Peer-Review comments and authors responses

"Hormone replacement therapy and risk of dementia in postmenopausal women: a systematic review and meta-analysis"

Dear editor and reviewers,
Thank you so much for your kind responses and insights. We highly value the time and effort you made in reviewing our paper and with that in mind we made careful revision of the manuscript and after critically discussing, we made the pertinent changes. In the following lines you will find our responses to the comments made by each one of you. Once again, we are grateful for the opportunity.

Reviewer 1

Dear Authors,

Thank you for the opportunity to review your manuscript. The topic is highly relevant, and the study is carefully conducted. I have a few suggestions to improve clarity, consistency, and scientific style:

TITLE AND ABSTRACT

1. **Comment:** Suggest removing "Use of" → "Hormone Replacement Therapy and Risk of Dementia in Postmenopausal Women: A Systematic Review and Meta-Analysis."

Response: *Thank you for the suggestion, we applied the change.*

2. **Comment:** Background: Use past tense consistently ("This review aimed" instead of "We intend").

Response: *Change applied*

3. **Comment:** Methods: Please check study count (should be 32 studies: 2 RCTs, 18 cohort, 12 case-control). Also, phrase as: "A total of 5,283 records were retrieved…"

Response: *Tenses and the study count is correct now*

4. **Comment:** Results: Replace symbols (<, >) with words (fewer than 200; more than 100,000). Write "women older than 65 years" instead of "women >65 years".

Response: *Change applied*

5. **Comment:** Conclusions: Rephrase final sentence for clarity → "Broader health status and environmental factors may play a more substantial role in dementia risk than HRT itself."

Response: *Change applied*

6. **Comment:** Keywords: Standardize "Alzheimer's Disease" and shorten "Estrogen-Progestin Combination Therapy" to "Estrogen-Progestin Therapy".

Response: *We standardized terminology as Combined Hormone Therapy, Estrogen Replacement Therapy or Hormone Replacement Therapy*

INTRODUCTION

7. **Comment:** The introduction section is well written and scientifically sound, but it can definitely be made more concise, and fluent. Some sentences are quite long (e.g., first one about global burden). Consider shortening long sentences to improve readability. For example:
   "Dementia is a significant global public health challenge, with an estimated economic burden of US$2.8 trillion in 2019, projected to rise to US$16.9 trillion by 2050 (Lin et al., 2025)."

Response: *Change applied*

8. **Comment:** Regarding terminology "plasmatic estrogen levels" is unusual — "circulating" or "blood estrogen levels", would be better.

Response: *Change applied*

9. **Comment:** Ensure consistency in formatting: Example: "Nerattini et al. 2023" → should include a comma before the year (Nerattini et al., 2023).

Response: *Change applied*

10. **Comment:** Same applies to Tang et al. 1996; Kawas et al. 1997 → should be Tang et al., 1996; Kawas et al., 1997.

Response: *Change applied*

11. **Comment:** Study aim: Suggested improvement for the final paragraph: "The aim of this study is to clarify the extent to which HRT influences dementia risk. We specifically target variables not extensively addressed in prior systematic reviews and re-evaluate outcomes using meta-analysis. This dual approach seeks to provide robust and clinically relevant evidence to guide decision-making."

Response: *Change applied*

METHODS

12. **Comment:** Overall, it is well-structured, thorough, and follows standard systematic review/meta-analysis methodology, including PRISMA guidelines, eligibility criteria, data extraction, data synthesis, and risk of bias assessment.

13. **Comment:** You mention the last search date, but you do not specify the start date or if there were language restrictions. This is important for reproducibility.

Response: *Suggestion applied*

14. **Comment:** You reference Figure 1 for the screening process, but it's not described in text. Consider briefly summarizing how many studies were screened, excluded, and included.

Response: *Suggestion applied*

RESULTS

15. **Comment:** The Results section is thorough and well-structured, with clear subsections covering study characteristics, interventions, qualitative findings, risk of bias, and quantitative analyses. The large sample and diversity of study designs are strengths; however, only 26 studies reported follow-up – suggestion: should be highlighted as a limitation.

