PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Study Protocol: A prospective cohort on non-communicable diseases among primary healthcare users living in Kosovo (KOSCO)
AUTHORS	Obas, Katrina; Gerold, Jana; Bytyçi-Katanolli, Ariana; Jerliu, Naim; Kwiatkowski, Marek; Ramadani, Qamile; Statovci, Shukrije; Zahorka, Manfred; Probst-Hensch, Nicole

VERSION 1 – REVIEW

REVIEWER	Max Bachmann Norwich Medical School University of East Anglia Unikted Kingdom
REVIEW RETURNED	11-May-2020

GENERAL COMMENTS	1/ Major comment. This a well written protocol for a cohort study, including a thorough review of relevant literature. My main concern is that, while the main focus of the study appears to be on effects of depression on changes in blood pressure and blood pressure control, the title and objectives appear very much broader than that, including other physical and mental conditions, and including quality of care. My main suggestions are that either this focus is made clearer in the title and objectives, or that the introduction and statistical methods are expanded to match the original title and objectives. a/ Please consider changing the title to “Study Protocol: A prospective cohort study of depression, blood pressure and other non-communicable diseases among primary healthcare users living in Kosovo” b/ Objective 1 includes assessing prevalence of NCD control. NCD control needs to be defined in the methods, in relation to the data to be collected. Is it just blood pressure control, or does it include control of other NCDs? c/ Objective 2: Please consider changing “EFFECT Of primary healthcare service quality and patient satisfaction and NCD outcomes” to “ASSOCIATION BETWEEN primary healthcare service quality and patient satisfaction and NCD outcomes”. Such associations might be at least partly due to unmeasured confounders, or to reverse causation, and thus not entirely causal.

	d/ Objective 3, to assess the effect of primary care interventions; it is unclear from the protocol how such an effect could be assessed without controls. Please consider deleting this objective, or explain in methods how it could be met. If you keep it, then the potential mediators and modifiers of interest should be mentioned in the statistical methods. e/ Objective 4, to assess the predictors of NCD incidence and NCD control. The methods only cover predictors of blood pressure control and, implicitly, blood pressure control. Again, the potential mediators of interest should be mentioned in methods. It seems unlikely that the proposed sample size, intended for assessing the association between baseline depression and change in blood pressure, will be large enough to provide sufficient power to predict the incident NCDs during 12 months follow-up. 2. Minor comments a/ The study population should be defined near the beginning of methods (and not only later under Recruitment), for example, “The study population comprises adults aged 40 years or older attending primary healthcare facilities in 12 municipalities of Kosovo”. b/ Please state how many primary healthcare facilities will be included in the study. c/ Sample size calculation. Please clarify that the blood pressure parameters of interest in this section are the mean and standard deviation of the CHANGE in blood pressure (where change is the outcome), and the mean and standard deviation of the RESIDUAL (with follow-up blood pressure as the outcome, and with adjustment for baseline blood pressure). d/ The sample size calculation should account for the cluster sample design, ie sampling of individuals within health facilities. e/ Please ensure that the statistical methods relevant to all of the objectives are described, as suggested in section 1 above.

REVIEWER	João Mário Pedro EPIUnit, Instituto de Saúde Pública, Universidade do Porto, Portugal
REVIEW RETURNED	11-May-2020

GENERAL COMMENTS	A good effort to start an important epidemiological survey in a geographical area needed of evidence in NCDs. Minor changes are needed for a approval. In line 354 you need to change the date from March 2019 to March 2020. You need to clarify that the follow-up are in a annual bases, with a touch-base in mid-year... not a 6 months follow-up. Before you have results for changes in this risk factors and impact of education you will need more than 1 year follow-up. Cardiovascular diseases are a group of diseases, not a single disease. In this way, please refer always in plural. You

	should included mental health or mental disorders in your keywords.

VERSION 1 – AUTHOR RESPONSE

Reviewers' comments to the authors:

Reviewer 1

1. Major comment. This a well written protocol for a cohort study, including a thorough review of relevant literature. My main concern is that, while the main focus of the study appears to be on effects of depression on changes in blood pressure and blood pressure control, the title and objectives appear very much broader than that, including other physical and mental conditions, and including quality of care. My main suggestions are that either this focus is made clearer in the title and objectives, or that the introduction and statistical methods are expanded to match the original title and objectives.

