LETTERS TO THE EDITOR

Response to letter to editor "Only ITT analysis provides information about the actual effects of a health policy":
Assessment of health policy effects of health checks requires a broader perspective than the ITT

We thank Bender et al for their reply and will briefly provide some comments. With its firm focus on internal validity, a randomized controlled trial (RCT) is first and foremost used to estimate intervention effects. Why else use such a firm design? In our reply to the original letter, we merely argued that under the assumption of noncompliance bias, that is first, incomplete participation, and second, differences between actual participants and nonparticipants, then a complier average causal effect (CACE) analysis will provide a less-biased estimate of the intervention effects (not the population effects) than an intention to treat (ITT) analysis and a per-protocol analysis [1]. In a CACE analysis, the intervention effect is estimated by comparing the mortality rate among actual participants and the would-have-been participants in the control group had they received the intervention. As such, a CACE actually intends to eliminate the bias seen between participants and nonparticipants by applying the counterfactual condition to causal inference in RCTs with incomplete participation. Therefore, we do not agree with Bender et al when they state that "the analyses performed by the authors are heavily biased—close to useless." [2]. On the contrary, an estimate of the intervention effect derived from a CACE analysis may be a valuable and less-biased supplement to estimates derived from ITT and per-protocol analyses.

In their original letter, Bender et al conclude that "In the future, we encourage researchers to be cautious when basing conclusions on results from effect analyses restricted to participants, as these results most likely will overestimate effects of general health checks." [3]. Because population-level effects from RCTs may well differ from real-world implementation, we add that researchers and policy makers should be cautious to base conclusions solely on ITT analyses derived from RCTs with an obvious noncompliance bias. Assessment of population-level effects of health checks may require studies that (1) capture the clinical complexity of health checks, (2) show effects on those who actually may benefit from health checks and not merely assess the effects on the general population whatever their risk and former health care usage, and (3) allow for changes to the intervention during implementation, to embrace contextual influences and new evidence. This is not an easy task and one that will require a broader analytical perspective than that of the RCT combined with an ITT.

Hard statements on the population-level effects of general health checks from RCTs may be convincing to policy makers but not fruitful to the scientific debate. We like to push a more nuanced debate informed by results from RCTs, observational studies, qualitative studies, and studies of contextual factors and use new designs and research methodologies to evaluate health checks and not just rely on the ITT. The first step is to come to some kind of agreement in the research community to move forward scientifically and to point to the direction. In our understanding, this will be more fruitful in a push for a more evidence-based use of health checks.

Finally, we support the statement of Bender et al that health checks may well be effective at an individual level. We furthermore suggest that the next step is to move from "What is the effect of health checks?" to "How do we translate the intervention effects from RCTs to the clinical setting and to a real-world population-level setting in such a way that both the intervention and population-level effects may be assessed while scaling up?".

Lars Bruun Larsen*
Trine Thilsing
Jens Sondergaard
Department of Public Health
Research Unit of General Practice
University of Southern Denmark
J.B. Winsløws Vej 9A DK-5000 Odense

Anne-Louise Bjerregaard
Department of Public Health
Institute of General Medical Practice
Aarhus University
Bartholins Allé 2 DK-8000 Aarhus C
*Corresponding author. Tel.: +45-65503058.
E-mail address: lblarsen@health.sdu.dk (L.B. Larsen)

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Only ITT analysis provides information about the actual effects of a health policy - Author response

We thank Bruun Lassen et al for their interest in our Inter99 study. Bruun Lassen has performed a CACE analysis, which compares mortality among actual participants of the intervention group with a hypothesized group of participants in the control group in the Inter99 study [1]. The authors suggest that there might be a beneficial effect of the Inter99 study on total mortality and argue that CACE analyses might be a more realistic approach to evaluate the effect of health checks.

Bruun Lassen has however missed an important information in our method section: in the Inter99 study, there was an oversampling of middle-aged persons in the intervention group and the proportion of older persons aged 55 or 60 years was considerably higher in the control group (31%) compared to participants in the intervention group (24%); thus, it was expected that there would be more deaths in the control group. Therefore, the CACE analyses performed by the Bruun Lassen et al. are not meaningful. In addition, despite the randomization, a larger proportion of the intervention group was of Danish/Western origin, had a better socioeconomic profile, and was healthier than the random sample of the control group. Other confounders may as well be unevenly distributed [2].

We agree with Bruun Lassen that it is important to discuss use and development of new statistical approaches. The intention to treat (ITT) approach might be regarded as "worst-case scenario" as it implies that participants are analyzed according to their original allocation. Studies with many nonparticipants or noncompliant persons cause speculations, "What if…?," and it is indeed very tempting to modify the ITT approach. A recent Cochrane review identified almost 500 studies using modified ITT analyses (primarily as secondary analyses), but the descriptions were very ambiguous indicating that modified ITT analyses are interpreted very differently and are difficult to handle [3].

We do not understand why Bruun Lassen uses the term "noncompliance bias" in relation to ITT analyses, as this is a premise: assessing effects of randomized controlled trials (RCTs) disregard of participation, compliance, and maintenance of treatment. We believe it is strength that ITT analyses provide information about the effectiveness of a performance under "real-world" conditions, in this case, the actual effects of a health policy, without a "What if…?".

Some lifestyle interventions are effective at individual level but apparently, they do not work at population level, when included in a screening program in a general population [4]. The possibility that health checks do not work is counterintuitive and it has been argued that health checks would obtain better results if all invited persons participated. However, the Inter99 study indicates a deleterious effect among women in the intervention group living in high-participation areas [5]. So, the question is not only whether it is possible to motivate nonparticipants to join such studies but also whether it will be of any benefit or might have harmful effects, e.g., due to overdiagnosis.

Randomized controlled trials using modified ITT analyses are increasingly being published, but we strongly believe that the ITT principle without modifications, without any "What if…?," should continue to be the gold standard of evidence in all RCTs.

Anne Mette Bender
Department of Public Health
University of Copenhagen
Copenhagen, Denmark

Charlotta Pisinger*
Centre for Clinical Research and Disease Prevention
Bispebjerg and Frederiksberg Hospital
The Capital Region
Copenhagen, Denmark

Torben Jørgensen
Department of Public Health
Faculty of Medical Sciences
University of Copenhagen
Copenhagen, Denmark
*Corresponding author. Tel.: +4538163055.

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