PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Where are the inequalities in colorectal cancer care in a country with universal healthcare? A systematic review and narrative synthesis
AUTHORS	Pickwell-Smith, Benjamin; Spencer, Katie; Sadeghi, Mahboobeh Haji; Greenley, Sarah; Lind, Michael; Macleod, Una

VERSION 1 – REVIEW

REVIEWER	Clouston, Sean Stony Brook University, Family, Population, and Preventive Medicine
REVIEW RETURNED	07-Nov-2023

GENERAL COMMENTS	I appreciate the authors' consideration of my prior comments. I continue to have concerns over the review, but they are less. I disagree with the author's view of meta-analysis, since you could (for example) report the estimates in a forest plot without then reporting an average and then you could see what the pattern of results would look like rather than just determining everything based on direction and "quality" of the results. I have, however, noted the below given the author's lack of comfort with the method. It would be helpful if the authors added confidence intervals to the numbers estimated in the paper. It's hard to say that a result is not statistically significant if the information is not provided, as is done here: "There was no significant 5 association between deprivation and time to treatment (HR 1.24)." This is done throughout the paper, but it's confusing and induces interpretation biases since the HR and OR are not interpretable without a confidence interval. I am going to ask you to re-read the Shack paper. Look at table 7.5, as you note. In the title, it says "Distribution (%) and adjusted odds ratios for receiving surgery…" but the title on the first column is "Surgery, (reference = surgery)" implying that this is reverse coded to what is described in the text or by the review authors. Consistent with this, the study results also suggest that the most advanced stages were protected from not receiving surgery, as you might expect. The reverse coding is annoying, but it implies that the current paper is also incorrectly interpreted. This is currently listed as Strong evidence against the hypothesis in the paper, but it is strong evidence for the hypothesis (more deprivation associated with increased risk of lacking surgery). It should be fixed in this study so that this error doesn't continue. Given this error in interpretation, I would also suggest (again) that the authors have a look at all their previously coded papers and ensure that none of the rest of the results are reverse-coded.

	MINOR: On page 14, you say “Five studies 15 adjusted for important variables,” The word “important” is vague. Please remove.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Sean Clouston, Stony Brook University

I appreciate the authors’ consideration of my prior comments. I continue to have concerns over the review, but they are less. I disagree with the author's view of meta-analysis, since you could (for example) report the estimates in a forest plot without then reporting an average and then you could see what the pattern of results would look like rather than just determining everything based on direction and "quality" of the results. I have, however, noted the below given the author's lack of comfort with the method.

We agree and thank the reviewer for their suggestion. We have produced forest plots (without an overall average) for the following outcomes: receipt of surgery, abdominoperineal resection, chemotherapy and radiotherapy. This has considerably enhanced the analysis and demonstrates that most studies present evidence of inequalities, even if this does not reach significance on statistical testing in individual studies. We have added a sentence to the methods on page 7 (under the heading synthesis methods) to reflect that we have produced forest plots.

It would be helpful if the authors added confidence intervals to the numbers estimated in the paper. It’s hard to say that a result is not statistically significant if the information is not provided, as is done here: “There was no significant 5 association between deprivation and time to treatment (HR 1.24).” This is done throughout the paper, but it’s confusing and induces interpretation biases since the HR and OR are not interpretable without a confidence interval.

Thank you. We agree with the reviewer and thank them for suggesting this. We have added confidence intervals to all the estimates provided in the paper. The exception is where we have presented a range of odds ratios, as doing so would affect the readability. However, we would be willing to look again if advised to.

I am going to ask you to re-read the Shack paper. Look at table 7.5, as you note. In the title, it says “Distribution (%) and adjusted odds ratios for receiving surgery…” but the title on the first column is “Surgery, (reference = surgery)” implying that this is reverse coded to what is described in the text or by the review authors. Consistent with this, the study results also suggest that the most advanced stages were protected from not receiving surgery, as you might expect. The reverse coding is annoying, but it implies that the current paper is also incorrectly interpreted. This is currently listed as Strong evidence against the hypothesis in the paper, but it is strong evidence for the hypothesis (more deprivation associated with increased risk of lacking surgery). It should be fixed in this study so that this error doesn’t continue. Given this error in interpretation, I would also suggest (again) that the authors have

a look at all their previously coded papers and ensure that none of the rest of the results are reverse-coded.