Response: *Highlighted in the discussion*

16. **Comment:** Quantitative analyses show very high heterogeneity ($I^2 > 98\%$), limiting confidence in pooled estimates, and subgroup/cumulative analyses could benefit from more discussion of observed trends.

Response: *We addressed this issue and mentioned it in the results section.*

17. **Comment:** Risk of bias is presented – suggestion: specifying which studies contributed most to concerns would strengthen transparency.

Response: *Mentioned in discussion now*

18. **Comment:** Table 1- Characteristics of the included studies. Consider standardizing the units of measurement and how results are displayed. For example, the table header says the results will be displayed as Baseline Age (Mean, SD)... but it's confusing, and each row displays the data differently. Sometimes as an average ± SD, sometimes average(SD XXX), etc... This applies to the Duration Y column.

Response: *We reformatted table 1 for better understanding.*

Reviewer 2:

I commend the authors for undertaking a very large and carefully assembled meta-analysis on a clinically important question. The topic is timely, the scope is impressive, and the potential to inform patient care and shared decision-making is high. The manuscript reflects substantial effort in study identification and data synthesis.

That said, several important methodological and reporting issues need to be addressed. These concerns significantly limit the interpretability of the findings, and as such, major revisions are required for publication. Please find my detailed comments and suggestions for each section of the manuscript in the attached files.

ABSTRACT

1. **Comment:** Background: Please provide more specific background evidence to establish the importance of the topic. “Novel variables” needs clarification—do you mean effect modifiers, confounders, or interactions?

Response: *We changed the term for better clarification*

2. **Comment:** Methods**:** From what date were studies eligible? "Covidence" does not need to be mentioned here. Please follow the PRISMA Abstract checklist for systematic review abstracts. Specify the statistical model used (random-effects vs fixed-effect), the qualitative assessment scale (if any), and any restrictions by language or age.

Response: *We specified now the time frame for eligibility and took out the mention of Covidence. Also added the specification for the model used.*

3. **Comment:** Results: Why does the abstract start in 1996? Consider omitting study designs from the Results, as they are not necessary in an abstract. Report the pooled estimate first; subgroup analyses should follow. Please report ORs (with 95% CI and p value) for each association. Consider not providing estimates by study type in the abstract, and report ORs rather than coefficients.

Response: *Change applied*

4. **Comment:** Conclusion: Please avoid prescriptive statements. Do not conclude that other covariates have stronger associations than HRT; that was not your primary hypothesis and the analysis was not designed to examine those variables. Limit conclusions to your hypothesis and the implications of your results.

Response: *Changes applied and final statement on conclusion now better suited for our research question.*

<u>INTRODUCTION</u>

5. **Comment:** Line 75: Please provide the effect-size difference and a reference. "Factors" for what—an increased risk of dementia or a decreased risk? Please be explicit.

Response: *Suggestion applied*

6. **Comment:** Line 78: What have researchers found about plasmatic estrogen levels and dementia? Please add a concise summary with a citation.

Response: *Suggestion applied and changed the statement.*

7. **Comment:** Line 81: Is HRT currently widely prescribed, or is its use declining? This sentence should establish the relevance of this systematic review.

Response: *We consider that the prescription habits could be better analyzed in the discussion*

8. **Comment:** Line 82: Consider "known factors associated with increased/decreased dementia risk," or restructure so it is clear these factors have evidence for association with a specified outcome.

Response: *Clarified now*

9. **Comment:** The paragraph is difficult to follow and mixes several topics without a clear logic. Please restructure and clarify the argument.

Response: *Paragraph restructured*

10. **Comment:** You begin with vasomotor symptoms, then list factors without stating whether they increase or decrease which outcome, and then move to cardiovascular morbidity and pivot to cognition/dementia.
    Please avoid overstatements such as "HRT is protective" or "prevents," which are causal. Neutral phrasing is preferable (for example, "associated with lower risk in some observational cohorts") and reporting effect sizes will help readers understand magnitude.
    Please define "early" explicitly (for example, years since menopause or age at initiation).
    Please clarify what you mean by "variables." Did you explore heterogeneity and assess differences in the overall estimate across subgroups? It would help to specify what you planned to evaluate when designing the study.