   Author response: Thank you for your kind comment and for your concern regarding the consistency throughout the manuscript. We recognize that the title and goal of the cohort are broad, while the introduction and objectives are more specific. Our cohort inherently has several objectives which fit under our overarching goal because the study was conceptualized and implemented in collaboration between scientists and healthcare workers to build a common platform to improve the quality and availability of epidemiological evidence on non-communicable disease in Kosovo. We therefore would prefer to retain the original title and goal of the study, since the eventual aim is to expand the cohort with other specific objectives related to NCDs. We however agree with the reviewer that the manuscript requires more consistency, therefore we have now reformulated the objectives and outlined the statistical methods by objective to better reflect the three focus areas described in the introduction. We hope that these changes convey that the objectives included in the protocol are starting points in contributing evidence on the most pressing issues on NCDs in Kosovo.

a. Please consider changing the title to "Study Protocol: A prospective cohort study of depression, blood pressure and other non-communicable diseases among primary healthcare users living in Kosovo"

   Author response: Thank you for the suggested change to the protocol title. As expressed in our response above, we would prefer to retain the original title, for the reason that we would like the cohort to remain a common platform for collaboration on important and highly needed NCDs research in Kosovo. The objectives, which are narrower in scope, are starting points towards the study's goal.

b. Objective 1 includes assessing prevalence of NCD control. NCD control needs to be defined in the methods, in relation to the data to be collected. Is it just blood pressure control, or does it include control of other NCDs?

   Author response: Thank you for bringing these important points to our attention. We have now stated the specific NCDs we will be looking at in Objective 1 on **page 10**. We have also defined the variables relating to Objective 1 (including control of each NCD) on **pages 19-20.**

c. Objective 2: Please consider changing “EFFECT Of primary healthcare service quality and patient satisfaction and NCD outcomes” to “ASSOCIATION BETWEEN primary healthcare service quality and patient satisfaction and NCD outcomes”. Such associations might be at least partly due to unmeasured confounders, or to reverse causation, and thus not entirely causal.

   Author response: Thank you for bringing this important detail to our attention. We have decided to merge objectives 2 and 3: objective 3 now becomes the primary analysis stated in the new objective 2 **(page 11)** and objective 2 becomes the secondary analysis mentioned in the variable definitions **(page 20-21)** and statistical methods **(page 24).** This new objective and analysis plan are more coherent with our research interests expressed in the introduction.

d. Objective 3, to assess the effect of primary care interventions; it is unclear from the protocol how such an effect could be assessed without controls. Please consider deleting this objective, or explain in methods how it could be met. If you keep it, then the potential mediators and modifiers of interest should be mentioned in the statistical methods.

   Author response: We agree with the reviewer’s comment, and appreciate that this has been brought to our attention. We have decided to keep the objective. To that end, we have further described the intervention on **page 21**, and specified that the intervention is non-randomized in the abstract (**page 2**), strengths and limitations of the study (**pages 27**), the objective (**page 11**), definition of main variable (**page 21**), and statistical methods (**page 24**). We have also changed the wording from “effect” to “longitudinal relationship” between the exposure and outcome in the objective (**page 11**). We have included separate statistical methods for this objective on **page 24**, where the effect modifiers and mediators are now mentioned. We have also stated there that in the absence of randomization and pure controls for this intervention, we have the following primary strategy: we will make comparisons between participants who have chosen not to participate in the intervention (motivational counselling). We have further added a statement on **page 27** that acknowledges the limitation of the analysis in the absence of randomization of the intervention.

e. Objective 4, to assess the predictors of NCD incidence and NCD control. The methods only cover predictors of blood pressure control and, implicitly, blood pressure control. Again, the potential mediators of interest should be mentioned in methods. It seems unlikely that the proposed sample size, intended for assessing the association between baseline depression and change in blood pressure, will be large enough to provide sufficient power to predict the incident NCDs during 12 months follow-up.

   Author response: Thank you for your comment, and please see the new objective on **page 11** where only the focus on blood pressure as the main outcome was retained. The objective now reflects the variables mentioned in the primary analysis in the statistical methods (**pages 24-25**). Potential mediators for this objective have now been specified in the statistical methods. Hypertension incidence and control are now described as secondary outcomes.

