Peer Reviewer 1

Comment 1: Clarification on Study Inclusion in Figure S1: In Figure S1 of the Results section, the final number of included " is reported as 16. Given that the text mentions 18 studies were initially considered and 3 were excluded, readers may question why the total does not align with the expected calculation (18 − 3 = 15).

Response 1: Thank you for highlighting this, I've amended the supplementary files and manuscript so that the number of studies included in the review are consistent.

Changes made to manuscript, please see page 6

Changed number of studies that satisfied inclusion criteria to 15 (from 16).

Changes made to manuscript, please see page 20

Removed "27. Bhaskaran" reference -> references and bibliography were subsequently updated to display the correct number.

Comment 2: Choice of Effect Model in Forest Plot (Figure 1): The forest plot in Figure 1 indicates very low between-study heterogeneity ($I^2 = 0$), which suggests no meaningful variability in effect sizes across included studies. In such cases, the fixed-effects model is statistically more appropriate for estimating the overall effect size, as it avoids unnecessary conservatism that may arise from the random-effects model. While technical guidelines permit the use of a random-effects model even when $I^2 = 0$, the fixed-effects model is preferable here to provide a more precise and unbiased summary of the pooled effect.

Response 2: Thank you for your comment. Figure 1 has now been amended to instead utilise the common effect model.

Changes made to manuscript, please see page 5

Replaced "For the meta-analysis…" sentence with "If heterogeneity was observed between studies…" sentence

Changes made to manuscript, please see page 7

Replaced "The random-effects model was created utilising the restricted maximum likelihood method" with "The common-effects model was utilised"

Comment 3: Justification for Excluded Studies in Qualitative Analysis: In the "Qualitative Analysis" subsection of the Results, Figure 3 is referenced to illustrate the exclusion process, but it lacks clear annotations or a supplementary table explaining why 7 specific studies were excluded from the meta-analysis. To improve transparency, the authors should elaborate on the exclusion criteria (e.g., methodological limitations, incomplete data, or relevance to the research question) applied during this phase, either in the text or via a footnote to the figure.

Response 3: Thank you for identifying this. I've summarised the reasons for these studies' exclusions from the meta-analysis.

Changes made to manuscript, please see page 8

Added "Reasons for exclusion from the meta-analysis included…" paragraph.

Added references numbers to each study in Figure 3

Comment 4: Structural Consistency of Paragraphs: The article's organizational structure could be strengthened. Several sections feature paragraphs with only 1–2 sentences, which are insufficient to function as independent units of discussion. For example, the "Findings from male meta-analysis" and "Findings from female meta-analysis" subsections under Results each contain overly brief content. Merging these into a single, more substantive section that synthesizes sex-specific results would improve readability and logical flow

Response 4: Thank you for raising this. I have joined subsections together that contained overly brief content as recommended.

Changes made to manuscript, please see page 8

Combined the "findings from male meta-analysis" and "findings from female meta-analysis" into a "findings from meta-analyses" subsection.

Changes made to manuscript, please see page 10

Combined "Severity of obesity on colon and rectal cancer development" with the "severity of obesity on CRC development" subsection. .

Comment 5: Placement of Figures in the Discussion Section: Three visually detailed figures are currently presented in the Discussion section. By convention, figures that directly present primary or secondary results (e.g., effect estimates, subgroup analyses) should be included in the Results section to immediately support the narrative of key findings. The Discussion should focus on interpreting these results rather than introducing new visual data.

Response 5: Thank you for highlighting this oversight. I have amended the manuscript by creating a section in the results section to summarise the proposed mechanisms linking obesity and colorectal cancer where I have placed the three figures. I have also edited the discussion accordingly to refer back to these figures introduced in the results section.

to better flow from the results as it now expands on the summarised figures

Changes made to manuscript, please see page 10

Added a "Summary of Proposed Mechanisms in the Obesity-Colorectal Cancer Association" subsection within the results. Figures 4,5 and 6 have also been introduced in this section.

