Author’s response to reviews

Title: Effects of low-dose computed tomography on lung cancer screening: a systematic review, meta-analysis, and trial sequential analysis

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Author’s response to reviews:

Dear editors and reviewers:

Thank you for your letter and for the reviewers’ comments concerning our manuscript entitled “Effects of low-dose computed tomography on lung cancer screening: a systematic review, meta-analysis, and trial sequential analysis” (Manuscript ID: PULM-D-19-00150R1). Those comments are all valuable and very helpful for revising and improving our paper. We have studied comments carefully and have made corrections accordingly. Our responses to the reviewers’ comments are as follows and we believe our manuscript is much improved as a result.

1. Please remove the PRISMA checklist from the file inventory as it is no longer needed at this stage of the editorial process.
Response 1: We thank the editor for this comment. We have removed PRISMA checklist (Table S3) from the file inventory.

2. We note that the current submission contains some textual overlap with other previously published works, in particular:


This overlap mainly exists on page 8 lines 26-39.

Response 2: We thank the editor for this comment. We have re-phrase these sections. (Methods section, lines 16-36, page 8)

We extracted the following data: study name, country, number of participants, characteristics of population, screening type and interval, definition of positive results and outcome measures.

Statistical analysis

We carried out analysis using Review Manager (RevMan) Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) software. Inverse variance meta-analysis for combining data was performed.


This overlap mainly exists on page 7 lines 26-44.

Response 3: We thank the editor for this comment. We have re-phrase these sections. (Methods section, lines 24-42, page 7)

Major complications were listed below: death, anaphylaxis, cardiac arrest, cerebral vascular accident/stroke, congestive heart failure, myocardial infarction, intervention-required thromboembolic complications, acute respiratory failure, respiratory arrest, bronchial stump leak requiring tube thoracostomy or other drainage for > 4 days, bronchopulmonary fistula, empyema, prolonged mechanical ventilation > 48 hours postoperatively, tube placement-required hemothorax, brachial plexopathy, lung collapse, chylous fistula, injury to vital organ or vessel, wound dehiscence, and infarcted sigmoid colon.
Replies to Reviewer’s Comments

Sourin Bhuniya (Reviewer 1):

Please include all comments for the authors in this box rather than uploading your report as an attachment. Please only upload as attachments annotated versions of manuscripts, graphs, supporting materials or other aspects of your report which cannot be included in a text format.

Please overwrite this text when adding your comments to the authors.

Response: We thank the reviewer for the supportive and constructive review. It is indeed our sincere hope that this report provides critical information that can raise awareness of issues associated with LDCT lung cancer screening.

José Belda (Reviewer 2):

Congratulations on the manuscript, it is extraordinary. I would like to make some simple questions.

1. Did you find any difference in terms of death and major complications between diagnostic and therapeutic procedures?

Response 1: We thank the reviewer for this comment. There were two studies (DANTE, NLST) reported number of death after invasive diagnostic evaluation procedures in our analyses. Nineteen deaths were reported after 2129 invasive procedures in persons screened by LDCT and 11 deaths were reported after 792 invasive procedures in the control group. No significant difference (RR 0.64, 95% CI 0.30–1.33, I2=0) was shown. Only one study (NLST) reported major complication rates following invasive procedures for LDCT and CXR group. The risk was higher among persons who underwent LDCT compared with CXR screening (4.1 vs 3.2 per 10,000 screened).

Our analyses did not have data to present the rates of death or major complications after patients receiving different therapeutic procedures.

2. What does mean: "2 studies were excluded because there were no relevant results"?

Response 2: We thank the reviewer’s valuable reminding. We have added a further explanation as follows: (Results section, lines 55-60, page 9)
Twenty-seven studies were excluded for the following reasons: eleven because they were review articles; two because there were no relevant outcomes (mortality data);........

3. After excluding the MILD trial, the LDCT screening showed a statistically significant reduction in lung cancer mortality; on the contrary, the same result was not observed when excluding the DANTE trial. For what reason?

Response 3: We thank the reviewer for this comment. Annual LDCT group in MILD trial exhibited a tendency to increase lung cancer mortality (RR 2.48, 95% CI 0.98-6.29). The impact of the MILD led to the pooled mortality results favoring the control over the LDCT group. On the contrary, DANTE trial did not exhibit such tendency (RR 1.01, 95% CI 0.70-1.44). That’s why after excluding the MILD trial, the LDCT screening showed a statistically significant reduction in lung cancer mortality.

Moreover, there were two RCTs (MILD, LUSI) reported the latest mortality results in April and June 2019. We updated our analyses and the results were slightly changed. The positive association was not substantially changed after excluding the MILD or DANTE trial. Robust results are displayed in Table 3. Reliability and stability of our conclusions were further confirmed. We have added some information as follows: (Results section, lines 47-52, page 12; Table 3)

Sensitivity analyses were robust. The positive association was consistent with any of these analyses. Reliability and stability of our conclusions were further confirmed.

4. What's the reason for such significant difference in the lung cancer mortality between subgroups of higher versus lower quality trials?

Response 4: Thank you for your comment. This is a fair point. According to the report of MILD in 2012 [1], annual LDCT group exhibited a tendency to increase lung cancer mortality (RR 2.48, 95% CI 0.98-6.29). The impact of the MILD led to the pooled mortality results favoring the control over the LDCT. However, lower quality trials such as DANTE and MILD were lack of precision on the method. Low quality trials have a possibility to have errors in the process of deriving the results and therefore distort the study. Even the RCT study design cannot eliminate all bias, which can occur at the conducting phase and can lead to derivation of incorrect results. The results from lower quality trials should be treated with caution.

5. Could you speculate about how a high quality RCT for lung cancer screening should be designed to minimise outcomes bias?

Response 5: We thank the reviewer for this comment. In our opinion, a high quality RCT for lung cancer screening should contain:

(1) selection of population with high risk
(2) sufficient power to test the hypothesis
(3) enough length of follow-up (>5 years)
(4) adequate number of screening rounds (annual or biennial)
(5) appropriate measurement of screen-detected lung nodules [volumetric or volume doubling time (VDT)]

Above requirements have an important effect on mortality and on cost-effectiveness. That will generalize an evidence-based content of lung cancer screening.