   In regards to our longitudinal study power calculation (**pages 22-24**), it indeed only relates to the main analysis assessing the association between baseline depression and change in blood pressure (and not incidence of hypertension), which would require a sample size of 883 for a power of 90% in case of a small effect (tau=0.25) and loss to follow-up of 20%. We considered the loss of power due to control for confounding and discretization of blood pressure measurement to a binary outcome (hypertension), therefore increased the sample size to 1000 participants. Mediation was not considered in our power calculation, but we would like to note that the total follow-up period for the cohort is 5 years and annual data collection allows us the opportunity for mediation analysis. We apologize that this was not

clear and have now clarified on **page 3** (study strengths and limitations) and on **page 11** (study design). Given the limitations in power for mediation analyses we prefer to not make this point more prominent and we hope the reviewer agrees with this decision to not overstate the value of the cohort with regard to mediation analysis.

2. Minor comments

a. The study population should be defined near the beginning of methods (and not only later under Recruitment), for example, “The study population comprises adults aged 40 years or older attending primary healthcare facilities in 12 municipalities of Kosovo”.

   Author response: Many thanks for the comment. The text about participants has been moved to the third position in the methods section as per STROBE checklist **(page 12).**

b. Please state how many primary healthcare facilities will be included in the study.

   Author response: Thank you for your comment. The fact that there is one MFMC per municipality is now specified on **page 4** in the introduction and **page 11** in the setting description, and that there are 12 MFMCs included in the study on **page 11**.

c. Sample size calculation. Please clarify that the blood pressure parameters of interest in this section are the mean and standard deviation of the CHANGE in blood pressure (where change is the outcome), and the mean and standard deviation of the RESIDUAL (with follow-up blood pressure as the outcome, and with adjustment for baseline blood pressure).

   Author response: Thank you for the comment. We made two sample size calculations, and we apologize that it was not presented clearly. We now removed the power calculations for the cross-sectional study because the cross-sectional analysis is not our primary interest. The power calculation now only refers to the longitudinal study of depression and change in blood pressure (**pages 22-23**). As the first calculation was for the cross-sectional association, we mentioned the outcome as blood pressure since change is not possible. For the calculation of the longitudinal study, we specified change in blood pressure as the outcome in the original submission and so it is in line with your proposal.

d. The sample size calculation should account for the cluster sample design, ie sampling of individuals within health facilities.

   Author response: Thank you for the comment. We apologize that this consideration was not clear in our original submission. It was not included in the first section on power calculation labeled “power calculation without local effects”. We accounted for clustering in the section after it called “power in the presence of clustering” **page 23**, which states that the study retains sufficient power as long as the overall effect of depression dominates the local variation in that effect (tau much greater than rho). To improve clarity that clustering effect was taken under consideration, we placed it as a sub-topic under a new larger section called “power calculation”.

e. Please ensure that the statistical methods relevant to all of the objectives are described, as suggested in section 1 above.

   Author response: Many thanks for this helpful comment. To ensure this, we have described the statistical methods by objective (**pages 24-25**).

Reviewer 2

1. A good effort to start an important epidemiological survey in a geographical area needed of evidence in NCDs. Minor changes are needed for a approval.

   Author response: Thank you very much for this positive feedback!

2. In line 354 you need to change the date from March 2019 to March 2020.

   Author response: Thank you for noticing this error. The date has been changed to March 2020 on **page 11.**

3. You need to clarify that the follow-up are in a annual bases, with a touch-base in mid-year... not a 6 months follow-up.

   Author response: Thank you for your suggestion for clarification. The study design (**page 11**) now specifies that follow-ups are conducted annually in 2 phases.

4. Before you have results for changes in this risk factors and impact of education you will need more than 1 year follow-up.

   Author response: Thank you for this important comment. We have planned a total follow-up time of 5 years minimum for the cohort, with annual follow-ups to permit mediation analysis. This has been now specified in the study design (**page 11**).

5. Cardiovascular diseases are a group of diseases, not a single disease. In this way, please refer always in plural.

   Author response: Thank you for the comment. Where there is mention of CVD, it has been corrected to the plural form.

6. You should included mental health or mental disorders in your keywords.

   Author response: Thank you. “Mental health” and “mental disorders” were added in the keywords