Author's response to reviews

Title: Most bowel symptoms do not indicate colorectal cancer and polyps: a systematic review

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Author's response to reviews:

Tim Shipley, PhD
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Floor 6, 236 Gray's Inn Road
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Dear Dr Shipley

RE: Response to reviewers:

MS: 1140363874550825

Most bowel symptoms do not indicate colorectal cancer and polyps: a systematic review. Barbara-Ann Adelstein, Petra Macaskill, Siew F Chan, Peter H Katelaris and Les Irwig

We thank the reviewers for their comments which have been helpful in improving our paper. We have addressed each of the comments below, and have made the changes referred to in the submitted paper. We have also uploaded separate files (1 main document text and 1 appendix) in the "additional files" section which show these changes, using Word’s “track changes” feature.

Adriana Perez
Major Compulsory Revisions

1. Omit the variable prediction given that the systematic review with different types of studies does not allow you to establish a prediction estimate but only associations

Response 1: We no longer refer to symptoms predicting cancer or polyps: we have changed the wording from “predict” to “are associated with” (page 3.)

2. Page 6 second paragraph line 4: please clarify which terms are used as random effects and which ones were used as fixed effects

Response 2: Paragraph 2 of the statistical methods section states that the threshold and accuracy are fitted as random effects in the HSROC model, and that the shape parameter is fitted as a fixed effect. This is consistent with the model specification in the references given for the model. It is now made clear in this paragraph that each covariate was fitted as a fixed effect (page 6).

3. Appendix 3: needs clarification on symbols within tables. What is CBH and others? There is not information in the table and the table has to stand alone. The order of the footnotes for the table does not match the table order; please re-arrange

4. Appendix 4: it is inconsistency between what is shown as DOR (spell out also) and what is stated in text regarding as OR authors need to explain to the readers what is shown inside the tables if not DOR values which is only summarize as one overall value in text. This is confusing. What is the definition of new in table? Please include the year of the publications.

5. Figure titles: all figure titles need to spelled out acronyms. Spell out to readers what is the line in figures. What are the ovals and what is the + sign. Also plots should start at 0,0 coordinates. These are continuous measurements therefore the XY coordinates should start at 0 and there should be no distance from 0 to the other 0 as shown in the current version. Also, maximum values should be 1,1 instead of additional values in graphs presented.

6. Figures: Authors need to define what is crc for readers standing alone in figures. The dotted lines from black dots to 45 degrees are confusing the purpose. They will need a different type of line given that dotted lines have different meanings in all figures.

Response to comments 3-6: The concerns raised by the reviewer relating to the presentation of the figures have been addressed by improved labelling and footnotes for each figure and improved description of the figures in the text. The elliptical regions and “+” symbol are described in footnotes for figures 1 to 8. Similarly, a footnote has been included to explain that paired points (one black
and one open joined by a dotted line) represent a within study comparison for figures 2 and 4. We believe that this, in conjunction with the descriptions in the study methods (addition made, page 9) and results sections make the interpretation of these figures clear. The publication year of papers is already in Appendix 4; we have clarified in the footnote what “year” refers to.

In relation to the offset that has been applied to the scales for sensitivity and 1-specificity on the figures, this is often done to avoid the problem of data points which have an x or y value of 0 (or both equal to 0) not being visible in the figure because they are obscured by an axis. Several studies in our figures take these extreme values, and hence using an offset to show the scaling ensures that these studies are not obscured. The rectangle in which the data are plotted is evident from the scaling and also from the diagonal line which ranges from (0,0) to (1,1). The diagonal line represents an ROC of no diagnostic value (AUC=0.5) and is often shown on SROC plots for reference. Even though a dotted line has been used for this as well as for the lines that join paired points, we do not believe that this causes confusion. Indeed, the other reviewers did not mention this. Because the focus should be on the fitted curves, we have used a faint dotted line type to avoid detracting from the most important content of the figure.

7. Authors listed the presence of figures 9-16 but these are not presented in current manuscript.

Response 7: There are 8 figures in the manuscript, which are numbered 1 -8

Tom Marshall

1. The authors should clarify whether the studies were selected on the basis of study methodology (case control, cohort or retrospective cohort) or entirely on the basis of whether a 2x2 table could be constructed (which is theoretically possible with a cross-sectional study)

Response 1: Rather than restricting included papers to certain study types, we have extensively explored whether study characteristics had any effect on the findings (abstract (under study eligibility criteria and results), p 2, Inclusion criteria p 4. and discussion page 12)

2. The authors should clarify in the abstract whether the studies concerned were only of symptoms in patients presenting to primary care or first contact with health professionals or included patients referred by primary care /first contact health professionals to secondary care professionals.

