Author’s response to reviews

Title: A pattern of unspecific somatic symptoms as long-term premonitory signs of type 2 diabetes: Findings from the population-based MONICA/KORA Cohort Study, 1984-2009

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Author's response to reviews: see over
Confidential comments to editors

Title: A pattern of unspecific somatic symptoms as long-term premonitory signs of type 2 diabetes: Findings from the population-based MONICA/KORA Cohort Study, 1984-2009

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Version: 2
Date: 24 September 2014

Comments: see over
Reviewer's report

Title: How useful is the assessment of an unspecific premonitory symptom pattern for the risk of newly diagnosed type 2 diabetes in the general population?

Version: 1 Date: 8 August 2014

Reviewer: Andre Pascal Kengne

Reviewer's report:

How useful is the assessment of an unspecific premonitory symptom (UPMS) pattern for the risk of newly diagnosed type 2 diabetes mellitus.

In this study, Baumert and co-workers have assessed the association between UPMS and diabetes occurrence in a large population of individuals who took part in the MONICA/KORA study in Germany. The found that a unit change in baseline UPMS score was associated with a 2-3% higher relative risk of incident diabetes during follow-up, and concluded that UPMS could substantially contribute to strategies for early detection of diabetes, alongside established cardio-metabolic risk factors.

A major strength of the study is the large sample size and the extended follow-up allowing an accumulation of sufficient outcomes and accordingly a high statistical power for data analysis. A unique contribution of the paper perhaps, is in demonstrating in prospective cohort data, an association between UPMS and future risk of type 2 diabetes.

Response: We appreciate the careful reading and positive feedback of the reviewer.

However, both the title and the overall conclusion of the paper are misleading. The investigators haven’t assessed the usefulness or added value of UPMS for diabetes risk screening, nor have they discuss the implications/challenges associated of the introducing UPMS assessment in routine setting for diabetes risk screening.

Response: We agree with the reviewer that the title and the overall conclusion are misleading. Unfortunately, with the given title (“How useful….) we unintentionally suggested involuntarily opened a perspective on the appropriateness of UPMS as a screening tool. However, the evaluation of the usefulness of the assessment of
UPMS in an early detection context is a step ahead of our aims for current investigation. We would like to emphasize that the main intention of our study was first to highlight the existence of a premonitory symptom pattern long before the clinical onset of T2DM and to examine how unspecific somatic symptoms as premonitory signs affect the risk for subsequent T2DM disease.

Thus, the rationale behind the present study was the role of unspecific symptoms as prodromal signs of a serious chronic disease condition long before the onset of the disease which is well established for a variety of disease outcomes (e.g. acute coronary syndrome) in internal medicine. However, beyond the known premonitory signs of an acute hyperglycaemia (e.g. polyuria, polydipsia, weight loss), no such study has examined the role of an unspecific symptom picture for T2DM development several years before diagnosis (to the best of our knowledge).

In a cross-sectional study we published recently (Lukaschek et al. 2013), a chance finding of an unadjusted, highly significant association of unspecific somatic symptoms with T2DM and prediabetes attracted our special attention and led us to the question of how such symptoms may affect T2DM risk in a prospective study with a long follow-up period. To highlight this perspective we changed the title now to:

“A pattern of unspecific somatic symptoms as long-term premonitory signs of type 2 diabetes: Findings from the population-based MONICA/KORA Cohort Study, 1984-2009” which describes our study more appropriately.

Moreover, we revised the conclusion part which is now stated as:

“This prospective population-based study found a substantial relationship of an elevated burden of unspecific premonitory symptoms and subsequent T2DM manifestation independent from established cardio-metabolic risk factors. Thus, a potential development towards the manifestation of T2DM may be considered if those signs are reported by patients. Further research is recommended to confirm or refute our findings and to obtain insight in potential underlying pathophysiological mechanisms.”

UPMS based only on the experience of this study is not
straightforward to assess, can be time consuming, and is not part of the routinely collected data for the purpose of risk screening where simplicity should be the rule.

