload) (24). These attributes might, to some extent, offset the low performance of the test (27).”
“Categorisation of the participants into Sami and non-Sami was based on the information provided from the SAMINOR 1 questionnaires. It is extremely unlikely that a non-Sami individual would report their ethnicity as Sami, while, due to decades of the governmental assimilation policy (Norwegianisation) and the stigmatisation of Sami people, it is quite likely that some Sami people might report their ethnicity as non-Sami. These misclassifications must be expected to be unrelated to the DM diagnosis, and have most likely substantially attenuated the measure of association (the possible ethnic difference in DM risk)”

“While incidence rates of type 2 DM have been reported to be on the rise worldwide in the last 30 years, the disease disproportionally affects indigenous populations (31, 32).”

This part is moved to the introduction section:
“Higher incidence and prevalence of type 2 DM among indigenous peoples, in comparison to the benchmark populations, seems to be a shared phenomenon worldwide (2). For example, the age-standardised incidence of type 2 DM of 1814 Australian Aboriginal and Torres Strait Islander adults from 1999 to 2007 was reported to be 30.5 in 1000 person-years. The estimated incidence rate is nearly four times higher than that for the non-Indigenous population and 50% higher than the incidence reported 10 years ago in Australian Aboriginals (3).”
Sufian Noor (Reviewer 2):
- There are many English language mistakes, the manuscript should be revised by native speaker.

Answer: The manuscript is already edited by a native English editor. We have checked the manuscript again and edited some parts.

Abstract:
Please involve the incidence of diabetes for each Sami & non-Sami groups.

Answer: The estimated 8-year cumulative incidence of DM is 6.1% for both Sami and non-Sami. This is now added to the abstract:
“Aafter 8 years of follow-up, 201 (6.1% for both Sami and non-Sami) incident cases of DM were identified.”

Introduction:
-Introduction is insufficient. You have written much about the results of the study in the introduction
-Better to write about the incidence of diabetes nationally, regionally and internationally -You should include the effect of ethnicity on the incidence of diabetes.

Answer: We have not given results of the study in the Introduction section, only presented some results from previous studies regarding diabetes prevalence, as well as the need for and lack of longitudinal studies. We have rewritten these sentences to make this clearer. The results from national and regional studies were presented in the Discussion section. We have moved some of this to the introduction. There are, however, few comparable international, national and regional studies (with comparable age span and methodology).

We have moved this part from the Discussion to the Introduction section:
“Higher incidence and prevalence of type 2 DM among indigenous peoples, in comparison to the benchmark populations, seems to be a shared phenomenon worldwide (2). For example, the age-standardised incidence of type 2 DM of 1814 Australian Aboriginal and Torres Strait Islander adults from 1999 to 2007 was reported to be 30.5 in 1000 person-years. The estimated incidence rate is nearly four times higher than that for the non-Indigenous population and 50% higher than the incidence reported 10 years ago in Australian Aboriginals (3).”

Methodology:
-In line10 you mentioned that Sami inhabitants are in the central & northern Norway, while in the introduction section you said they live in northern Norway?

Answer: We acknowledge that the regions Northern and Central Norway, and the counties therein are not familiar to foreign readers. The traditional Sami settlement region in Norway covers northern and central parts of the country. The region “Northern Norway” refers to the counties Finnmark, Troms and Nordland, while the county Trøndelag is situated in the region “Central Norway”. The SAMINOR 1 Survey included 24 municipalities located in the four mentioned counties, hence, in both Northern and Central Norway. The present study, however, included only 10 municipalities, all of them located in Northern Norway.

To clarify, the sentence
“The survey was conducted in 10 rural municipalities in Finnmark, Troms, and Nordland counties, all previously included in SAMINOR 1: Kautokeino, Karasjok, Tana, Nesseby, Porsanger, Lyngen,
Storfjord, Kåfjord, Skånland, and Evenes (Figure 1)

in the Methods section has been changed to:

“The survey was conducted in 10 of the municipalities that were included in SAMINOR 1. All 10 municipalities were rural municipalities located in Northern Norway (Finnmark, Troms, and Nordland counties): Kautokeino, Karasjok, Tana, Nesseby, Porsanger, Lyngen, Storfjord, Kåfjord, Skånland, and Evenes (Figure 1).”

