

## 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>	Psychosocial consequences of false positives in the Danish lung cancer CT-screening trial: a nested matched cohort study
<b>AUTHORS</b>	Rasmussen, Jakob; Siersma, Volkert; Malmqvist, Jessica; Brodersen, John

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Likwang Chen National Health Research Institutes, Taiwan
<b>REVIEW RETURNED</b>	09-Dec-2019

<b>GENERAL COMMENTS</b>	<p>This is an interesting paper that explored whether false-negative results from lung-cancer CT screening might cause a person's loss in psychosocial welfare. The article was well-written in general, and the methodology was appropriate.</p> <p>To further strengthen the article, I suggest that the authors try to elaborate in the following three aspects.</p> <p>First, in the first paragraph of the Results section, the authors reported that 20% of participants who received a positive screening results never received the COS-LC due to administrative reasons, and thus did not respond to the survey. This ratio was significant. The authors had better explain further why so many participants did not receive the COS-LC due to administrative reasons.</p> <p>Second, it is confusing why persons in the control group experienced more negative psychosocial consequences. If the authors can give more discussion on possible reasons for why persons in the control group (those receiving no screening) had those worse feelings. Such discussion can offer more enlightening information regarding whether provision of CT screening can bring psychological benefits.</p> <p>Third, this study discussed participants' psychosocial consequences on the basis of survey data collected by the study. I wonder whether the authors also had any data regarding the participants' use of psychiatric care or medication. Some additional discussion on this aspect can help readers have further understanding with respect to how provision of CT screening and how results from such screening can affect a person's psychosocial conditions.</p> <p>One minor concern is that the English writing is generally acceptable, but the manuscript still had some grammatical errors. It is better to further polish the writing.</p>
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<b>REVIEWER</b>	Andrea Vodermaier The University of British Columbia, Faculty of Medicine, School of Population and Public Health, CANADA
<b>REVIEW RETURNED</b>	06-Jan-2020

<b>GENERAL COMMENTS</b>	<p>The manuscript reports about an observational study investigating the effects of CT-screening for lung cancer, specifically the effects of false positive screening results on psychosocial distress across 18 months after initial screening. The study represents an ancillary study. It builds on a randomized controlled which investigates the effectiveness of a newer low dosage CT-scan for lung cancer targeting early diagnosis and improved survival.</p> <p>The authors can be commended for this carefully designed study. Specifically, the methods development deserves appreciation. Because the authors developed and validated (based on item response theory) a domain-specific questionnaire to examine the emotional distress of individuals undergoing lung cancer screening, their questionnaire development went way beyond what widely used quality of life measures offer in terms of questionnaire validation.</p> <p>The study demonstrated that CT-screening for lung cancer involved transient increases in emotional distress among false-positives compared to true negatives and a control group who had not undergone screening.</p> <p>I have a few minor comments:</p> <ol style="list-style-type: none"> <li>1. Abstract, results section: The last sentence is too non-specifically worded.</li> <li>2. Methods section, p. 9, line 2: Please explain why a quadratic function for the analysis of a certain number of demographic and clinical variables had been used.</li> <li>3. P. 18, lines 2-5: Please provide a more in-depth explanation why greater negative psychosocial consequences should occur in countries with higher numbers of false-positive test results, when the negative psychosocial impact of CT-screening is time-limited, if not minimal.</li> <li>4. Why was Appendix D (about PET scanning) added to the manuscript?</li> </ol>
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### VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Likwang Chen

Institution and Country: National Health Research Institutes, Taiwan

Please state any competing interests or state 'None declared': None declared

This is an interesting paper that explored whether false-negative results from lung-cancer CT screening might cause a person's loss in psychosocial welfare. The article was well-written in general, and the methodology was appropriate.

To further strengthen the article, I suggest that the authors try to elaborate in the following three aspects.

First, in the first paragraph of the Results section, the authors reported that 20% of participants who received a positive screening results never received the COS-LC due to administrative reasons, and thus did not respond to the survey. This ratio was significant. The authors had better explain further why so many participants did not receive the COS-LC due to administrative reasons.

Reply: Thank you for your comment. We received all contact details on participants with positive screening results consecutively from the administrative personnel in the screening clinic. In 20% of the cases, we did never receive the information from the screening clinic. We have not been able to identify a specific reason other than that it had been forgotten by the administrative personnel in charge that day. We have explained this error in the manuscript. Please see page 9, line 21

Second, it is confusing why persons in the control group experienced more negative psychosocial consequences. If the authors can give more discussion on possible reasons for why persons in the control group (those receiving no screening) had those worse feelings. Such discussion can offer more enlightening information regarding whether provision of CT screening can bring psychological benefits.

Reply: Thank you for your comment on this topic. In the article "Psychosocial consequences in the Danish randomised controlled lung cancer screening trial (DLCST)" (reference 29 in the manuscript) we have discussed this issue further. A potential reason for the more negative psychosocial consequences in the control group compared with the CT group (mixed positive and negative results) could be the reassurance of receiving a normal result (96% of the screened participants).

Third, this study discussed participants' psychosocial consequences on the basis of survey data collected by the study. I wonder whether the authors also had any data regarding the participants' use of psychiatric care or medication. Some additional discussion on this aspect can help readers have further understanding with respect to how provision of CT screening and how results from such screening can affect a person's psychosocial conditions.

