

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

## ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	A RANDOMIZED TRIAL EXAMINING CARDIOVASCULAR MORBIDITY AND ALL-CAUSE MORTALITY 24 YEARS FOLLOWING GENERAL HEALTH CHECKS – The Ebeltoft Health Promotion Project (EHPP)
<b>AUTHORS</b>	Bernstorff, Martin; Deichgræber, Pia; Bruun, Niels; Dalsgaard, Else-Marie; Fenger-Gron, Morten; Lauritzen, Torsten

## VERSION 1 – REVIEW

<b>REVIEWER</b>	Lasse Krogsbøll Bispebjerg Hospital, Denmark. Have authored a Cochrane review that included the present trial.
<b>REVIEW RETURNED</b>	22-Mar-2019

<b>GENERAL COMMENTS</b>	<p>Thank you for letting me review this clear and straightforward report of an important study in its field. I have the following comments:</p> <p>Abstract, conclusion Suggest bringing the phrasing in line that used in the conclusion. The phrase “little effect” is ambiguous. The phrase “No harms were registered” is not quite meaningful as the authors did not look for harms. I suggest removing it to avoid giving the wrong impression of having shown no harms.</p> <p>Page 10 line 17 - 25 Why do adjusted analyses in a randomized trial with neatly balanced baselines? Would be good if reasons were explained. The adjusted HR’s are also reported in the abstract, but why?</p> <p>Table 2 Could be amended to show or describe that half of the control group was censored after 15 years, rather than 24 years, which explains the confusing results in raw numbers, e.g. much lower mortality in the control group.</p> <p>Page 12 line 57 – 59 I don’t understand how spill-over effects can ameliorate the reduced contrast in the comparison between invited and non-invited that was introduced by randomising one quarter of the invited group to no health checks.</p> <p>Page 13 line 15-19: This speculation in the effect of statins on the effectiveness of health checks was not supported by the results of the Inter99 trial that ran from 1999-2009, i.e. in an era with much statin use. I</p>
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	<p>personally think it is a stretch to maintain this view after that trial came out.</p> <p>Page 13 line 22-25: I very much agree. The effects of health checks may be completely different in very poor countries.</p> <p>Pag 13 line 49-55: The lack of formalised follow-up of detected abnormalities means the trial was pragmatic and likely better reflects the effects health checks would have if implemented.</p> <p>Page 14 line 34-38 This sentence is misleading, as it does not mention the randomised comparison in ADDITION-Cambridge, but instead quotes other less important analyses from the ADDITION study. In the ADDITION study, only the Cambridge part studied the effect of screening for diabetes, as the other centres did not include unscreened control groups. ADDITION-Cambridge (Simmons 2012) did not find an effect on mortality. With 16,000 randomised participants and 10 years of follow-up, this is a highly relevant result that definitely should be mentioned if the authors really wish to discuss screening for diabetes in this paper.</p>
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<b>REVIEWER</b>	Tea Skaaby Frederiksberg Hospital Center for Clinical Research and Prevention Denmark
<b>REVIEW RETURNED</b>	29-Mar-2019

<b>GENERAL COMMENTS</b>	<p>Review BMJ Open March 2019</p> <p>The authors use the Ebeltoft Health Promotion Project (EHPP) as a randomised controlled trial to study the effect of general health checks on registry-based CVD and all-cause mortality. A total of 3,464 individuals were randomised as invitees (n = 2,000) or non-invitees (n =1,464). All participants were analysed by intention to screen. The authors found no statistically significant effect of general health checks on CVD or all-cause mortality. The authors concluded that there was little effect of general health checks offered to the general population on CVD or all-cause mortality. The study seems well done and the research question is interesting. I have the following comments:</p> <ol style="list-style-type: none"> <li>1. Have the authors considered competing risk regarding the CVD outcomes?</li> <li>2. Are there any differences in hazard ratios of ischemic heart disease and stroke?</li> </ol>
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#### VERSION 1 – AUTHOR RESPONSE

Reviewer 1 (Krogsbøll):

Thank you for letting me review this clear and straightforward report of an important study in its field. I have the following comments:

Authors: Thank you for this very encouraging overall response to our manuscript and for your concise and highly relevant suggestions below.

Reviewer 1:

Abstract, conclusion

Suggest bringing the phrasing in line with that used in the conclusion. The phrase “little effect” is ambiguous.

The phrase “No harms were registered” is not quite meaningful as the authors did not look for harms. I suggest removing it to avoid giving the wrong impression of having shown no harms.

Authors: We agree, both suggested revisions have been performed (and the abstract extensively restructured to comply with another editorial request).

Reviewer 1:

Page 10 line 17 - 25

Why do adjusted analyses in a randomized trial with neatly balanced baselines? Would be good if reasons were explained. The adjusted HR's are also reported in the abstract, but why?

Authors: We fully agree that adjustment should be unnecessary (but, on the other hand, unlikely to do much harm) in the comparison of the randomized groups. Contrarily, adjustment is clearly warranted for the supplementary comparison with the Danish background population. We acknowledge that “choosing the optimal analysis for the primary comparison” may be a better approach.