Changes made to manuscript, please see page 11

Changes made to the discussion. The first and second paragraph have been combined to improve readability. Additionally, the sentence: "The specific biological mechanism describing the linkage between obesity and CRC remains unclear; however, as mentioned earlier in this review, is believed to be multifactorial in nature" was replaced with "As mentioned earlier in this review, the current proposed mechanisms between obesity and CRC is multifaceted but can be broadly classified into two categories" to allow for better flow from the results section.

Comment 6: Minor Editorial and Formatting Issues: Several details require attention to ensure consistency and adherence to formatting standards: • In the "Severity of obesity on colon and rectal cancer development" subsection, some sentences lack terminal punctuation (e.g., periods), which disrupts readability. • The second and third paragraphs of the "Limitations" section similarly omit

closing punctuation, which should be corrected. • Additionally, the first line of the "Altered gut microbiome" subsection in the Discussion is indented inconsistently with other paragraphs (e.g., it may use a half-inch indent versus full alignment with the margin). Standardizing paragraph indentation across the manuscript will enhance visual coherence. Overall, this study makes a valuable contribution to the field, and addressing these points will further strengthen its clarity, rigor, and impact.

Response 6: Thank you for identifying the missing punctuation marks in some sections of the manuscript as well as the mis-aligned margins. This has been amended. Thank you again for your time reviewing our manuscript and providing your feedback.

Changes made to manuscript, please see page 17

Periods added to the end of the second and third paragraphs of the limitations section.

Changes made to manuscript, please see page 14

First line under "Altered gut microbiome" amended to use same paragraph indentations as all other paragraphs in the manuscript.

Peer Reviewer 2

Comment 1: Although prior reviews exist, more emphasis could be placed in the Introduction on how recent changes in obesity trends, diagnostic practices, or molecular understanding justify this updated analysis.

Response 1: Thank you for your suggestion. I have added a few sentences within the introduction to describe that, since 2008 (which the studies from the most recent systematic review were from), obesity rates have increased dramatically, especially in that of the countries of low to middle-income demographics. I have also acknowledged that since the proposed mechanisms linking CRC and obesity have updated, an updated analysis is warranted.

Changes made to manuscript, please see page 3

Added paragraph: "However, global obesity rates since 2008 have increased exponentially, particularly… recurrent delve into the current literature."

Comment 2: The search strategy, although mentioned, lacks detailed explanation in the main text. It is unclear how comprehensively the grey literature or unpublished data were searched. PRISMA guidelines were followed, and data sources were clearly reported. Briefly summarize key search terms and strategy in the main text, not just in supplementary materials. Mention if PROSPERO registration was considered.

Response 2: Thank you for your comment to more comprehensively describe the search strategy used in this meta-analysis. While we did mention the data sources used, it's clear that specific reference to the key terms used would greatly improve the clarity of the manuscript. Additionally, although we did mention in our exclusion criteria that unpublished papers were not to be included in the meta-analysis, we did not mention our exclusion of grey-literature as well and have subsequently updated the manuscript. For this systematic review and meta-analysis, PROSPERO registration was not considered, and as such it was no mentioned in the manuscript.

Changes made to manuscript, please see page 4

Listed key terms used for the meta analysis: "obesity, BMI, colorectal cancer, colorectal carcinoma, bowel cancer and registry"

Changes made to manuscript, please see page 5

Updated the exclusion criteria to include "Grey literature".

Comment 3: Clarify why more of the 16 included studies were not eligible for meta-analysis. Was this due to lack of compatible effect size metrics?

Response 3: Thank you for your feedback. The reasons for the included studies not being eligible for meta-analysis included: studies utilising different measures of association (e.g. odds ratios [OR] and relative risk [RR]), studies utilising other measures of obesity in addition to the WHO obesity diagnostic criteria, and studies with methodological limitations that prevent accurate comparisons with other studies included for meta-analysis. This limitation of the manuscript was also identified by the previous reviewer, and as such, has been amended to include these reasons under the "Qualitative Analysis" subsection on page 8.