Response: *We carefully reviewed these comments to avoid language that suggests causality. As the introduction section is intended to be brief we considered that adding reported effect sizes at this point could be confusing. We did explore subgroups and their corresponding heterogeneity, however, this is addressed with further detail on the result sections*

METHODS

11. **Comment:** Please omit the time constraint for PROSPERO registration. If registration in PROSPERO is no longer possible due to advanced work, consider making the a priori protocol publicly accessible (for example, OSF Registries or protocols.io), including a timestamped version in the supplement, and providing a brief table of protocol deviations.

Response: *Suggestion applied*

12. **Comment:** Eligibility criteria should be reported before the search strategy, as this is the standard order for a systematic review. Because the search strategy used only MEDLINE and Scopus, please remove the term "comprehensive." Current guidance generally recommends at minimum MEDLINE, EMBASE, and CENTRAL for a comprehensive review, and encourages inclusion of trial registries and grey literature.

Response: *Suggestion applied. We highly appreciate the clarification on the term comprehensive.*

13. **Comment:** Please specify the types of studies included and excluded in the eligibility criteria.
    Lines 124–125: Please do not list the absence of inclusion criteria as exclusion criteria.

Response: *We corrected these lines*

14. **Comment:** The study designs included in the review should appear in Eligibility criteria. Systematic reviews include primary evidence only (clinical studies on individuals). Secondary evidence (systematic reviews, narrative reviews, editorials) does not need to be discussed here. There is no description of the screening process or full-text selection. Please add this per PRISMA.

Response: *Suggestion applied*

15. **Comment:** Line 133: Keep tense consistent (past). If a third independent reviewer resolved disagreements, please write this in past tense.

Response: *Suggestion applied*

16. **Comment:** Line 135: "The main characteristics of the studies included are summarized in Table 1" belongs in the Results section.

Response: *Suggestion applied*

17. **Comment:** Please list the most important data items extracted (per PRISMA). If possible, include the data-extraction template as supplementary material. *Data Analysis*: You state you "elaborated contingency tables… to obtain unadjusted ORs." For observational studies of HRT and cognitive outcomes, confounding is substantial (age, education, vascular risk, surgical menopause, formulation/route/dose, timing). Pooling primarily unadjusted ORs would likely bias summary effects.

Response: *Thank you for this important observation. We understand that considering unadjusted OR is subject to confounding effects. However, even in adjusted models comparability is limited because the set of covariates that each one of the studies considered for their models is widely different. Even with this evident limitation that we expressed now on our discussion, we conducted separate meta-analyses models trying to analyze the phenomenon and for sure the findings add to the final conclusions of our review.*

18. **Comment:** Please pre-specify that you will prioritize adjusted estimates (aOR, aRR, aHR) and use unadjusted 2×2 ORs only when adjusted effects are unavailable; then perform sensitivity analyses excluding unadjusted studies or stratifying by adjustment status.

Response: *We now pre-specified in the methods section the plan to conduct the different meta-analysis models and their corresponding subgroup analysis and sensitivity analysis.*

19. **Comment:** Please choose one primary model (fixed-effect or random-effects). Using both as joint primary analyses is not recommended. Selecting FE vs RE based on Q/I^2 is discouraged. If there is clear clinical or methodological diversity, random-effects should be the default primary model; FE can be a sensitivity analysis if heterogeneity is limited.

Response: *Suggestion applied. We pre-specified random-effects model for the meta-analysis in this new revision.*

20. **Comment:** Please report odds ratios (OR) in the text; the log scale can remain internal. Do not report results in log scale.

Response: Forest plots and the manuscript text now report OR instead log OR.

21. **Comment:** Some cohorts may report risk ratios (RR) or hazard ratios (HR) rather than ORs. If you converted any RR or HR to ORs for pooling, please state how and justify.

Response: *We are now stating what was the procedure for converting HR and RR into OR.*

22. **Comment:** Please clearly define the pooled outcome (for example, incident dementia or cognitive decline by scale).