Response: The reviewer is right that UPSM is currently not part of routinely collected data. And again, the usefulness of such an unspecific symptom pattern within an early detection assessment is not the subject of the present investigation. However, assessment of these symptoms may have a value on its own and may be even more useful in cases who are already suffering from more than one risk constellation (subjects with intermediate risks).

However, we would like to state that the documentation of a UPSM pattern consisting of several unspecific somatic symptoms would be easy to assess in routine settings with limited time costs. We added two sentences to the limitations part.

The proportion of participants with missing data on UPMS (10%) speaks to the challenges of assessing UPMS routinely.

Response: Data on UPMS was assessed by the MONICA psychosocial data set following recommendations of the WHO MONICA study protocol (WHO MONICA Project Principal Investigators: MONICA Psychosocial Optional Study. Suggested Measurement Instruments. Copenhagen: WHO Regional Office for Europe; 1989). This data was assessed in a sub-group (n=12,886) of the total MONICA Augsburg study population (n=13,426). The “real” number of missing information on UPMS is lower than 10% (n=840). We included this information in the revised manuscript and rewrote the definition of the study population including a new reference.

Diabetes risk screening is not new and many simple risk factors have already been identified for this purpose. Many of these factors have already been combined into risk models for predicting diabetes occurrence, including interestingly, some based essentially upon non-invasively measured predictors which have been shown to perform well across countries in Europe (Lancet
Diabetes Endocrinol. 2014 Jan;2(1):19-29.). In this context what is expected of new investigators is not to make claims of utility of biomarkers based on small size hazard ratios or Kaplan-Meier separations, but to really follow the necessary steps involved in such an assessment.

This should include extending the current analyses by actually constructing predictions models from the current data based on common predictors of diabetes, then expanding these models by incorporating UPMS and comparing the performance of the two sets of model though c-statistics comparison augmented if needed with the computation of novel measures such as the integrated discrimination improvement or the net reclassification improvement.

Response: We agree with the reviewer that an additional analysis regarding the predictive value of UPMS on T2DM risk is important to report. Therefore, we examined how the UPMS improved the predictive ability of developing T2DM within the FU period by estimating the AUC (area under the curve), the IDI (integrated discrimination improvement) and the NRI (net reclassification improvement) following the approach of Pencina et al. (Statistics in Medicine 2008) as measurements for accuracy of T2DM risk prediction.

These analyses estimated that within 10 years, with adjustment for all cardio-metabolic risk factors (model 5), the AUC was 0.7995 in the model without and 0.7999 with the UPMS score indicating a very low improvement of predictive ability. Similar findings were observed when applying IDI and NRI. Nevertheless we think that our findings give important indications to consider a particular array of somatic symptoms as premonitory signs of T2DM within a long time period before clinical recognition.

In the revised manuscript, we provide these estimates for predictive ability of UPMS in the results, and include a sentence regarding the limitations in the discussion.

The authors will then be able to tell if UPMS adds discriminatory information to that based upon already accepted predictors. If so, then the must discuss the implication of motivating for UPMS assessment in routine setting. It is very likely that added
information if any will be very tiny to justify the challenges of incorporating UPMS measurement alongside traditional risk factors as suggested by the authors.

Response: *We revised and re-worded the conclusions of the manuscript to point out that it was not our intention to add UPSM to diabetes prediction scores.*

If the authors were to go this route, then the long discussion on the pathophysiology would be less useful for this paper.

Response: *We consider the paragraph addressing potential pathophysiological mechanisms of the UPMS-T2DM-risk relation as essential as it gives possible explanations for the risk increase by the UPMS score.*

Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests:
I declare that I have no competing interests

Reviewer’s report
Title: How useful is the assessment of an unspecific premonitory symptom pattern for the risk of newly diagnosed type 2 diabetes in the general population?
Version: 1 Date: 10 August 2014
Reviewer: Ali Abbasi
Reviewer’s report:
In this prospective cohort study, Baumert et al aimed to investigate the association between unspecific premonitory symptom pattern and T2D risk. This is a well-written study using a general population based study. However, there are concerns to be further clarified.
Response: We appreciate the careful reading and overall positive feedback of the reviewer.

