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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].

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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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Issues in interpreting and estimating the excess risk in case of count data

1. On the interpretation of the excess risk

Redelmeier, D. and Tibshirani, R. (2018) [1] introduce the concept of "excess risk" for matched studies when outcomes are count variables. Authors suggest the excess risk as an effective measure of exposure for people whose observed individual outcome (in the case of the article, "deadly accident" vs. "no deadly accident") depends on the exposure status itself. I believe such interpretation is questionable for three reasons:

1. The outcome is a stochastic measure, so for which people exposure status is decisive (i.e., they would have the outcome under one treatment status and would not have it under the alternative one) also depends on a random part. On the contrary, authors seem to suggest that whether the outcome changes or not depending on exposure status is a deterministic variable, the stochastic part only intervening in deciding whether such people would undergo the event only as exposed or only as unexposed.
2. One cannot rule out that, even in case there is no effect of the exposure at the global level, there are some people affected by it. For example, if there are 119 car accidents in a day in case of election and 119 in case of no election, it could happen that there are some people only having the accident in case of elections and others only in case of no-election (it may even happen that 238 different people would be involved, so that no one would have the accident under both the factual and the counterfactual situation). This holds unless we want to assume that, for every election day, only one possible effect may take place for each person (i.e., there are either only people who would not undergo the accident as unexposed but would as exposed or only people who would undergo the accident as unexposed but would not as exposed).
3. By calculating, for each observation, the difference with respect to its matched lowest value, we are also including differences between controls, i.e., between individuals sharing the same exposure status.

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2. On the issue of dependency of the excess risk estimate on the number of chosen controls

Although authors describe the situation with two controls for each exposed, it seems to me the use of a double control is due to the specific problem analyzed (i.e., the rate of deadly car accidents on the election days vs. days as similar as possible, apart for the fact there was no election) rather than to statistical reasons. In the case of doctors' diagnostic accuracy reported by authors for the binary case, for example, only one control is used for each exposed, thus suggesting that the concept of "excess risk" could be applied to the case of an arbitrary number of controls (or, at least, of one control per exposed as well). However, I believe that the distribution of estimated excess risk rate strongly depends on the number of chosen controls. For example, in case the exposed always have a higher rate than the controls (typically, if the effect is positive and strong enough with respect to the variance of the error to make the probability of the outcome value for a control being higher than its exposed counterpart negligible), with only one control per exposed individual the excess risk would be infinity (and symmetrically, in case of negative effect, 0). The more the number of controls increases, the more both the numerator and the denominator do (because we are subtracting the minimum among a larger number of observations in both cases). This addition of the same number (on average) to both the numerator and the denominator will result in an expected estimate of the excess risk closer to 1.

For example, let us suppose that the exposed follow a uniform discrete distribution from 6 to 10 and the controls from 1 to 6. It may be easily seen that the excess risk with only one control would always be infinity (or indeterminate, in the unlikely case of only having $<6, 6>$ couples). By introducing another control, we would have a denominator different from 0 (again, apart from the unlikely case of all pairs of controls being equal). In particular, the average values would be: in the controls a minimum of $91/36$ and a maximum of $161/36$, in the treated an average of 8. This implies a number of events in excess of 0 in one of the controls, and an average for the control with the maximum value of $35/18$, while for the treated of $8 - 91/36 = 197/36$. This implies the estimated excess rate would converge to $\frac{197}{36}/\frac{35}{36} = \frac{197}{35} = 5.63$. By increasing the number of controls, the average minimum of the controls would converge to 1 (from above), and the mean of the excess risk of the controls to the average of the difference between 3.5 (the average of the control distribution) and the minimum, thus the average excess risk for the controls would converge to: $3.5 - 1 = 2.5$. The average excess number of events for the exposed would converge to the difference between the average outcome of the exposed and the average minimum of the controls, i.e., $8 - 1 = 7$, thus the excess rate would converge to $7/2.5 = 2.8$. To sum up, we would