-Random blood sugar alone is not diagnostic for diabetes, why did not you confirm newly discovered diabetic patient by doing fasting blood sugar and two-hour postprandial glucose?

Answer: We used random plasma glucose measurement only to identify those with prevalent diabetes in SAMINOR 1, with cut-off ≥ 11.1mmol/L. However, most prevalent cases were identified based on self-report. Participants were not requested to be fasting when attending the clinical examination, as opening hours were until late afternoon. Due to limited resources, it was not feasible to confirm the diagnosis with 2-hour postprandial glucose measurements. Incident diabetes cases were determined with HbA1c ≥ 6.5%, and/or self-report.

Non-fasting glucose measurements have been added as a limitation to the study. In addition, the following sentence has been added: “As a large number of people were included, confirmation of diabetes diagnosis with 2-hour post-prandial glucose measurement was not feasible.”

-What are your inclusion & exclusion criteria?

Answer: Those who had participated in both SAMINOR 1 and SAMINOR 2 were included in the analysis. Exclusion criteria are described both in the Methods section and in Figure 2 (flow chart), and were as follows: We excluded those who did not complete the questionnaires, did not give any ethnicity information or had diabetes at baseline, and one person who lacked HbA1c measurement in SAMINOR 2.

-Sample selection technique is not obvious, how did you select the 10 municipalities to be representative of northern Norway inhabitants?

Answer: Due to limited resources and time constraints, only 10 municipalities were included in the SAMINOR 2 Clinical Survey. The included municipalities were selected due to a considerable proportion of Sami people. They were not chosen in order to be representative of the entire population of Northern Norway, but to maximize the number of Sami participants. Therefore, the municipalities are not representative for Northern Norway as a whole, as they included municipalities with a larger proportion of Sami inhabitants than other municipalities in Northern Norway. The following has been added to the manuscript:

“The included municipalities were chosen due to a relatively high number of Sami inhabitants.”

-How did you calculate the sample size?

Answer: We invited all inhabitants of the 10 municipalities in the selected age span, and as mentioned in our answer to the previous question, we unfortunately did not have resources to investigate more than 10 municipalities.
-Tables in the section of methodology are results, should be in the section of results.

Answer: Tables 1 and 2 are now moved to the Results section.

Results:

-Table 2 is table 1 duplication.

Answer: We apologize that table 2 were omitted and table 1 duplicated in our submission. We have rectified it in the revised manuscript.

Discussion:

-You should compare your results with previous studies conducted in Norway & outside Norway, including incidence of diabetes ethnicity and other risk factors, etc..

Answer: We have mentioned examples from both other indigenous peoples and national and regional studies in Norway, but unfortunately, there are few comparable studies among indigenous people presenting cumulative incidence or even incidence rates.

Ulrike Rothe (Reviewer 3):
Thank you for your interesting manuscript. But, there is an important mistake: table 1 and 2 are similar, please, delete and change table 2, respectively and write correct headlines for both.

Answer: We apologize for this mistake and have deleted the duplicate Table 1 and replaced it with Table 2.

And another question: why do you have calculated odds ratios, but not the risks (e.g. relative risks) since incidences are risks. I am afraid that could be the reason for missing significance.

Answer: We have no information about when during the follow-up the new cases of DM were diagnosed, only that it was before the SAMINOR 2 screening or as a result of it. Therefore, it is not possible to calculate person-years and the incidence density, and we are left with computing the cumulative incidence, and logistic regression if performing adjustments.

In this situation, with a low incidence, the OR and RR (based on the cumulative incidence) are very similar (the crude, unadjusted figures were in fact 1.10 and 1.09, respectively, for men and 0.91 and 0.92 in women) and the p-value for the 2-by-2 table (giving both the RR and OR) will be identical (here p=0.66 and 0.67, for men and women, respectively).

Another concern is that most likely the disease has been present for a considerable time before date of diagnosis. We agree, however, that it would have been a strength if date of diagnosis had been known and that it would have been possible to perform e.g. Cox regression analysis. Although it is impossible to know with certainty, it is highly unlikely that this would have changed the conclusions, as the crude, cumulative, incidence was very similar for Sami and non-Sami.
BEND-D-18-00325

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Editor comments:

1) Please state whether the map in Figure 2 has been taken from other sources. Please acknowledge the source in the figure legend, and if it is under copyright, also state the written permission given to use and adapt it.

