Peer-Review comments and authors responses

"Effects of Intermittent Fasting on Brain-Derived Neurotrophic Factor Levels in Adults withOverweight or Obesity: A Scoping Review"

Dear Editors and Reviewers,

We would like to sincerely thank the reviewers for their careful and thorough evaluation of our manuscript and for the time and expertise dedicated to providing constructive feedback. Their insightful comments and suggestions have been invaluable in improving the clarity, scientific rigor, and overall focus of our work. We have carefully addressed each point raised and made substantial revisions to the manuscript, as detailed below. We hope that these changes meet the reviewers' expectations and strengthen the quality and impact of our study.

Reviewer 1

1. **Comment:** Excellent idea to run this scoping review that broadly bring to the reader a wide vision about this interesting possible influence of intermittent fasting over cognitive issues. Congratulations.

Response: *Thank you for your kind words.*

Reviewer 2

1. **Comment:** Please confirm the values regarding scoping review protocol. In the METHODS Section of the ABSTRACT, I found 'A systematic search was conducted in six databases' though 'from 5 electronic databases' in RESULTS Section 3.1.

Response: *You are correct — the number of databases is five. We have corrected the METHODS section of the abstract to match the RESULTS (now it states "A systematic search was conducted in five databases").*

METHODS

2. **Comment:** It would be great to point out the beginning of the search in Methods Section. From inception?

Response: *Our search covered all available records in each database from their inception until April 26, 2025. We have revised the Methods section to clarify this, now stating: "A comprehensive search was conducted in PubMed, Scopus, Embase, Cochrane Library, and Web of Science, covering all records from each database's inception to April 26, 2025 (date of last search)."*

3. **Comment:** Please confirm the numbers, Figures and Tables. For instance, in METHODS Section, I found 'The systematic search retrieved a total of 22,108 references' in the text although '22117' in Figure 1.

Response: *Thank you for pointing out this potential source of confusion. The systematic search retrieved 22,108 records from the electronic databases, and an additional 9 records were found by manual screening of reference lists, for a total of 22,117 records, as shown in Figure 1. To avoid misunderstanding, we have revised the text to state the combined total clearly. Revised sentence (Results 3.1): "The systematic search retrieved 22,108 records from the five electronic databases, and an additional nine records were identified through manual screening of the reference lists of relevant publications, for a total of 22,117 records."*

RESULTS

4. **Comment:** In RESULT Section, please do not do a summary of each individual study, instead identify patterns and you can cite examples.

Response: *As we also explain in our response to Reviewer #3 (comment 3), we carefully examined the included trials to identify meaningful subgroups or common patterns. However, the studies proved highly heterogeneous, with each trial differing simultaneously in intermittent fasting regimen, participant characteristics, duration, and BDNF measurement methods. Due to this extreme variability, we were unable to synthesize results beyond a descriptive level or reliably categorize studies into comparable groups. Instead, we have clarified this limitation directly in the Discussion and explicitly described the main axes of heterogeneity so that readers understand why a pattern-based synthesis was not feasible.*

DISCUSSION

5. **Comment:** Please consider the organization or order of paragraphs in DISCUSSION Section. For example, 'Significant methodological limitations undermine …' before 'This review has some limitations that should be acknowledged.' would be confusing.

Response: *We agree that the previous sequence in the Discussion could be confusing. We have reorganized the paragraphs to improve logical flow: the section on "Significant methodological limitations" now comes after the general acknowledgment of the review's own limitations. This reordering makes the discussion easier to follow and more coherent.*

REFERENCES

6. **Comment:** In REFERENCE Section, please follow APA style. For example, I cannot find the pages, volumes of the journals in the section as well as the internet homepage address.

Response: *We have carefully revised all references to comply with APA 7th edition. Where page ranges and volume/issue numbers were available, we have included them; where journals provide only article numbers, we formatted the citations accordingly (volume(issue), article number, DOI). We have also added DOI or URL for all references where available.*

Reviewer 3

1. **Comment:** Justification of Scoping Review Design: The manuscript applies risk of bias assessments (RoB 2.0) and includes exclusively RCTs. This is more for a systematic review rather than a scoping review. Recommendation: Justify why a *scoping* design was chosen (mapping evidence, heterogeneity of outcomes, exploratory nature) and clarify differences from a systematic review in the introduction.

