

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Trends in known and undiagnosed diabetes, HbA1c levels, cardio-metabolic risk factors and diabetes treatment target achievement in repeated cross-sectional surveys – the population-based Tromsø Study 1994-2016
AUTHORS	Langholz, Petja Lyn; Wilsgaard, Tom; Njolstad, Inger; Jorde, Rolf; Hopstock, Laila

VERSION 1 – REVIEW

REVIEWER	Sukhyang Lee Ajou University South Korea
REVIEW RETURNED	03-Aug-2020

GENERAL COMMENTS	<p>The diagnosis of DM was defined as a self-reported and undiagnosed DM with the HbA1c level measured in the study. A total of DM should be reported for the trends of treatments with self-reported and undiagnosed DM since the HbA1c level is a good standard of DM diagnosis. The number of undiagnosed DM could be interpreted for the role in the healthcare system considering for the small number compared to that of self-reported. The trends in change of undiagnosed DM was overly presented considering small numbers in a total study population. The prevalence of DM was too small (2.3- 5.3%) comparing the worldwide prevalence(~10%) while the study included type 1 and 2 DM.</p> <p>The style and contents of table 2 with men and women or Tromso study 4-7 were fully understood for the prevalence. Undiagnosed DMs were women 32.6%(32 out of 120) in Tromso 4 and 20.4%(111 out of 540) in table 2. Where did the numbers 120 or 540 come from if 32 means the undiagnosed DM? Overall, the data presentation was not enough to explain the study results and conclusions with the long term epidemiology of Tromso study.</p> <p>In the method section, the description can be reduced with reference if the details were presented in the published article of the previous Tromso study.</p>
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REVIEWER	Miguel Castillo Sánchez IDIAP JORDI GOL GVA SPAIN
REVIEW RETURNED	23-Sep-2020

GENERAL COMMENTS	An interesting study is presented on the evolution and management of diabetes and metabolic syndrome over decades in the population of Tromsø. The methodology and the manuscript are adequate, I
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	<p>only consider important to assess some details:</p> <ul style="list-style-type: none"> - A single HbA1c determination is not a diagnosis of diabetes: there must be at least two determinations to confirm a high number. I miss any mention of the limitation that it could be. - The definition of "undiagnosed diabetes" includes patients who answered "Yes, previously". Eventually there may be a bias in those patients who have well-controlled diabetes without drugs and who express that they "no longer have it." I think this point should have been clarified better since it determines inclusion in one group or another. It would be interesting if the authors clarify this point in Methods or reflect on it in Discussion. - The change of criteria in the target HA1c figure for people older than 75 years of the last measurement (it goes from 9% to 7%) is transcendental in the interpretation of the results, and yet the authors do not seem to give it value. <p>Congratulations to the authors.</p>
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REVIEWER	Jocelyne Benatar Auckland District Health Board New Zealand
REVIEW RETURNED	17-Dec-2020

GENERAL COMMENTS	<p>This is a wonderful study in that it does give a timeline regarding trends in a decent number of patients. The paper is well written but it might be useful to have diagrams to show trends for readers who are more visual. The study and its finding are however not new and have been found in many larger studies like the NHANES, the meta-analysis done on Asian Pacific populations etc.. The authors describe an increase in abdominal circumference and HbA1c and reduction in BP and LDL-c . A major limitations is that there is no data on uptake of BP lowering medication or use of statins in their population which likely account for this finding. This study would be best served in a regional journal. I wish the authors good luck.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Sukhyang Lee, Ajou Univ

Comments to the Author:

The diagnosis of DM was defined as a self-reported and undiagnosed DM with the HbA1c level measured in the study. A total of DM should be reported for the trends of treatments with self-reported and undiagnosed DM since the HbA1c level is a good standard of DM diagnosis. The number of undiagnosed DM could be interpreted for the role in the healthcare system considering for the small number compared to that of self-reported. The trends in change of undiagnosed DM was overly presented considering small numbers in a total study population. The prevalence of DM was too small (2.3- 5.3%) comparing the worldwide prevalence(~10%) while the study included type 1 and 2 DM.

The style and contents of table 2 with men and women or Tromso study 4-7 were fully understood for the prevalence. Undiagnosed DMs were women 32.6% (32 out of 120) in Tromso 4 and 20.4% (111 out of 540) in table 2. Where did the numbers 120 or 540 come from if 32 means the undiagnosed DM? Overall, the data presentation was not enough to explain the study results and conclusions with the long term epidemiology of Tromso study.

We thank the reviewer for these remarks and have followed the suggestion to show the prevalence of a total diabetes measure combining self-reported diabetes and HbA1c levels $\geq 6.5\%$. We have added the prevalence of total diabetes to Table 2 (page 8) and the results section (page 7). We find that this addition makes the numbers in Table 2 more understandable as well. Here, 120 and 540 (120 and 593 in the revised manuscript) are the number of women in Tromsø 4 and 7, respectively, who have either self-reported diabetes or HbA1c levels $\geq 6.5\%$ among participants with available data on HbA1c and metabolic risk factors. HbA1c was only measured in a sub-sample of participants in Tromsø 4, which explains the discrepancy between the N in Table 1 and Table 2. We explain this in the beginning of the method section (page 4-5).