Answer: We assume you refer to Figure 1. The map of the study area is used with permission from the Centre for Sami Health Research (CSHR) at UiT The Arctic University of Norway. It is designed by one of the authors, Marita Melhus at CSHR.
We have added this phrase to the legend: “Published with permission from Centre for Sami Health Research”.

In the Authors’ contributions section, MM’s contribution is changed to:
“MM designed the map of the study area and assisted in statistical analyses as well as material and methods’ descriptions.”

Reviewer reports:

Marit Eika Jørgensen (Reviewer 1):
The paper aims to compare the cumulative incidence of type 2 diabetes (T2D) among Sami and non-Sami in Northern Norway. The topic is of interest, the study is well conducted, and the paper generally well written. I have however some concerns about the methods applied.

Specific comments:
BACKGROUND:
- The hypothesis is not well stated. Why is it relevant to test a difference in T2D risk according to Sami status? Is the population suggested to differ genetically, socially, culturally from the Norwegian population in a way that should affect diabetes risk?

Answer: Sami people are distinct from benchmark (Norwegian) population. Firstly, they may have their own genetic predisposition/protective factors. Secondly, historically the Sami have had their own culture, rituals, diet, lifestyle, and so forth, which might affect the risk of diabetes. Several international studies have shown a striking difference in the prevalence and incidence of diabetes mellitus between indigenous peoples and majority populations, and previous studies showed (as mentioned in the introduction) differences in the prevalence of diabetes mellitus between Sami and non-Sami. To elucidate more the need for such a study and make the hypothesis clearer, we have added some sentences in the introduction section:

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Is changed to:

“The Sami are an indigenous people, who for centuries have inhabited northern parts of Norway, Sweden, and Finland, and the Kola Peninsula of Russia. Sami people might possess genes that either predispose them to or protect them against development of diseases like DM. Furthermore, they have their own culture, diet, and so forth, which might play a role in increasing or decreasing the risk of DM. Internationally, studies have shown a striking difference in the prevalence and incidence of diabetes mellitus between indigenous populations and majority populations (3-6). Higher incidence and prevalence of type 2 DM among indigenous peoples, in comparison to the benchmark populations, seems to be a shared phenomenon worldwide (2). For example, the age-standardised incidence of type 2 DM of 1814 Australian Aboriginal and Torres Strait Islander adults from 1999 to 2007 was reported to be 30.5 in 1000 person-years. This incidence rate is nearly four times higher than that for the non-Indigenous population and 50% higher than the incidence reported 10 years ago in Australian Aboriginals (7).

Previous research based on data from 24 municipalities in the SAMINOR 1 Survey (2003–2004), showed no statistically significant difference between Sami and non-Sami in the prevalence of DM, defined by self-report and/or non-fasting plasma glucose ≥ 11.1 mmol/L.”
“To our knowledge, there are no previous studies investigating the incidence of DM in the Sami population of rural municipalities in Northern Norway.”

- From the introduction we know that baseline diabetes prevalence is not different according to ethnicity, but higher at follow up in SAMINOR 2 among Sami compared to non-Sami. Does this information apply to the total study population at baseline and follow up, or to the population participating in both surveys? While the study shows no difference in cumulative incidence of T2D across ethnic groups, the difference in prevalence at follow up must then necessarily be explained by a higher prevalence of non-incident cases among Sami due to lower mortality, lower migration rates or higher participation rate among Sami with T2D. This should be explained (and discussed) more thoroughly.

Answer: The mentioned studies in the introduction are based upon the total study populations in each of the surveys. Lack of difference in the prevalence of DM (all types of DM) in SAMINOR 1, applies to the total study population of this survey (n=16208). Higher prevalence of type 2 DM in SAMINOR 2 applies to the total population participated in SAMINOR 2 (n=5878). We emphasize that SAMINOR 1 covered a much larger geographical area (24 municipalities) compared to SAMINOR 2 (10 municipalities), so the targeted populations differed in the two surveys. Another explanation for different results is the use of different methodologies in SAMINOR 1 and 2 to ascertain DM. We used non-fasting plasma glucose and/or self-report in SAMINOR 1, but HbA1c and/or self-report in SAMINOR 2 to categorize diabetics. The reason for this is that HbA1c was not measured in SAMINOR 1. As there is not a high concordance between glucose-based measures and HbA1, it is quite likely that if we had used HbA1c in the SAMINOR 1 study, the estimated prevalence and the individuals categorized as diabetics would have been different.