Response: *We have clarified in the Introduction why a scoping review design was selected. Although we anticipated heterogeneity in study designs, fasting regimens, and outcomes — and initially included both interventional and observational studies in our eligibility criteria — only randomized controlled trials met these criteria. We retained the scoping framework because the field is still emerging and exploratory, and our primary aim was to map and describe the breadth and characteristics of the available evidence rather than formally pool data or evaluate efficacy. We also acknowledge that the use of RoB 2.0 is not mandatory for scoping reviews but can add interpretative value by helping readers understand the quality and reliability of the available studies. For this reason, we decided to include a risk of bias assessment to better contextualize our findings. We have revised the final paragraph of the Introduction to make this rationale explicit.*

<u>METHODS</u>

2. **Comment:** Search Strategy and Transparency: The supplementary material provides extensive search strings ppcr-review-assignment-467-Othe…, but these are not summarized in the main text. Recommendation: Add a concise table/paragraph in the methods summarizing the databases, search dates, and key terms. Clarify whether grey literature, trial registries, and unpublished data were considered, as their exclusion may bias *results*.

Response: *We agree that summarizing the search strategy directly in the main text enhances transparency and accessibility. In the revised Methods section, we have added a concise paragraph summarizing the databases searched, the time frame, the core concepts used, and our approach regarding grey literature and trial registries. We maintained the full detailed search strings in the Supplementary Material for reproducibility.*

3. **Comment:** Heterogeneity and Synthesis: The included RCTs differ widely in fasting protocols, populations (premenopausal vs. postmenopausal women, mixed sexes), duration, and BDNF measurement (serum vs. plasma, different ELISA kits). Recommendation: Provide a more structured subgroup discussion (e.g., by IF type, sex distribution, biomarker method). Clarify to what extent results can be pooled or compared.

Response: *We carefully examined the included trials to identify meaningful subgroups; however, the studies proved highly heterogeneous, with each trial using a distinct intermittent fasting protocol, population characteristics, duration, and BDNF assay. Because of this extreme variability, no stable or comparable subgroups could be formed, and pooling or structured subgroup analysis was not feasible. To address your suggestion, we have clarified this point in the*

Discussion and described the main axes of heterogeneity (participants, fasting protocol, intervention duration, BDNF measurement methods) to help readers understand why synthesis was limited.

DISCUSSION

4. **Comment:** Outcome Relevance and Interpretation: The discussion highlights increase in BDNF but does not evaluate whether observed magnitudes are clinically meaningful. Recommendation: Add interpretation of effect sizes in biological/clinical context. Discuss whether changes are large enough to plausibly impact cognition.

Response: *We have revised the Discussion to explicitly contextualize the magnitude of BDNF changes observed in the included RCTs. We now report that peripheral serum BDNF in adults typically ranges around 20–30 ng/mL with broad interindividual variability, whereas plasma levels are generally lower and more variable. Against this background, the changes seen across our trials—generally small to moderate (approximately 1–5 ng/mL)—represent modest shifts relative to baseline concentrations, and their clinical significance remains uncertain. We also note that no minimal clinically important difference has been established for peripheral BDNF in relation to cognitive outcomes, and that matrix/assay heterogeneity further complicates interpretation. Consequently, we caution against inferring cognitive benefit from the observed magnitudes and highlight the need for future trials using standardized BDNF analytics and prespecified, adequately powered cognitive endpoints.*

5. **Comment:** Cognitive Outcomes: Only two trials assessed cognition. This is acknowledged but underdeveloped in discussion. Recommendation: Reframe cognitive outcomes as exploratory evidence. Suggest the need for trials with cognition as a primary endpoint.

Response: *We appreciate this insightful recommendation. We have expanded the Discussion to more clearly frame the available cognitive findings as exploratory and to emphasize that the current evidence is insufficient to support conclusions about neurocognitive benefit. We also explicitly highlight the need for well-powered RCTs that use validated cognitive endpoints as primary outcomes, in parallel with standardized BDNF measurement.*

6. **Comment:** Risk of Bias and Evidence Quality: Figure 2 presents RoB assessment but the manuscript underexplains implications. Recommendation: Discuss whether the more positive findings came from trials with lower or higher bias risk. Consider briefly using GRADE to communicate evidence certainty.

Response: *We have expanded the Discussion to better integrate the risk of bias assessment and its implications for interpreting the findings. We now explicitly note that several of the studies reporting increases in BDNF were rated as having moderate to high risk of bias due to limitations such as small sample size, unclear randomization, and incomplete outcome reporting. We also comment on the overall low to moderate certainty of evidence, using GRADE principles, although a formal GRADE assessment was beyond the scope of this scoping review.*

Reviewer 4

INTRODUCTION

1. **Comment:** Can you explain more why a scoping review was chosen over a systematic review or meta-analysis.