Comment 4: Consider subgroup analyses (e.g., geographic region, menopausal status, ethnicity) to identify heterogeneity sources

Response 4: Thank you for your comment. While we believe subgroup analyses would be beneficial in highlighting potential heterogeneity sources, unfortunately we do not possess sufficient data to achieve this and believe this reveals a new area of further research.

Comment 5: Some subsections (e.g., adiponectin, leptin) include highly specific signalling pathways, which, while accurate, may overwhelm readers not specialized in molecular oncology. Consider condensing or moving some of this content to supplementary materials or summarizing with more emphasis on how these mechanisms reinforce the epidemiological findings

Response 5: Thank you for your insightful comment. While we understand that the detailed signalling pathways related to adiponectin and leptin may be complex for some readers, we have chosen to retain this content in the main text due to the growing interest in molecular oncology among clinicians and researchers. These mechanistic insights directly support the epidemiological findings and add valuable context. However, we are happy to move these detailed sections to the supplementary materials if the reviewers feel it would improve the manuscript's accessibility.

Comment 6: Figures 1–6 are well-constructed, but they are not embedded in the document text. It's unclear where they are located. Ensure figures are placed immediately after their first mention in the main text and are of publication-quality resolution and are self-explanatory each figure should be understandable on its own with a descriptive title and legend, without requiring the reader to refer back to the main text for interpretation

Response 6: Thank you for your comment about our figures. We've ensured that each figure has been embedded in the text document and are placed immediately after their first mention. To ensure each figure is self-explanatory, I've simplified Figure 1 and Figure 2 to remove the logHR and SE(logHR) subsection. Additionally, I've ensured all figures are of publication-quality resolution.

Changes made to manuscript, please see page 7

Simplified Figure 1 and Figure 2 by removing the logHR and SE(logHR) subsection. Also increased the resolution of Figure 1 and Figure 2 to ensure its of publication-quality resolution.

Comment 7: Language and Style: A thorough language edit is required to improve flow, consistency, clarity and also font size/style

Response 7: Thank you for your comment. We have made changes where we thought flow and clarity of the manuscript could be improved. The font size/style was also changed to be consistent throughout the manuscript.

Comment 8: Future research directions could also explore genetic predisposition and interaction with obesity, or more concrete policy/screening implications.

Response 8: Thank you for your suggestion. While we did suggest further research to optimise screening guidelines, we believe adding screening implementations as well as genetic predispositions to CRC and its interaction with obesity would also be great future research directions. We have revised the manuscript accordingly.

Comment 9: Use consistent units and notations (e.g., "BMI ≥ 30 kg/m²")

Response 9: Thank you for this comment. The manuscript has been amended to ensure all units and notations remain consistent.

Comment 10: Ensure all abbreviations (e.g., AMPK, IGF-1, OB-Rb) are defined at first use.

Response 10: Thank you for identifying this oversight in our manuscript. This has been amended to ensure all abbreviations are defined at first use.

Comment 11: While the manuscript presents a valuable and methodologically strong contribution to the field, it requires revisions to clarify methodological decisions, refine the writing, address heterogeneity, and better integrate biological mechanisms into the overall interpretation of the data.

Response 10: Thank you for your time in reviewing our manuscript.

Peer Reviewer 3

Comment 1: The topic is highly relevant and timely, addressing the global obesity epidemic and its potential public health consequences, particularly in relation to CRC

Response 1: Thank you for your positive feedback.

Comment 2: The study design is robust, with a well-conducted meta-analysis using large sample sizes, which enhances the reliability and generalizability of the findings

Response 2: Thank you for your positive feedback.

Comment 3: The manuscript is well-structured, clearly outlining the methodology, inclusion criteria, and statistical techniques used

Response 3: Thank you for your positive feedback.

Comment 4: The inclusion of a qualitative analysis for studies not part of the meta-analysis provides a well-rounded perspective

Response 4: Thank you for your positive feedback.