Reply: Thank you for highlighting this issue. We have now added a section about this in the Discussion section page 17 lines 21-24 and page 18 lines 1-4.

One minor concern is that the English writing is generally acceptable, but the manuscript still had some grammatical errors. It is better to further polish the writing.

Reply: Thank you for paying attention to this. The article has now been through language editing by a language editing company. The changes are highlighted with track changes throughout the manuscript.

Reviewer: 2

Reviewer Name: Andrea Vodermaier

Institution and Country: The University of British Columbia, Faculty of Medicine, School of Population and Public Health, CANADA

The manuscript reports about an observational study investigating the effects of CT-screening for lung cancer, specifically the effects of false positive screening results on psychosocial distress across 18 months after initial screening. The study represents an ancillary study. It builds on a randomized controlled which investigates the effectiveness of a newer low dosage CT-scan for lung cancer targeting early diagnosis and improved survival.

The authors can be commended for this carefully designed study. Specifically, the methods development deserves appreciation. Because the authors developed and validated (based on item response theory) a domain-specific questionnaire to examine the emotional distress of individuals

undergoing lung cancer screening, their questionnaire development went way beyond what widely used quality of life measures offer in terms of questionnaire validation.

The study demonstrated that CT-screening for lung cancer involved transient increases in emotional distress among false-positives compared to true negatives and a control group who had not undergone screening.

I have a few minor comments:

1. Abstract, results section: The last sentence is too non-specifically worded.

Reply: Thank you for your comment. We have tried to make the sentence clearer. Please see page 3 lines 1-2.

2. Methods section, p. 9, line 2: Please explain why a quadratic function for the analysis of a certain number of demographic and clinical variables had been used.

Reply: Thank you for your question. Age and pack years are continuously valued variables. In order to relax (a rather strong and possibly untenable) assumption of a linear effect, the effect of both these variables was assumed quadratic, i.e. both the variable and the variable squared were included in the model.

3. P. 18, lines 2-5: Please provide a more in-depth explanation why greater negative psychosocial consequences should occur in countries with higher numbers of false-positive test results, when the negative psychosocial impact of CT-screening is time-limited, if not minimal.

Reply: Thank you for your comment. We have tried to provide the reader with a more in-depth explanation. Please see page 18 lines 18-21

4. Why was Appendix D (about PET scanning) added to the manuscript?

Reply: We apologise if an appendix D about PET scanning has been added to the manuscript. It is a mistake.

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	Likwang Chen National Health Research Institutes, Taiwan
<b>REVIEW RETURNED</b>	06-Mar-2020

<b>GENERAL COMMENTS</b>	I found the revisions acceptable, and have no further request for revision.
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<b>REVIEWER</b>	Andrea Vodermaier UBC School of Population and Public Health
<b>REVIEW RETURNED</b>	21-Mar-2020

<b>GENERAL COMMENTS</b>	I would like to come back to #3 of my first reviewer comments and the authors' reply. The discussion the authors provided is not convincing to me. Whether a negative effect on psychosocial functioning following a false-positive screening result occurs matters most when the overall positive predictive value of the screening program is low and cancer specific mortality does not decrease following the introduction of the screening program. The argument the authors introduce that the effects matter because of the population relevance appears vage to me and would need to be more substantiated at best. I also wonder why the authors did not compare the false-positives with the true-positives in terms of their psychosocial adjustment. If so, the magnitude effects and possible adversity shown on the lung cancer-specific scale could be better put into context. To my knowledge no further data exist
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	whether participants indeed showed subclinical or even clinical levels of emotional symptoms. In summary, I would like the authors to be more specific regarding the interpretation and discussion of their findings and provide an explanation why false-positives and true-positives were not directly compared with each other.
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### VERSION 2 – AUTHOR RESPONSE

Reviewer 2:

1. I would like to come back to #3 of my first reviewer comments and the authors' reply. The discussion the authors provided is not convincing to me. Whether a negative effect on psychosocial functioning following a false-positive screening result occurs matters most when the overall positive predictive value of the screening program is low and cancer specific mortality does not decrease following the introduction of the screening program. The argument the authors introduce that the effects matter because of the population relevance appears vage to me and would need to be more substantiated at best.

Reply: Thank you for your comment. We have further elaborated on this topic in the discussion. Please see pp.18 lines 19-24 and 19 lines 1-5.

2. I also wonder why the authors did not compare the false-positives with the true-positives in terms of their psychosocial adjustment. If so, the magnitude effects and possible adversity shown on the lung cancer-specific scale could be better put into context. To my knowledge no further data exist whether participants indeed showed subclinical or even clinical levels of emotional symptoms. In summary, I would like the authors to be more specific regarding the interpretation and discussion of their findings and provide an explanation why false-positives and true-positives were not directly compared with each other. Reply: Thank you for your question. We did compare TP and FP directly with each other. The scales and assessments where these differences were significant, are marked by an asterisk or a cross in the figures 2 and 3.

### VERSION 3 – REVIEW

<b>REVIEWER</b>	Andrea vodermaier The University of British Columbia School of Population and Public Health
<b>REVIEW RETURNED</b>	22-Apr-2020
<b>GENERAL COMMENTS</b>	The two concerns I raised in the previous review had been adequately considered.