Author’s response to reviews

Title: Trends in electrocardiographic abnormalities and risk of cardiovascular mortality in Lithuania, 1986-2015

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Reply to Editor and Reviewers’ Comments

Dear Editor and Reviewers,

Thank you for your helpful critique of our manuscript. We hope that we have successfully addressed all of the concerns raised, and we believe that the manuscript has been substantially
improved. Our detailed responses to the comments and the description of changes we have made to the manuscript are provided below.

Editor

‘As this is a secondary data analysis article, please state in the Methods and Declarations ("Ethics approval and consent to participate") whether the databases are publicly available or not. If they are not, please include a statement that all necessary permissions were obtained to access and use the data and who gave this permission.

Response:

We would like to inform you that primary data analysis was used in preparing the manuscript. All authors of the manuscript participated in the surveys and/or follow-up study. Lithuanian University of Health Sciences that is our employer is the owner of the databases used for preparing of the manuscript. We do not need any permission to access and use the data for analysis and publication.

Please note that listed author contributions of DL does not automatically qualify them for authorship. Contributing to the writing of the manuscript is not sufficient to qualify for authorship

Response:

DL participated in data collection and analysis. She was one of the authors of the idea of the manuscript. By the mistake, it was not mentioned. We added to authors’ contributions that DL developed the idea for this manuscript and the data analysis plan.

Reviewer 1 (Juhani Juhani)
‘The authors have made most of the suggested revisions to the manuscript. Although there were no point-by-point reviewer response letter included and additional references from Nordic countries large epidemiological ECG studies were not included’

Response:

Because of a very long review period, we have been asked to resubmit the manuscript as a new one. Submission process did not allow us to include response to the reviewer comments. Moreover, we did not receive any request from the Editors to include the response. However, we tried to address all of the concerns raised. Sorry for not including additional references from Nordic countries. In this version of the manuscript, we added two additional references from Norway and Finland (references No 41 and 43 in the Reference list) and discussed them in the Discussion section.

Reviewer 2

‘Respondents with clinically diagnosed documented acute myocardial infarction (MI) were excluded from analysis. In total, data of 11,904 individuals (5,427 men and 6,477 women) were analysed.” Comment: Why was only this group excluded? There is a need to define all the Inclusion and Exclusion criteria for the surveys’

Response:

According to the suggestion of Reviewer 2 and Reviewer 3, the Methods section was edited and exclusion criteria were explained: ‘Participants with missing or inadequate ECG data (1.2%, similar numbers in all surveys) were excluded. Respondents with clinically diagnosed documented acute myocardial infarction (MI) were also excluded from analysis (the proportion of excluded respondents was 7.5% (8.5%, 6.0%, 7.1%, 6.5%, and 7.0% in the respective surveys). In total, data of 11,904 individuals (5,427 men and 6,477 women) were analysed.

‘Follow up data of the individuals from Kaunas surveys were used for analysis of associations between ECG abnormalities and CHD or CVD mortality risk (n=6,090). Follow up period started from the health examination date and finished on 31st of December, 2015. The mean duration of follow-up was 12.8+7.79 years (12.5+7.82 years in men and 13.1+7.75 years in women).’
Comment: Please, this should be in the Results Section’

Response:
This paragraph was moved to the Results section

‘Were the interpretation of the ECG findings in the survey performed by trained cardiologists? Was there any data quality assessment of the reporting of the ECGs? E.g., concordance in reports by two persons or two cardiologists?’

Response:
Following the comments by Reviewer 2, we explained ECG coding procedure in the Methods section: ‘ECG records were read by 2 independent experienced coders (trained cardiologists) using the 1982 edition of the Minnesota Code (MC) [14]. Discrepancies between two coders were resolved by a senior coder (experienced cardiologist).’

‘The Limitations of the study is well reported. However, I feel the authors need to highlight the potential limitations of poor response rate. It may be likely that healthier persons may want to decline from participating in the survey?’

Response:
The potential limitation of low response rate was added to the Discussion section:

‘Finally, the response rates lower than 70% might have resulted in selection bias and potential underestimation of the prevalence of ECG abnormalities, if non-response was associated with a more adverse risk profile. However, it is unlikely that the strength of this association has changed substantially between the surveys. This assumption together with the relatively similar response rates over time minimizes the potential impact of non-response on our estimates of the trends in the prevalence of ECG abnormalities.’

Reviewer 3 (Denes Stefler)
‘In the methods section, some more detail is needed in the description of the study sample. In the text, or potentially in supplementary table, please provide response rates for all four survey waves separately. Also, please indicate how many (what proportion of) participants were excluded due to previously diagnosed MI in each of the waves.’

Response:

Addressing the reviewer’s comment, we modified the Methods section adding response rates and proportions of excluded individuals with previously diagnosed MI: ‘The response rates in the five cross-sectional surveys were 70.2%, 69.6%, 58.6, 62.4%, and 58.1% respectively. Respondents with clinically diagnosed documented acute myocardial infarction (MI) were also excluded from analysis (the proportion of excluded respondents was 7.5% (8.5%, 6.0%, 7.1%, 6.5%, and 7.0% in the respective surveys).’

How were individuals invited to the study? Were they sent letters or via phone calls?

This sentence was included into Methods section: ‘The selected individuals were invited to health examination sending them the invitation letters by mail.’

‘Regarding the measurements, please state where the measurements were taken place (in hospital? In GP office? at home?) and who did the measurements (doctor? trained nurse?).’