Response: *This is not possible because each paper used different methods to ascertain the diagnosis of dementia. We addressed this issue with further detail in the discussion section.*

23. **Comment:** Describe that you will do Heterogeneity exploration and subgroup analyses, and please specify your pre-specified subgroup analyses clearly. You list four pooled analyses (overall; Mixed HRT; CHT; ERT) and also note "subgroup.

Response: *Suggestion applied. Now we distinguish among different meta-analysis models and their correspondent subgroups.*

24. **Comment:** Analyses and cumulative meta-analyses stratified by type of study." This plan reads as partially redundant. It would be clearer to present one primary analysis (overall), then explore heterogeneity through pre-specified subgroups, and finally present sensitivity analyses. Cumulative meta-analyses are typically chronological (by year) to assess time trends.

Response: *Suggestion applied in the correspondent section.*

25. **Comment:** "Mixed HRT," "CHT," and "ERT" are not clearly defined. Please define each category in the methods section.

Response: *Suggestion applied in the corresponding section*

26. **Comment:** Additional supportive sensitivity analyses could include excluding high–risk-of-bias studies and excluding studies that only report unadjusted Ors from observational studies. Please report Stata software as: Stata/BE 19.5.

RESULTS

27. **Comment:** Overall, the results section is confusing, and presents the findings in a way that is difficult for the reader to understand. Please follow a standard order for presenting results to improve readability and clarity. Guidance is available in the Cochrane Handbook:https://www.cochrane.org/authors/handbooks-and-manuals/handbook/current/chapter-

    Please follow a standard Results flow: study selection → study characteristics → risk of bias → primary quantitative synthesis (overall) → pre-specified subgroups → sensitivity analyses → small-study effects/publication bias → cumulative/time-trend (if retained).

Response: *Suggestions applied*

28. **Comment:** *Description of the included studies*: Please include a brief sentence that describes the selection process and reference to the PRISMA flow diagram.

Response: *Suggestions applied*

29. **Comment:** Line 173: "The population of interest were women with natural or surgical menopause" is part of the inclusion criteria. There is no need to include this in the main Results section. Instead, provide a written summary of the mean age and range, gender, and other important characteristics of the population included.

Response: *Suggestions applied*

30. **Comment:** Lines 180–183 should be included in the Methods section rather than the Results section.

Response: *Suggestion applied*

31. **Comment:** Lines 183-187: You can state: Fifteen studies evaluated estrogen-only therapy (ERT), and eight evaluated combined estrogen–progestin therapy (CHT) for clarity.

Response: *We revised again the study count and clarified on the outcomes that ech study is assessing*

32. **Comment:** Line 186: "Exposure groups were defined as women who initiated HRT after menopause onset" is also inclusion criteria and does not need to appear in the Results section.

Response: *Suggestion applied*

33. **Comment:** Lines 187–190: Please clarify what "most" means in "most studies specifying initiation within the first 10 years post-menopause." How many studies and how many participants? Ideally, include a median time to initiation in the studies.

Response: *It is not possible to include a "median time-to-initiation" since this measurement is not available in the included studies. However, in table 1 we now include information on timing.*

34. **Comment:** Lines 188–190: "This information is relevant because of the critical window of opportunity hypothesis…" belongs in the Background and/or Methods, not in Results.

Response: *Suggestion applied*

35. **Comment:** Lines 195–197: The description of control groups is redundant. Consider a singlesentence: "Control groups were postmenopausal women who never received HRT in observational studies, and placebo was used in RCTs."

Response: *We simplified the description of the control groups.*

36. **Comment:** Section 3.2 reads as general characteristics of included studies and would fit better in the description of included studies.

Response: *We suppressed this section and included it into general characteristics of included studies.*

37. **Comment:** A "Qualitative results" subsection is not standard in a meta-analysis report and is likely unnecessary. It is also long and mixes subgroup interpretations before the pooled effects are presented. Consider starting with quantitative results. If you keep narrative content, please limit it to a brief paragraph after the main pooled estimates, or preferably, address these points in the Discussion. Please also clasiffy heterogeneity as very high (I^2 = 99%).