Response 2: We have added in comment about results in different settings. (abstract, p2)
3. The observation that there were issues of uncertainty or discrepancy between the data extraction sets in 50% of papers probably merits some comment in the discussion.

AND

5. The high degree of discrepancy in data extraction from papers merits some comments

Response 3 and 5: We have included additional discussion addressing this issue (page 12 and 13)

4. The discussion is reasonable, although the authors should comment on the interpretation of the finding in relation to primary care/first contact settings and symptoms record in referred patients.

Response 4: We have included this result in the discussion (page 11).

6. There is a very recent systematic review that could be referred to in the discussion (ShapleyM, BJGP Sept 2010)

Response 6: We have added reference and comment to this review in the discussion (page 12)


Response 6: repetitions omitted (abstract p2; and page 17)

Floris Van de Laar

Major

1. One of the conclusions is that weight loss is a predictor for colon cancer and indicates the need for colonoscopy. I doubt that any doctor will, after reading this paper refer every patient with weight loss for colonoscopy, at least not as the first diagnostic step. Most (if not all) data is derived from selected patient groups in which at least a part of them already had symptoms (probably gastrointestinal). Probably a better conclusion would be that colonoscopy is indicated in patients with weight loss and a high prior probability. But then, when do we have a high probability in primary care when we do not have good predictive signs and symptoms?

Response 1: We agree with the reviewer, and have clarified our interpretation of
investigation for weight loss to reflect that results and conclusions are for a population already selected for colorectal cancer risk (page 12)

2. In real life, the decision whether or not to refer someone for colonoscopy is a subtle mix of items from history, physical examination, specific patient characteristics (age, family etc) and ‘gut feeling’ of the doctor. In this review the signs and symptoms are investigated more or less in isolation. I do not see how statistics do or may account for this.

Response 2: We agree with the reviewer that in practice symptoms are seldom assessed in isolation. However, any meta-analysis is limited by the data provided in the papers describing the studies, and as few of the papers provided the type of detailed information described by the reviewer, it is not possible for us to undertake such analysis. This limitation is already mentioned in our discussion in relation to age (page 13). We have now discussed this more explicitly (page 14)

3. In their final conclusion, authors suggest that we should focus on screening programs rather than ‘attempting to identify cancers and polyps through investigating people with symptoms. I do not agree with this conclusion for two reasons. First, I miss the point that mass screening is better than current practice in which we try to indentify people with (pre)cancer as early as possible. Second, people will keep going to their doctors with signs and symptoms that might relate to serious disease. Referring everyone for colonoscopy is simply not an option.

Response 3: We agree with the reviewer that patients will still present to their doctors with symptoms for investigation, and that should obviously continue. However, as symptoms are not good predictors of the presence of cancer, waiting for patients to present with symptoms for investigation is not the optimum way of ensuring early diagnosis of colorectal cancer. We point out in our discussion that the LR of FOBT is 47, compared to the LR of weight loss of less than 3. We have changed the wording of our conclusion slightly to clarify that we are not precluding investigation of patients who present to their doctors (page 14). We are also not suggesting that everyone has a colonoscopy; rather screening should be by FOBT, and we have clarified this (page 14).

4. The discussion section could be improved if authors elaborate a little more on the comparison with existing reviews (refs 76 and 77). Please note that a third systematic review was published last year on rectal bleeding and the value of additional signs (Olde Bekkink Br J Cancer 2010; 102:48-58)

Response 4: we have added reference and comment to this review in the discussion (page 12 and 14)

Minor:
5. The authors excluded studies that did not differentiate between cancers and polyps. This decision might seem logical at first sight, but there are arguments to include those studies and to have an (additional) analysis with studies that don’t differentiate between cancer and polyps. Both polyps and (of course) cancer are a good reason to refer for colonoscopy. In fact, a suspected polyp is even a better reason because for polyps colonoscopy is both a diagnostic and a therapeutic procedure. Therefore most physicians will be more interested in the question “is colonoscopy of added value in this patient” rather than “does this patient have cancer/polyp.” I don’t think the authors should redo their analyses (maybe in future update?) but they might give it some thought in the discussion section.

Response 5: There are several reasons that we did not include studies that did not differentiate between cancers and polyps. Only 8 papers (across all symptoms) provided this information. We do not believe that an analysis including both would provide a great deal of additional information – the results for the predictive value of symptoms for a combination of cancer and polyps would be somewhere between those already given for polyps and cancer alone.

We have no acknowledgments to add to the paper.

We believe we have addressed the reviewers’ comments. The resulting revisions and additions have improved the paper considerably. We look forward to the opportunity for it to now appear in BMC Gastroenterology.

Yours sincerely

Barbara-Ann Adelstein