Lack of statistically significantly different cumulative incidence of DM (all types of DM, not only type 2 DM) might (as also explained in the discussion section) be due to a small number of participants in the present study (those who participated in both SAMINOR 1 and 2) (n=3303). However, we cannot exclude the possibility of different mortality, migration or participation rates among Sami with type 2 DM.

METHODS
- How is the study population selected from the general population in the 10 municipalities? From households? A random geographic sample? And what is the population size in these municipalities? Have any efforts been done to ensure representation of both Sami and non-Sami? Is it likely that the name of the survey (SAMINOR) influences the motivation to participate for the non-Sami population?

Answer: Based on previous knowledge, the 10 included municipalities were selected due to a high proportion of inhabitants with Sami background. This was done to maximize the number of Sami in the sample. All these municipalities are rural municipalities with populations less than 5000 inhabitants. In both SAMINOR 1 and SAMINOR 2, everyone in the predefined age span living in these municipalities were invited to participate, regardless of their ethnic background. That is, the whole population in the selected age groups was invited. The surveys were promoted as surveys on health and living conditions, and invitees were encouraged to participate to provide information about the health situation in their own municipality, in addition to get personal feedback of their own health status. The name “SAMINOR” was not used at the time of invitation to SAMINOR 1, and was not emphasized when conducting SAMINOR 2. However, the fact that the surveys were conducted by the Centre for Sami Health Research and that some questions (especially in SAMINOR 1) were directed to Sami
participants, may have influenced participation. Both ethnic groups might have had their own concerns regarding the study and the net effect of such potential non-participation bias is unknown to us as there is no ethnic registry in Norway. Regarding this, we have added a section in the Methods section:

“The included municipalities were chosen due to a high number of Sami inhabitants. The invitees were informed that the study aimed primarily at collecting knowledge about health, diseases, and living conditions in regions with Sami and Norwegian populations and provide a health profile for their county/municipality, in addition to getting personal feedback of their own health status.”

- Study sample: A bit of information on the SAMINOR 1 would be useful. How many participated, how many were invited? It seems that 11,558 invited from SAMINOR 1 might have been invited for SAMINOR 2. Is it correctly understood that non-participants in SAMINOR 1 potentially could have participated in SAMINOR 2? Would you be able to track such information? And would it be possible to connect to Norwegian registers for information on death, diagnosis of T2D?

Answer: For both SAMINOR 1 and 2, we have referred to the original paper, which have described in detail all aspects of the survey. In SAMINOR 1, 24 municipalities were included, but in the present study, the data are based on inhabitants from the 10 municipalities that were included in both SAMINOR 1 and 2. We were concerned that if we described more in detail about SAMINOR 1, the text would be extensive and the reader would get bewildered. We have, however, added some new information about SAMINOR 1 in the beginning of the Study sample section.

Inhabitants of the 10 municipalities included in SAMINOR 2, were invited regardless of having been invited or participated in SAMINOR 1. It is therefore correct that non-participants in SAMINOR 1 may have participated in SAMINOR 2. In fact, out of the 6004 participants in SAMINOR 2, only 3872 had previously participated in SAMINOR 1. After exclusions (see Figure 2), 3303 of these persons were included in our analyses.

It would have been possible to obtain data from the cause of death registry (the entire follow-up, but diabetes is not often registered as the cause of death), the prescription database (from 2004) and specialist health care (from 2008), but due to limited resources and time constraints, this was not prioritized. We acknowledge, however, that this is a weakness of our study.

The following changes has been done:

“The present analyses are based on longitudinal data of those participating in both SAMINOR 1 and SAMINOR 2 from the above-mentioned ten municipalities. In SAMINOR 2, 12,455 subjects, aged 40–79 years, were invited to take part, and 6004 participated (48.2%).”

was changed to:

“In SAMINOR 1, a total of 27,987 subjects, aged 30 or 36–79 years were invited, and 16,865 participated (60.6%). In SAMINOR 2, 12,455 subjects, aged 40–79 years, were invited to take part, and 6004 participated (48.2%), whereof 3872 persons had previously participated in SAMINOR 1. The present analyses are based on longitudinal data including individuals participating in both SAMINOR 1 and SAMINOR 2 who did not fill the exclusion criteria detailed below.”