Thank you for your thorough review of the results. We agree this is a very unusual and unexpected finding. We also agree that the title on the first column, "Surgery (reference = surgery) is confusing and suggests that the authors have reverse coded. The findings of increased odds of surgery for older age groups also support the interpretation that it is reverse-coded. Given the confusion, we have contacted the author, who confirmed that it is ***not*** *reverse-coded. We have pasted the entire email thread at the bottom of this document.*

We have considered that this was an analysis of regional data (from the North West of England) in a historical population (those diagnosed 1997-2004) and our collective caution with the results. We have added this discussion to page 12 (lines 17-24). We have not amended our judgment that, methodologically, this appeared to be a robust study, but we have amended our overall conclusion. We agree with you that in light of the forest plots we have presented (figure 4) and the caution regarding this study, we have changed our conclusion that there is strong evidence for inequalities in surgery. This is reflected in lines 1-6 on page 13 and table 1 (row headed "likelihood of receipt of surgery"). We have checked the other results and verified those that are reverse-coded.

MINOR:
On page 14, you say "Five studies 15 adjusted for important variables," The word "important" is vague. Please remove.

Thank you for your suggestion; we have removed this word.

Email trail between ourselves and Dr Lorraine Shack:

From: Lorraine Shack <lorraine.shack@albertahealthservices.ca>
Date: Friday, 10 November 2023 at 18:43
To: Benjamin Pickwell-Smith <Benjamin.Pickwell-Smith@hyms.ac.uk>
Cc: Katie Spencer <K.Spencer@leeds.ac.uk>
Subject: RE: Systematic Review Advice

Hi Ben,

That's interesting research. When it's complete I'd be interested in reading it.

It has been quite a while since I completed it, so I needed to refresh my memory. There is a higher proportion of affluent patients receiving surgery (Table 7.5). The percentage of patients having surgery is highest in affluent (89.5%) and decreases to 87.8% in deprived group. However, after

adjusting for sex, age at diagnosis, tumor site, stage (imputed) and comorbidity the OR for surgery increased with increasing deprivation. This can be explained by the fact that deprived patients were more likely to receive surgery only treatment (less likely to receive chemo/RT in combination with surgery or chemo/RT alone) (Table 7.6 & 7.7), more likely to be treated by a low volume surgeon (Table 7.9) and less likely to be treated in accordance with clinical guidelines (Table 7.13). This can also be partly attributed to comorbidity differences.

Please reach out if you have any other questions.

Lorraine

From: Benjamin Pickwell-Smith <Benjamin.Pickwell-Smith@hyms.ac.uk>
Sent: Thursday, November 9, 2023 5:26
To: Lorraine Shack <lorraine.shack@albertahealthservices.ca>
Cc: Lorraine Shack <lorraine.shack@ahs.ca>; Katie Spencer <K.Spencer@leeds.ac.uk>
Subject: Systematic Review Advice

> You don't often get email from benjamin.pickwell-smith@hyms.ac.uk. Learn why this is important

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Dear Dr Shack,

I am a PhD student from Hull York Medical School in England. I have been working on a systematic review of socioeconomic inequalities in bowel cancer treatment in the United Kingdom.

We have included your thesis from 2009 (I appreciate this is some years ago!). The reason for our email is that we are publishing the review but are currently having discussions with our peer reviewers about a result we are quoting from your thesis.

The results showed that the most deprived patient group were more likely to have surgery for colorectal cancer than the most affluent group (OR 1.63, 95% CI 1.17-2.26), adjusting for sex, age, subsite, stage and comorbidity. This result has sparked debate with the peer reviewers, who have asked if we can clarify this, as it is the opposite of what we would expect. We appreciate it was such a long time ago, and you will be incredibly busy, but we just wondered if you might remember this unusual result!

VERSION 2 – REVIEW

REVIEWER	Clouston, Sean Stony Brook University, Family, Population, and Preventive Medicine
REVIEW RETURNED	22-Nov-2023

GENERAL COMMENTS	The new manuscript accomplishes what I think is necessary and is much easier to read, and is sufficiently rigorous. I thank the authors for their work and for their investment in this study.