Response:

This was clarified in the Methods section: ‘The measurements were taken in outpatient departments by the team consisting of trained doctors and nurses.’

‘Do the authors have any information on the participants socio-economic position (i.e.: education) and other chronic diseases? If they do, have they considered including them in the Cox models?’

Response:
We had information on the participants’ education level. Such variable was included into the Cox model; however, this was not indicated in the notes under the table 4 and 5. This mistake was corrected. Unfortunately, we had no information about the prevalence of other chronic diseases among study participants; therefore, we did not include it in the Cox models.

‘In table 4, please indicate the number of men and women who died during follow up due to CVD or CHD. Some of the associations are likely to be not significant only because of the low number of outcomes and the consequent inadequate statistical power (i.e.: ischemia or possible MI vs CHD mortality in women). Also in table 5, the differences in NRI between men and women are probably only the result of the different statistical power in these groups (point estimates are identical or very similar).’

Response:
We indicated the numbers of men and women who died during the follow up due to CVD and CHD in Tables 4 and 5.
We agree with the reviewer’s comment and discuss this limitation in the Discussion section: ‘The low prevalence of some ECG abnormalities could be another limitation of our study. A relatively small number of deaths within ECG categories may limit the power to demonstrate the association between ECG abnormalities and mortality risk.’

‘It is interesting to see that the prevalence of ST abnormalities (and the related ischemia) was more than double in women compared to men in 1986-87 but the rates were similar in 2006-08. The authors provide some explanation for this (i.e.: change in lipid levels), but can the differences in lipid levels explain the large gender gap in 1986-87?’

Response:
The reviewer raised an interesting question about possible reasons of decreasing trends in the prevalence of ischemia in ECG of women that was associated with the decrease in the difference of the prevalence of ST-T abnormalities between men and women. We mentioned some explanations in the Discussion section including positive changes in nutrition habits, lipid profile and the prevalence of obesity that were more pronounced in women than in men. It should be mentioned that ‘the reduced prevalence of ischemia on ECG of women was associated with decreasing trends in CVD mortality among Lithuanian women between 1985 and 2013’ [11].
men, the reduction of CVD mortality was observed only from 2008’. These sentences were added to the Discussion section.

‘The conclusion in the abstract and in the manuscript text is just the repetition of the study’s main findings. It would be preferable to add some thoughts about the potential clinical and public health implications of these findings.’

Response:

Following the reviewer’s advice, the conclusions were edited: ‘In 1986-2008, the decreasing trends in the prevalence of ischemia on ECG in women and increasing trends in the prevalence of left VH in men were observed. ECG abnormalities were associated with higher risk of CVD mortality and modestly improved the prediction of CVD mortality beyond traditional CVD risk factors. Given the wide availability, low cost and safety, the ECG might be used to improve CVD risk prediction and to identify the individuals for more intensive preventive interventions. Further studies are needed to ascertain whether ECG should be incorporated in routine screening.’

‘In the limitations, please add some comments about the moderate response rates and their potential implication on the generalisability of the findings.’

Response:

As the Reviewer 2 also recommended, such limitation was added: ‘Finally, the response rates lower than 70% might have resulted in selection bias and potential underestimation of the prevalence of ECG abnormalities, if non-response was associated with a more adverse risk profile. However, it is unlikely that the strength of this association has changed substantially between the surveys. This assumption together with the relatively similar response rates over time minimizes the potential impact of non-response on our estimates of the trends in the prevalence of ECG abnormalities’.

‘Abstract line 38: The HR for the association between possible MI and CVD death for women is missing.’
Response:

We added the missing HR values for the association between possible MI on ECG and CVD for women in the abstract.

‘Background page 3 line 28: please add "age-standardised" before the term "mortality rate".’

Response:

We added in the indicated page “age-standardised” before the term “mortality rate”.

Reviewer 4 (Domantas Jasilionis)

‘The authors restrict their study to the period until 2008. I would recommend to add some information about developments after 2008 which marks the beginning of the period of remarkable mortality decline in Lithuania. It would be interesting to have at least a paragraph about a more recent decline in CVD mortality and its sustainability in the future in the context in the changing risk factors. This information can be obtained from relevant literature, published statistics, and smaller scale studies. It would be also desirable to have a short description of recent changes in treatments and prevention. Finally, few sentences are needed to highlight public health importance of the observed long-term and ongoing changes for general CVD mortality trends and reducing the life expectancy gap against Western countries’

Response:

We would like to remind the reviewer that the last cross-sectional survey with ECG registration was performed in 2008; however, data of follow up for death from CVD was presented until 31st of December 2015. Comprehensive analysis of the trends in total and cause specific mortality of Lithuanian population and their associations with the trends in risk factors during the last decades were presented in our previous article (11 in the Reference list).
Addressing the reviewer’s comment, we included several sentences about trends in mortality of Lithuanian population in relation to trends in ECG abnormalities to the discussion section:

‘The reduced prevalence of ischemia on ECG of women was associated with decreasing trends in CVD mortality among Lithuanian women between 1985 and 2013 [11]. In men, the reduction of CVD mortality was observed only from 2008. These positive trends could be attributed to a combination of long-term increase in income, improvements in health care, and implementation of public health programmes leading to changes in health behaviour of Lithuanian population.’

Respectfully,

On behalf of all authors,
Abdonas Tamosiunas