- It is stated that the participant rate was 56.2% (3303 of 5875). However, usually, the participant
rate is calculated from the eligible population (those still alive, still living in the relevant municipalities). Thus, I assume, the correct participant rate is actually higher than 56.2%?

Answer: We acknowledge that the term “participation rate” is not correct in this regard, so we change it to “follow-up rate” in the Methods section, study sample.

- **Covariates:** It seems that some of the covariates (e.g. income, SCL-10, marital status) may affect diabetes risk through other risk factors (e.g. obesity, physical activity). If the primary purpose is to adjust for confounders that may mask potential ethnic differences, I suggest that you include primarily covariates with an independent and biologically plausible influence on diabetes risk.

Answer: We have assessed the effect of covariates which either directly influence development of the DM (e.g. obesity, inactivity) or indirectly affect the risk of developing DM (e.g. income, marital status, and mental health). In the last model (table 4), we have included all relevant covariates that were shown to have significant effect on the risk of DM (WHtR and education). We also refer to the answer to the next, related, question from the reviewer.

- **Statistical analysis:** The long list of separate analyses for each diabetes risk factor (beyond age and gender) seems inappropriate. Again, if the purpose is to adjust for confounders to un-mask an association between ethnicity and incident T2D, the relevant analytical approach should be a multivariable regression including all relevant confounders.

Answer: The applied approach consisted of two steps. In the first step, some possible risk factors for DM were assessed (in combination with age and ethnic group and separately for each sex). In the second step (the last line in table 4), only covariates that had significant effect (“all relevant confounders”) were included. Education (in women) and several variables related to body composition/obesity were statistically significantly associated with diabetes risk, even after adjustments for age and ethnic group. As the obesity-related variables (WC, WHtR and BMI) are highly correlation with each other, we chose to include one of them (WHtR) in the multivariate model together with age and ethnic group.

- Why is the SCL score categorized instead of using the continuous information?

Answer: As the applied cut-off (1.85) for categorizing individuals with symptoms of anxiety and depression has been validated and used in several studies, we believe dichotomization makes it easier to compare with other studies. Regardless of including SCL as a continuous or dichotomized score, the odds ratio is not statistically significant (results not shown).

- It seems inadequate to stratify for sex unless a significant interaction is observed (no indication of this in the data). The current approach assumes an interaction between sex and all covariates. It would be more correct to simply adjust for sex.

Answer: Generally speaking, we prefer to do sex-specific analyses if the data allow so. As results from SAMINOR 1 showed a higher obesity prevalence and a more sedentary lifestyle among women (particularly Sami women) than among men, we expected that women had a higher risk of developing type 2 DM. Therefore, we wanted to do our analyses separately for each sex. We did also examine a combined model adjusting for sex, but neither in this model a statistically significant difference was
found between Sami and non-Sami in the 8-year cumulative incidence of DM (results not shown).

RESULTS:
- Para 2: Differences in risk factor levels for Sami and non-Sami (men and women) are described with table 2 as reference. Table 2 however, only describes differences between participants and non-participants.

Answer: Yes. Table 2 was unfortunately omitted from the original version and Table 1 was repeated. We have rectified this in the new version.

- Table 3: The age-groups are VERY broad, and as mentioned before, I find no good argument for sex-stratification. For presentation, I suggest instead a figure showing the cumulative T2D incidence as a function of age with a line for each ethnic group (men and women together). Alternatively that the estimated cumulative incidence is predicted for a specific age, sex, smoking status, BMI level etc.

Answer: In Table 3, we have presented the cumulative incidence of DM both in two age groups and in total. The broad age-groups were chosen to avoid groups with a very low number of diabetes cases.

DISCUSSION
- The discussion is very long and could easily be shortened by one third. E.g. the discussion about misclassification of diabetes with HbA1c is not really relevant here. Although the discussion about non-participation is important, this section could also be much shorter.

Answer: Some parts of the Discussion section which seemed less important are now shortened. These parts are now deleted:

“The HbA1c reflects average plasma glucose concentration during the preceding two to three months (27). The test has high levels of pre-analytical stability and reproducibility, fewer day-to-day perturbations during periods of stress and illness, and convenience (no need for fasting state or glucose overload) (24). These attributes might, to some extent, offset the low performance of the test (27).”

