A third perspective on the effects of general health checks may provide a less biased estimate (letter commenting J Clin Epidemiol 2016;71:120-2)

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A third perspective on the effects of general health checks may provide a less biased estimate (letter commenting J Clin Epidemiol 2016;71:120–2)

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Conflicts of interest: None.

We welcome the findings from Bender et al on the differences in effect between the two analytical perspectives on general health checks detailed in the Inter99 study (1). They present estimates of effects on total mortality and cardiovascular mortality based on the intention-to-treat (ITT) principle and on a participant-only analysis that compare participants to the intervention with participants in a sub-group of the control group that merely received a questionnaire on lifestyle. The analyses show a hazard ratio (HR) of 0.99 of death from the ITT analysis and a HR of 0.63 from the participant-only analysis. They conclude that 1) the ITT perspective clearly shows no effects, and 2) future purely participants-only analyses of health
checks should be interpreted cautiously as this perspective may overestimate the effects. However, in the present commentary we will nonetheless argue, that a third perspective in the form of a Complier Average Causal Effect (CACE) analysis may provide an even less biased estimate as this perspective is not subject to the same risk of bias as the ITT and the participant-only analyses (2,3). A CACE analysis basically asks the question “What if the intervention had also been available to the control group?” (4). It does this by comparing the risk of an outcome in the group of actual participants with the risk of a potential outcome in a hypothesized group of participants from the control group.

Two assumptions precede the CACE analysis: 1) People allocated to the control group have the same probability of non-compliance as do people allocated to the intervention group, 2) merely being offered the treatment has no effect on outcome (3). The Inter99 study complies with both. The control group was selected from the same geographic area as the intervention group and would therefore, in all likelihood, be expected to have the same probability of non-compliance. Further, past research indicates that merely being invited to a survey on lifestyle does not affect hard endpoints in a Danish context (5).

We undertook the following steps: 1) We calculated the number of hypothesized participants and non-participants in the control group from the total number of people allocated to the control group and the participation rate in the intervention group; 2) we calculated the total number of deaths in the group of hypothesized participants and non-participants in the control group from the actual deaths among the participants and non-participants in the intervention group. We know that 185 deaths occurred among 6091 participants in the intervention group, and that 406 deaths occurred among the 5538 non-participants (6). We also know that the non-participation rate in the intervention group is 5538/11629 = 48 %.
Therefore, if the control group was invited to preventive health checks this would result in 22853 non-participants. If we assume that the hypothesized non-participants have the same risk of death as the actual non-participants, this would amount to 1675 deaths. As the total number of deaths in the control group was 2547 we can estimate the number of deaths among hypothesized participants in the control group to 872.

Table 1 – Hypothesized number of participants/non-participants

<table>
<thead>
<tr>
<th>Study population at baseline (N)</th>
<th>Deaths after 10 years of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total intervention group</td>
<td>11629</td>
</tr>
<tr>
<td>Participants</td>
<td>6090</td>
</tr>
<tr>
<td>Non-participants</td>
<td>5539</td>
</tr>
<tr>
<td>Total control group</td>
<td>47987</td>
</tr>
<tr>
<td>Hypothesized participants</td>
<td>25134</td>
</tr>
<tr>
<td>Hypothesized non-participants</td>
<td>22853</td>
</tr>
</tbody>
</table>

From these figures we can now calculate a CACE estimate from the actual risks of deaths among actual participants (intervention group) and the risk of death among hypothesized participants (control group). We can also calculate an ITT-based estimate of the relative risks of death from the actual number of deaths in the intervention group and the control group. Lastly, we can calculate a per-protocol (PP) estimate of the effects on actual participants compared to the entire control group.

Table 2 – Three perspectives on the relative risks (RR) of death from general health checks

<table>
<thead>
<tr>
<th>Analytical perspective</th>
<th>Calculation</th>
<th>Relative risk (RR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT estimate</td>
<td>(591/11629)/(2547/47987)</td>
<td>0.96</td>
</tr>
<tr>
<td>CACE estimate</td>
<td>(185/6090)/(872/25134)</td>
<td>0.88</td>
</tr>
</tbody>
</table>
The ITT analysis shows a RR of 0.96. The CACE shows a RR of 0.88 and the PP a RR of 0.57.

The RR from the ITT analysis is not far from the hazard ratio (HR) of 0.99 described in the analysis by Bender et al (1). The RR of the PP analysis is lower than the HR of the participant-only analysis of 0.63. The difference is possibly due to confounding factors of the PP analysis.

As would be expected the CACE estimate is in-between the ITT estimate and the PP estimate (3).

We conclude that an ITT analysis should be supplemented by an analysis that is not subject to the ITT analysis-related risk of non-compliance bias, and we encourage researchers to base their interpretations of studies on health checks on multiple perspectives, this could include a CACE analysis or similar. We also encourage policy-makers to look beyond ITT based estimates for more complex and nuanced interpretations of the effects of preventive health checks as such an ITT-based perspective may well underestimate the effects, and fail to capture the complexity of implementing health checks.

References
HIGHLIGHTS

- A novel analytical perspective on general health checks may provide a less biased estimate of the long-term effects
- Complier average causal effects (CACE) analyses on data from the Inter99 study show a 12% reduction in a 10 year risk of dying
- Researchers and policy-makers should consider other perspectives than the intention-to-treat (ITT) when interpreting the effects of health checks