Response: *Please see our detailed explanation provided in the response to Reviewer #3 (comment 1), where we clarified the rationale for choosing a scoping review design over a systematic review.*

METHODS

2. **Comment:** I noticed you added a detailed of your search strategy in the supplementary files, but it would be great if you can add then in the main article, such the full reproducible search strings and boolean operators (e.g., ("intermittent fasting" OR "time-restricted eating") AND ("BDNF" OR "brain-derived neurotrophic factor") AND ("obesity" OR "overweight"). In addition you missed to add the field where was the search for example: title, abstract or all fields.

Response: *As also noted in our response to Reviewer #3 (comment 2), we have now added a clear and concise summary of the search strategy directly in the Methods section of the main manuscript, including the key concepts and an example of the Boolean structure. We also specified that the searches were conducted in all available fields) for each database. In line with PRISMA and PRISMA-ScR recommendations, which encourage providing a readable summary in the main text while making full reproducibility available as supplementary material, we have retained the complete database-specific search strings — including all synonyms, Boolean operators, and field specifications — in Supplementary Material 1. This ensures transparency and reproducibility without overloading the main text with technical details.*

3. **Comment:** Primary outcome: in the result you mentioned that BDNF is the primary outcome, cognition and metabolic parameters are secondary, but in the results y some cognitive outcomes are described almost as co-primary (e.g., Keawtep et al. 2024 trial), please clarify for consistency.

Response: *Our review clearly defines BDNF as the primary outcome and cognition and metabolic parameters as secondary outcomes (Methods, section 2.4). In the Results, we provided a detailed description of cognitive findings only to give the reader a complete view of the available data; this was not intended to suggest that cognition was treated as a co-primary endpoint. We have checked the text and confirmed that the outcome hierarchy remains consistent throughout the manuscript.*

RESULTS

4. **Comment**: Risk of Bias assessment. You presented the results of the ROB 2, but I believe you can extend more, and explain the bias concerns and related them the findings, which results are stronger or weaker depending on trial quality. For exmaple the studies reporting

positive effects of intermittent fasting on BDNF were among those with moderate to high risk of bias, raising uncertainty about the reliability of these findings. In contrast, the trial with the lowest risk of bias (Schübel et al. 2018) did not detect significant changes in BDNF, suggesting that better-quality evidence may not support a consistent effect. This aligns with your comment in the conclusion that future RCT with rigorous methodology are needed to clearly understand the relationship between intermittent fasting and BDNF modulation.

Response: *As also noted in our response to Reviewer #3 (comment 6), we have expanded the Discussion to integrate better the risk of bias assessment and its implications for interpreting the findings.*

5. **Comment:** Only two studies addressed cognition, please emphasized more clearly to avoid overstating conclusions.

Response: *As also addressed in our response to Reviewer #3 (comment 5), we have revised the Discussion to make it clear that only two included trials evaluated cognitive outcomes and that these data should be considered exploratory. We explicitly caution against overstating conclusions on neurocognitive benefits and emphasize the need for future well-powered RCTs with cognition as a primary endpoint to clarify potential effects.*

6. **Comment:** Some studies reported BDNF changes are statistically significant but may not be clinically meaningful, please expand more and provide interpretation of effect sizes and potential clinical impact.

Response: *As also detailed in our response to Reviewer #3 (comment 4), we have expanded the Discussion to explicitly address the biological and clinical meaning of the observed BDNF changes.*

7. **Comment:** Cognitive outcomes: In the results you said: "no cognitive benefit attributable to IF." And in the discussion you added: Keawtep et al. reported global cognitive improvements across all groups", maybe add "there were not specific to IF" , if that is the case.

Response: *We agree and have clarified this point for accuracy and consistency. In the Results section, we now specify that the cognitive improvements reported by Keawtep et al. occurred across all intervention groups and were not specific to IF. This addition ensures that the text does not imply a unique cognitive benefit attributable to intermittent fasting.*

<u>OTHER</u>

8. **Comment:** As part of PRISMA, please remember to add a statement on funding and conflicts of interest.

Response: *We have now added a clear statement on funding and conflicts of interest at the end of the manuscript.*

9. **Comment:** Number of databases, in the abstract you say 6, and in the results you mentioned 5.

Response: *As also noted in our response to Reviewer #2 (comment 1), the correct number of databases is five. We have corrected the Methods section of the abstract to match the Results, and it now consistently states: "A systematic search was conducted in five databases."*

It has been a true pleasure to read and consider all your comments. Thank you for taking the time to explore deeply the methodological meaning of our choices and helping us find the best way to interpret and describe our results. Your review highlighted weak points with great clarity but also guided us with precise and thoughtful recommendations. As an author, I have learned a lot; but also, as a scientist and reviewer myself, I am always enriched by the expertise and perspective of colleagues like you. And like me, all my co-authors have learned and benefited greatly from this process as well. Thank you sincerely to all of you.

Best Regards,

Yannick Hurni, MD

On behalf of all co-authors