“Categorisation of the participants into Sami and non-Sami was based on the information provided from the SAMINOR 1 questionnaires. It is extremely unlikely that a non-Sami individual would report their ethnicity as Sami, while, due to decades of the governmental assimilation policy (Norwegianisation) and the stigmatisation of Sami people, it is quite likely that some Sami people might report their ethnicity as non-Sami. These misclassifications must be expected to be unrelated to the DM diagnosis, and have most likely substantially attenuated the measure of association (the possible ethnic difference in DM risk)”

“While incidence rates of type 2 DM have been reported to be on the rise worldwide in the last 30 years, the disease disproportionally affects indigenous populations (31, 32).”

This part is moved to the introduction section:
“Higher incidence and prevalence of type 2 DM among indigenous peoples, in comparison to the benchmark populations, seems to be a shared phenomenon worldwide (2). For example, the age-standardised incidence of type 2 DM of 1814 Australian Aboriginal and Torres Strait Islander adults from 1999 to 2007 was reported to be 30.5 in 1000 person-years. The estimated incidence rate is nearly four times higher than that for the non-Indigenous population and 50% higher than the incidence reported 10 years ago in Australian Aboriginals (3).”
Sufian Noor (Reviewer 2):
- There are many English language mistakes, the manuscript should be revised by native speaker.

Answer: The manuscript is already edited by a native English editor. We have checked the manuscript again and edited some parts.

Abstract:
Please involve the incidence of diabetes for each Sami & non-Sami groups.

Answer: The estimated 8-year cumulative incidence of DM is 6.1% for both Sami and non-Sami. This is now added to the abstract:
“After 8 years of follow-up, 201 (6.1% for both Sami and non-Sami) incident cases of DM were identified.”

Introduction:
-Introduction is insufficient. You have written much about the results of the study in the introduction
-Better to write about the incidence of diabetes nationally, regionally and internationally -You should include the effect of ethnicity on the incidence of diabetes.

Answer: We have not given results of the study in the Introduction section, only presented some results from previous studies regarding diabetes prevalence, as well as the need for and lack of longitudinal studies. We have rewritten these sentences to make this clearer. The results from national and regional studies were presented in the Discussion section. We have moved some of this to the introduction. There are, however, few comparable international, national and regional studies (with comparable age span and methodology).

We have moved this part from the Discussion to the Introduction section:
“Higher incidence and prevalence of type 2 DM among indigenous peoples, in comparison to the benchmark populations, seems to be a shared phenomenon worldwide (2). For example, the age-standardised incidence of type 2 DM of 1814 Australian Aboriginal and Torres Strait Islander adults from 1999 to 2007 was reported to be 30.5 in 1000 person-years. The estimated incidence rate is nearly four times higher than that for the non-Indigenous population and 50% higher than the incidence reported 10 years ago in Australian Aboriginals (3).”

Methodology:
-In line10 you mentioned that Sami inhabitants are in the central & northern Norway, while in the introduction section you said they live in northern Norway?

Answer: We acknowledge that the regions Northern and Central Norway, and the counties therein are not familiar to foreign readers. The traditional Sami settlement region in Norway covers northern and central parts of the country. The region “Northern Norway” refers to the counties Finnmark, Troms and Nordland, while the county Trøndelag is situated in the region “Central Norway”. The SAMINOR 1 Survey included 24 municipalities located in the four mentioned counties, hence, in both Northern and Central Norway. The present study, however, included only 10 municipalities, all of them located in Northern Norway.
To clarify, the sentence “The survey was conducted in 10 rural municipalities in Finnmark, Troms, and Nordland counties, all previously included in SAMINOR 1: Kautokeino, Karasjok, Tana, Nesseby, Porsanger, Lyngen, Storfjord, Kåfjord, Skånland, and Evenes (Figure 1)” in the Methods section has been changed to:

“The survey was conducted in 10 of the municipalities that were included in SAMINOR 1. All 10 municipalities were rural municipalities located in Northern Norway (Finnmark, Troms, and Nordland counties): Kautokeino, Karasjok, Tana, Nesseby, Porsanger, Lyngen, Storfjord, Kåfjord, Skånland, and Evenes (Figure 1).”

- Random blood sugar alone is not diagnostic for diabetes, why did not you confirm newly discovered diabetic patient by doing fasting blood sugar and two-hour postprandial glucose?

