Author’s response to reviews

Title: Preventing misdiagnosis of diabetes in the elderly: Age-dependent HbA1c reference intervals derived from two population-based study cohorts

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Point-by-point response to editorial and reviewer comments

Editor Comments:

1) Please describe the role of the funding body in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript should be declared.

Answer: The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. This statement has been included within the manuscript in the section “Declarations - Funding” p. 13 line 322

2) Please clarify the author contributions of AM as writing of the manuscript is not sufficient to qualify for authorship.

Answer: We apologize for being not precise enough. AM analyzed and interpreted the data, drafted and finalized the manuscript. This has been added to the section “Declarations – author contributions” p. 13 line 325
Reviewer reports:
Lea Smiricic Duvnjak (Reviewer 2): This is an excellent study investigating the association between age and A1c in nondiabetic Caucasian population and providing age-dependent reference intervals for A1c. The epidemiological studies performed so far that has formed the basis for recommending A1C to diagnose diabetes included adult populations in general. While some studies have shown increase in A1c in elderly nondiabetic population, these reports have not been recognized by current guidelines leading to overtreatment of diabetes in elderly population. That's why the present results may have important implications for every day clinical practice I have some minor suggestion:

Answer: We would like to thank Dr. Duvnjak for these kind word and will try to address the issues raised.

It should be clearly stated that for diagnosis of Diabetes it is recommended to perform A1C test using a method that is certified by the NGSP (www.ngsp.org) and standardized or traceable to the Diabetes Control and Complications Trial (DCCT) reference assay.

Answer: Thank you very much for this advice, we agree that this is an important point to be noted. We added this notion within the introduction first paragraph section on page 3 line 63.

The advantages of A1c in comparison with fasting plasma glucose and OGTT include less day to day variability during acute illness and greater convenience as fasting is not required. However, it is important to emphasize that A1C is an indirect measure of average blood glucose levels and that other factors that may impact hemoglobin glycation independently of glycemia need to be taken into consideration.

Answer: We absolutely agree to this view and pointed this already out in the introduction section in second paragraph. We expand the first paragraph by the following notion: “In daily practice, the advantages of HbA1c include less day to day variability during acute illness and greater convenience as fasting is not required compared to fasting plasma glucose measurements and oral glucose tolerance tests.” Page 3 line 59

In addition to age and ethnicity, the interpretation of A1c level in the presence of anemia and hemoglobinopathies should be discussed (in patients with an abnormal hemoglobin but normal red blood cell turnover - the sickle cell trait-an A1C assay without interference from abnormal hemoglobins should be used).
In this context in the patients section- all above mentioned conditions need to be included in the exclusion criteria.

Answer: We agree, that thalassemia and hemoglobinopathies may impact the interpretation of HbA1c results. We included this notion in the discussion section on page 11 line 255

To account for anemia, we included hemoglobin concentration as a parameter to detect anemia in our cohorts. Anemia was defined as based on the WHO definition as hemoglobin below 8.07 mmol/L among men and below 7.45 mmol/L among women. However, the results did not substantially change (see Table 3).

However, in SHIP genetic disorders of hemoglobinopathy or thalassemia have not been recorded
specifically. Therefore, we cannot include this as exclusion criterion. Nevertheless, it has to be noted that thalassemias and hemoglobinopathies are mainly found in people from the African ancestry, from the former Malaria areas in the Mediterranean Basin, and from the Middle East and Southeast Asia, while SHIP is a study consisting of Caucasians. Also from the daily clinical practice we observed less than 1 newly diagnosed patients per year at the University Medicine Greifswald.

Therefore, we believe, it is unlikely that thalassemia or hemoglobinopathy patients are present in the cohort. Moreover, to influence the results of the study, a substantial number of participants would need to be affected. In regard of the low incidence we believe this can be regarded as subordinate in the present study.