Comment 5: Clarification of Methodology: While the manuscript mentions the use of "random-effects models," it does not fully explain how confounding factors such as age, sex, and physical activity were handled. It would be beneficial to elaborate on the specific confounding variables considered and how they were controlled during the analysis

Response 5: Thank you for your comment surrounding the explanation of confounding factors. As sex was the main confounding factor that wasn't controlled for in studies by covariate analysis, we have explained in our methodology that two meta-analyses were conducted, separated by sex. Other potential confounders, such as age and physical activity, were adjusted for within many of the included observational studies, but this was not consistent across all studies. As our analysis synthesised published effect estimates rather than re-analysing individual-level data, we did not perform additional adjustments for these variables.

Changes made to manuscript, please see page 5

Discussed that two meta-analyses were performed, comparing the association between obesity and CRC development for the male and female sex separately to reduce the risk of between-study heterogeneity.

Comment 6: Discussion of Heterogeneity: Although the male meta-analysis shows low heterogeneity, the female meta-analysis exhibits moderate heterogeneity. The authors should delve deeper into the potential sources of variability (e.g., lifestyle factors, dietary differences, or regional characteristics) and consider conducting additional subgroup analyses to explore these differences further

Response 6: Thank you for your feedback regarding the discussion of heterogeneity in our manuscript. We agree that discussing the potential sources of variability would be beneficial in improving the overall quality of the manuscript and have subsequently included this in our "limitations" section. While conducting subgroup analyses is an excellent idea, unfortunately we do not possess sufficient data to achieve this and believe this reveals a new area of further research.

Changes made to manuscript, please see page 17

Described the potential sources of heterogeneity: "These sources of heterogeneity may be due to a variety of factors, such as dietary differences (e.g. western vs eastern diet), lifestyle factors (e.g. smoking, exercise) and genetic predisposition."

Comment 7: Inclusion of More Recent Studies: The manuscript includes studies published until 2024, but given the rapid pace of research, it may be worthwhile to extend the search period or incorporate more recent studies from 2024 onwards to ensure the findings are as current as possible

Response 7:

Thank you for your comment. Our literature search was conducted up to Aug 2024, which is ~ one year before submission. Given the short interval and the time required for peer-reviewed publications to appear in databases, it is unlikely that a significant number of eligible new studies have emerged that would materially alter the findings. Nonetheless, we will note this as a consideration for future updates of the review.

Comment 8: Enhancing the Biological Mechanisms Section: The manuscript provides a solid overview of the biological mechanisms linking obesity to CRC. However, a deeper discussion on the role of gut microbiota and its interaction with obesity-induced inflammation would strengthen this

section. Additionally, exploring genetic predispositions or biomarkers linked to CRC could offer valuable insights for future research directions

Response 8: Thank you for your feedback. We have expanded on how CRC-inducing gut microbiota can induce an oncogenic environment in obese individuals, including inflammation and altered dietary metabolism.

Changes made to manuscript, please see page 14

Added "Fusobacterium, as well as other high risk CRC-inducing microbiotas are hypothesised to cause chronic inflammation, dysregulation of immune responses and altered dietary metabolism (49). This ultimately may result in the formation of harmful metabolites"

Comment 9: Expanded Limitations Section: While the authors acknowledge certain limitations, such as the potential for publication bias and the use of BMI as a measure of obesity, a more detailed discussion on how these limitations might impact the conclusions would be helpful. The authors could also outline any steps taken to minimize these biases during the analysis

Response 9: Thank you for your comment. We've refined the "Limitations" subsection of the manuscript to describe the potential impacts of publication bias and BMI on the conclusions made in this manuscript. To minimise the impact of publication bias, we performed a funnel plot analysis, which did not reveal evidence of gross asymmetry. Additionally, we conducted separate sex-stratified meta-analyses to reduce between-study heterogeneity and enhance the reliability of effect estimates. While BMI remains a widely used and standardised metric, we acknowledge that it does not account for body fat distribution or composition.

Changes made to manuscript, please see page 17

Considered the impact of publication bias on the conclusion of this review: "potentially resulting in overstated HR measures between obesity and CRC."

Included that separate sex-stratified meta-analyses were conducted to reduce heterogeneity.

Considered the impact of using BMI on the conclusion of this review: "introduces the possibility for stronger associations to be present between CRC and other measurements of overall fatness than what was observed in this meta-analysis."