They were aware of some limitation of observational studies; they could provide any other evidence, for instance accounting for competing risk?

Response: It cannot be excluded that our findings are affected by other diseases, especially by incident diseases within the follow-up period. We included the following sentence to the limitations in order to address this point: “Moreover, our findings may be affected by other incident diseases within the follow-up period which we are not able to assess.”

As they mentioned both outcome and the symptom pattern are based on self-report. They could explain or explore if patients were more likely to report symptoms?

Response: Among the eight single symptoms, T2DM cases reported to suffer significantly more pronounced pain in the joints, temporary shortness of breath, dizziness, feeling tired and insomnia than T2DM non-cases (p values <= 0.002). However, single symptoms may contribute their adverse impact on T2DM risk mainly in synergism with other symptoms. Thus the cumulative severity of symptom burden rather than suffering from single symptoms may increase T2DM risk. For this reason, we set the focus of our analyses on the symptoms score and not on the single items.

It should be noted that the evaluation of new incident cases is not based on self-reports but relies on patient records in hospitals or reports from physicians in charge of the patients.

Also, they mainly analyzed T2D risk, and they did not report whether data on CVD risk were available?

Response: The present study was performed under the patronage of the Competence Network for Diabetes Mellitus, subproject DIAMANT (DIAbetes and Mental Aspects NeTwork). This network has been sponsored by the German Federal
Ministry of Education and Research (BMBF) as part of the governmental program "Health Research: Research for People" and is aimed to improve the knowledge regarding prevention, treatment and development of diabetes mellitus. We agree with the reviewer that the potential impact of unspecific premonitory signs for CVD risk is also of great interest but unfortunately this issue was out of the scope of the present project. However, future investigations in this field seem to be worthwhile.

The authors could evaluate to what extent additional information about the score improve T2D prediction.

Response: We agree with the reviewer and performed an assessment of how the UPMS score improved the predictive ability of developing T2DM within the follow-up period by estimating the area under curve (AUC) as measurement for accuracy of T2DM prediction. Within 10 years, adjusted for all cardio-metabolic risk factors (model 5) the AUC was 0.7995 in the model without and 0.7999 with the UPMS score indicating a rather low improvement of predictive ability. Similar findings were estimated for other measure of predictive abilities (IDI, NRI).

In the revised manuscript, we added the estimated measures for predictive ability of UPMS to the results part and the Table 3 and include a sentence to the limitations part.

Did the study have sufficient power to test the components of the score?

Response: As explained above, the rationale behind defining a score was that not one single symptom alone may have an impact on T2D risk but a combination of these components, i.e. the cumulative severity of symptom burden rather than suffering from single symptoms has an impact on T2DM risk. The higher the severity the higher the T2DM risk may be.

The authors examined potential impact of sex or age on the associations, but it is still unclear if the observed estimates were consistent over time, also provide separate analyses for 5-year, 5-to 10-year, and 10-year risk and for those who
developed T2D after 5 years.

Response: We tested the PH assumption before the analyses required for applying the Cox regression which revealed that proportional hazards could be assumed over the observation period. However, to exclude subjects potentially being in pre-diabetic states, we repeated the Cox regression for excluding subjects with less than 2 years of follow-up which was already reported in the manuscript (HR: 1.019, 95% CI: 1.003-1.034, p value: 0.018 in model 5). An analogous analysis excluding subjects with less than 5 years of follow-up led to similar estimates; the hazard ratio in model 5 was 1.016 (95% CI 0.999-1.033); however, the UPMS effect on T2DM risk was not significant anymore (p value 0.072).

Additionally, to assess the short term impact on T2DM risk, we performed a Cox regression for the risk to develop T2DM within 5 years. The association showed a HR of 1.04 (95% CI 1.01-1.07, p value 0.006) in model 1 and a HR of 1.033 (95% CI 1.003-1.063, p value 0.033) in model 5. We provided this finding in the revised manuscript as a further sensitivity analysis.

Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.