Answer: We used random plasma glucose measurement only to identify those with prevalent diabetes in SAMINOR 1, with cut-off ≥ 11.1mmol/L. However, most prevalent cases were identified based on self-report. Participants were not requested to be fasting when attending the clinical examination, as opening hours were until late afternoon. Due to limited resources, it was not feasible to confirm the diagnosis with 2-hour postprandial glucose measurements. Incident diabetes cases were determined with HbA1c ≥ 6.5%, and/or self-report.

Non-fasting glucose measurements have been added as a limitation to the study. In addition, the following sentence has been added: “As a large number of people were included, confirmation of diabetes diagnosis with 2-hour post-prandial glucose measurement was not feasible.”

- What are your inclusion & exclusion criteria?

Answer: Those who had participated in both SAMINOR 1 and SAMINOR 2 were included in the analysis. Exclusion criteria are described both in the Methods section and in Figure 2 (flow chart), and were as follows: We excluded those who did not complete the questionnaires, did not give any ethnicity information or had diabetes at baseline, and one person who lacked HbA1c measurement in SAMINOR 2.

- Sample selection technique is not obvious, how did you select the 10 municipalities to be representative of northern Norway inhabitants?

Answer: Due to limited resources and time constraints, only 10 municipalities were included in the SAMINOR 2 Clinical Survey. The included municipalities were selected due to a considerable proportion of Sami people. They were not chosen in order to be representative of the entire population of Northern Norway, but to maximize the number of Sami participants. Therefore, the municipalities are not representative for Northern Norway as a whole, as they included municipalities with a larger proportion of Sami inhabitants than other municipalities in Northern Norway. The following has been added to the manuscript: “The included municipalities were chosen due to a relatively high number of Sami inhabitants.”

- How did you calculate the sample size?
Answer: We invited all inhabitants of the 10 municipalities in the selected age span, and as mentioned
in our answer to the previous question, we unfortunately did not have resources to investigate more
than 10 municipalities.

-Tables in the section of methodology are results, should be in the section of results.

Answer: Tables 1 and 2 are now moved to the Results section.

Results:

-Table 2 is table 1 duplication.

Answer: We apologize that table 2 were omitted and table 1 duplicated in our submission. We have
rectified it in the revised manuscript.

Discussion:

-You should compare your results with previous studies conducted in Norway & outside Norway,
including incidence of diabetes ethnicity and other risk factors, etc..

Answer: We have mentioned examples from both other indigenous peoples and national and regional
studies in Norway, but unfortunately, there are few comparable studies among indigenous people
presenting cumulative incidence or even incidence rates.

Ulrike Rothe (Reviewer 3):
Thank you for your interesting manuscript. But, there is an important mistake: table 1 and 2 are similar,
please, delete and change table 2, respectively and write correct headlines for both.

Answer: We apologize for this mistake and have deleted the duplicate Table 1 and replaced it with
Table 2.

And another question: why do you have calculated odds ratios, but not the risks (e.g. relative risks)
since incidences are risks. I am afraid that could be the reason for missing significance.

Answer: We have no information about when during the follow-up the new cases of DM were
diagnosed, only that it was before the SAMINOR 2 screening or as a result of it. Therefore, it is not
possible to calculate person-years and the incidence density, and we are left with computing the
cumulative incidence, and logistic regression if performing adjustments.

In this situation, with a low incidence, the OR and RR (based on the cumulative incidence) are very
similar (the crude, unadjusted figures were in fact 1.10 and 1.09, respectively, for men and 0.91 and
0.92 in women) and the p-value for the 2-by-2 table (giving both the RR and OR) will be identical
(here p=0.66 and 0.67, for men and women, respectively).

Another concern is that most likely the disease has been present for a considerable time before date of
diagnosis. We agree, however, that it would have been a strength if date of diagnosis had been known
and that it would have been possible to perform e.g. Cox regression analysis. Although it is impossible
to know with certainty, it is highly unlikely that this would have changed the conclusions, as the crude,
cumulative, incidence was very similar for Sami and non-Sami.

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Declarations
- Ethics approval and consent to participate
- Consent for publication
- Availability of data and materials
- Competing interests
- Funding
- Authors' Contributions
- Acknowledgements
- Authors' Information

Answer: The mentioned declaration sections are all present at the end of the text (before references).