The reviewer points out that the prevalence of diabetes in our study was too small compared to the worldwide prevalence. We acknowledge a potential underestimation of prevalence due to selection bias towards healthy participants (as described in the discussion section, page 11), which is common in population-based surveys dependent on attendance. The proportion of type II diabetes in Norway is estimated to be 90% of the total diabetes population (*Bakke Å, Cooper JG, Thue G et al. Type 2 diabetes in general practice in Norway 2005-2014: moderate improvements in risk factor control but still major gaps in complication screening. BMJ Open Diabetes Res Care 2017; 5: e000459.*). In a recent study based on the Norwegian Prescription Database, the Norwegian Patient Registry and the primary care database (*Ruiz PLD, Stene LC, Bakken IJ et al. Decreasing incidence of pharmacologically and non-pharmacologically treated type 2 diabetes in Norway: a nationwide study. Diabetologia 2018; 61: 2310–8.*), Ruiz and colleagues found the diabetes type II prevalence in Norway to be 6.1% in 2014, which is considerably lower than the world average. Therefore, we believe that our results are valid.

In the method section, the description can be reduced with reference if the details were presented in the published article of the previous Tromsø study.

Thank you for pointing this out. We agree that, ideally, the method section could be shortened if previous references were available. However, several details provided in the method section have not been published before, thus we wish to keep the level of detail for information purposes.

Reviewer: 2

Dr. Miguel Castillo-Sánchez, IDIAP Jordi Gol, Valencian Community
Comments to the Author:

An interesting study is presented on the evolution and management of diabetes and metabolic syndrome over decades in the population of Tromsø. The methodology and the manuscript are adequate, I only consider important to assess some details:

- A single HbA1c determination is not a diagnosis of diabetes: there must be at least two determinations to confirm a high number. I miss any mention of the limitation that it could be.

We agree with the reviewer and have included the following two sentences in the manuscript: *"Moreover, the definition of undiagnosed diabetes in our study was based on a single HbA1c measurement for each participant at each survey. However, the clinical diagnosis of diabetes requires confirmation through a repeated HbA1c test unless clinical symptoms and glucose levels >11.1mmol/l are present."* (page 11)

- The definition of "undiagnosed diabetes" includes patients who answered "Yes, previously". Eventually there may be a bias in those patients who have well-controlled diabetes without drugs and who express that they "no longer have it." I think this point should have been clarified better since it determines inclusion in one group or another. It would be interesting if the authors clarify this point in Methods or reflect on it in Discussion.

We thank the reviewer for this remark. The option to answer *"Yes, previously"* was only available in the last survey (Tromsø 7). In Tromsø 4-6, participants could only answer *"Yes"* or *"No"* to the question whether they have or had diabetes. We have therefore decided to combine the answers

“Yes” and “Yes, *previously*” in the diabetes category for Tromsø 7 as well, in order to maintain consistency across all surveys.

We have revised the corresponding sentence in the method section (page 5) and updated all analyses and tables accordingly. Note that in most cases there were also slight changes in prevalence for Tromsø 4 to 6 due to the age-adjustment across surveys.

-The change of criteria in the target HA1c figure for people older than 75 years of the last measurement (it goes from 9% to 7%) is transcendental in the interpretation of the results, and yet the authors do not seem to give it value.

We agree with the reviewer, and have added the following sentence acknowledging the change in guidelines to the discussion about treatment target achievement: *“The recommended treatment target for HbA1c decreased throughout the study period, posing higher demands on diabetes management especially in the elderly cohorts”* (page 12).

Reviewer: 3

Dr. Jocelyne R. Benatar, Auckland City Hosp

Comments to the Author:

This is a wonderful study in that it does give a timeline regarding trends in a decent number of patients. The paper is well written but it might be useful to have diagrams to show trends for readers who are more visual.

We thank the reviewer for this suggestion and have added figures (visualization of trends) for Table 1 and 2 as supplementary files.

The study and its finding are however not new and have been found in many larger studies like the NHANES, the meta-analysis done on Asian Pacific populations etc.

We thank the reviewer for this comment and have now added an additional reference to one of the relevant NHANES study to the discussion section (page 11).

The authors describe an increase in abdominal circumference and HbA1c and reduction in BP and LDL-c. A major limitations is that there is no data on uptake of BP lowering medication or use of statins in their population which likely account for this finding. This study would be best served in a regional journal. I wish the authors good luck

The reviewer comments that the lack of data on uptake of medication is a major limitation. However, we did include the use of antihypertensive medication in the definition of hypertension, as recommended in several definitions of the metabolic syndrome. We did not include LDL cholesterol, as it is not part of the metabolic syndrome definition that we used in this study.

Although antihypertensives were included in the definition of hypertension, we still see a decline in the proportion of people with hypertension, indicating that medication does not entirely account for the decreasing trend. This has also been shown in previous publications from the Tromsø Study (longitudinal and secular trends in blood pressure and lipids, respectively), which we now refer to more clearly in the discussion section (page 10).

VERSION 2 – REVIEW

REVIEWER	Miguel Castillo Sánchez IDIAP JGol, Spain
REVIEW RETURNED	01-Mar-2021
GENERAL COMMENTS	Congratulations.