The abstract has been revised to mention only unadjusted results for the comparison of the randomized groups, and the mentioned passage in the Methods section has been revised accordingly.

Reviewer 1:

Table 2

Could be amended to show or describe that half of the control group was censored after 15 years, rather than 24 years, which explains the confusing results in raw numbers, e.g. much lower mortality in the control group.

Authors: Agreed, we have added clarification.

Reviewer 1:

Page 12 line 57 – 59

I don't understand how spill-over effects can ameliorate the reduced contrast in the comparison between invited and non-invited that was introduced by randomising one quarter of the invited group to no health checks.

Authors: Completely agreed. This applies only for the comparison of invitees to the general Danish population. This has been clarified in the text.

Reviewer 1:

Page 13 line 15-19:

This speculation in the effect of statins on the effectiveness of health checks was not supported by the results of the Inter99 trial that ran from 1999-2009, i.e. in an era with much statin use. I personally think it is a stretch to maintain this view after that trial came out.

Authors: We agree. Our intention with the cited passage was to express scientific humility due to the fact that temporal generalizability can (and should) always be discussed in studies with long follow-up periods. However, we acknowledge that it could be read otherwise (i.e. as a claim that our intervention has an effect although it is not documented in the data). The paragraph has been extensively revised for clarification of this point.

1. Extent of undertreatment and overtreatment with cholesterol-lowering therapy according to European guidelines in 92,348 Danes without ischemic cardiovascular disease and diabetes in 2004-2014. 2017;257:9–15. doi:10.1016/j.atherosclerosis.2016.11.025

Reviewer 1:

Page 13 line 49-55:

The lack of formalised follow-up of detected abnormalities means the trial was pragmatic and likely better reflects the effects health checks would have if implemented.

Authors: We agree that general health checks being performed by a third party (rather than at the GPs office) is likely, making Inter99 a pragmatic trial, and we have added this important point to the manuscript.

Reviewer 1:

Page 14 line 34-38

This sentence is misleading, as it does not mention the randomised comparison in ADDITION-Cambridge, but instead quotes other less important analyses from the ADDITION study. In the ADDITION study, only the Cambridge part studied the effect of screening for diabetes, as the other centres did not include unscreened control groups. ADDITION-Cambridge (Simmons 2012) did not find an effect on mortality. With 16,000 randomised participants and 10 years of follow-up, this is a highly relevant result that definitely should be mentioned if the authors really wish to discuss screening for diabetes in this paper.

Authors: Upon re-examining the referenced sentence we agree that the sentence does not accurately reflect the combined evidence from the ADDITION-trials. Thank you for pointing this out. We have culled the section.

Reviewer 2 (Skaaby):

The authors use the Ebeltoft Health Promotion Project (EHPP) as a randomised controlled trial to study the effect of general health checks on registry-based CVD and all-cause mortality. A total of 3,464 individuals were randomised as invitees ( $n = 2,000$ ) or non-invitees ( $n = 1,464$ ). All participants were analysed by intention to screen. The authors found no statistically significant effect of general health checks on CVD or all-cause mortality. The authors concluded that there was little effect of general health checks offered to the general population on CVD or all-cause mortality. The study seems well done and the research question is interesting. I have the following comments:

(Authors: Thank you for your on-point summary of our paper and for the highly relevant questions regarding the subject matter.)

1. Reviewer 2: Have the authors considered competing risk regarding the CVD outcomes?

Authors: Yes and no. As the primary outcome measure for CVD risk is an event hazard (ratio), there is no competing risk issue in the traditional sense ("Competing risks and the clinical community: irrelevance or ignorance?" by Koller et al, *Statistics in Medicine* 2012, could be a standard reference for this statement). Intuitively phrased: because the rate analysis approach intrinsically accounts for the amount of time persons are at risk of the event of interest, hazard ratios are not influenced by differences in the risk of competing events.

However, considered in full technical detail, it is true that a difference in the risk of complementary/competing events may (slightly) influence even hazard ratios, in that it could induce a skewed violation of the assumption of non-informative censoring. That would be the case, if our intervention prolonged the life (or the opposite) particularly for the most (or least) fragile persons.

In fact, this mechanism is not completely unlikely in the present study, but in light of the very small group differences in overall mortality, it will have absolutely diminutive impact of the results. We have chosen not to include this rather technical consideration in the manuscript, as we consider it likely to impart more confusion than clarification. Yet, we are fully open to divergent reviewer/editor opinions in this matter.

Reviewer 2:

2. Are there any differences in hazard ratios of ischemic heart disease and stroke?

Authors: We share the reviewer's curiosity with respect to these questions, which, however, we hesitate to pursue due to the combination of two important premises. Firstly, for the analysis of the composite CVD outcome, the statistical precision is low when considered in relation to the very small (null-like) effect of the intervention. Secondly, as the scope of the EHPP was prevention of CVD, there is no obvious reason to hypothesize a particular effect for IHD or stroke. Hence, we are concerned that reporting results for multiple subcategories of CVD (with low statistical precision) could be judged as an unjustified "fishing expedition" in the data.