Response: *Suggestions applied.*

38. **Comment:** Please avoid phrasing such as "first meta-analysis." There is a primary analysis, followed by subgroup analyses, and then sensitivity analyses. If your primary analysis was the summary effect for all-cause dementia, present this analysis first, then present subgroups by dementia diagnosis in the subgroup section.

Response: *Suggestions applied.*

39. **Comment:** Please state the summary estimate effect in text with 95%CI and p value. Present effectsin OR (not log scale) as it is more clinically interpreatable for the readers. (In text and Forest plots).

Response: *Forest plots and text now display results as OR with its corresponding uncertainty measures.*

40. **Comment:** After presenting the overall summary effect, move to subgroups and present results for ERT vs CHT, by timing of initiation, by study design, and by dementia diagnosis, or the subgroups you have clearly defined, with clear quantitative subgroup results in writing and in Forest plot (if available).

Response: *Suggestions applied*

41. **Comment:** Please provide in text complete quantitative reporting for each pooled analysis (OR, 95% CI, heterogeneity metrics, and prediction intervals, if available).

Response: *Suggestions applied*

42. **Comment:** There provide concrete results on the RoB of the observational studies, with most being overall low, unclear or high risk of bias, and what major domains drove these results.

<u>DISCUSSION</u>

43. **Comment:** Please begin the Discussion with a succinct summary of your main findings. In the following paragraphs, it would help to place your results in the context of prior meta-analyses and explain possible reasons for differences, highlighting why your results add to the literature.

Response: *Suggestions applied, discussion now includes analysis comparing to previous works.*

44. **Comment:** Please comment on the very high heterogeneity observed, potential reasons for it, whether pre-specified subgroups explain it, and whether pooling across all studies was appropriate. Consider keeping the Discussion as a single integrated section rather than dividing it into multiple small sections.

Response: *Suggestions applied. We have now one single discussion section instead multiple subsections and also included commentaries on the sources of heterogeneity.*

45. **Comment:** Please comment on the clinical relevance of the subgroup results. I do not see the quantitative results that support the conclusion that timing of initiation has a strong effect. Was there a significant effect in the subgroup analysis by timing of initiation? If so, please describe it in the main Results section and present Forest plot of the subgroup analysis by timing of initiation.

Response: *This statement was suppressed as we do not have a quantitative estimate on the effect of timing initiation.*

46. **Comment:** Please discuss the limitations inherent in pooling observational studies, including potential biases you identified, and how you expect these might have influenced theresults.

Response: *Suggestions applied*

47. **Comment:** Please revise the strengths and limitations paragraph for clarity and coherence; several sentences are currently not well connected. The phrase "high heterogeneity of concepts" needs clarification.

Response: *We revised and re wrote the discussion section to apply the suggestions.*

48. **Comment:** Conclusions should reflect the findings of the meta-analysis. The current conclusion is not fully supported by the presented evidence. If the main analysis does not show a statistically significant effect, please avoid concluding that there is a protective effect.

Response: *Suggestions applied*

49. **Comment:** Subgroup analyses are exploratory and should be interpreted cautiously. Given the differing signals from RCTs and cohorts, statements implying protection should be avoided; instead, focus on associations and acknowledge design limitations of observational evidence

Response: *Suggestions applied*

Reviewer 3

1. **Comment:** First, I want to thank you for their excellent and thorough work on this important study. The manuscript is well-structured, comprehensive, and provides valuable insights into the association between hormone replacement therapy and dementia risk. I have provided detailed comments and suggestions to improve clarity, methodology reporting, and interpretation, which I believe will further strengthen the manuscript. Additionally, I have uploaded a file containing the same comments for the authors' reference and response. I encourage the authors to carefully consider these suggestions to enhance the quality and rigor of their work.

Response: *Thank you so much for the kind commentaries and the important insights. We will be responding to each point in the following text.*

2. **Comment:** Title : Clear and informative.

<u>ABSTRACT</u>

3. **Comment:** The abstract addresses an important and timely clinical question with a clear structure. However, several issues should be corrected: Terms such as hormone replacement therapy (HRT), randomized controlled trial (RCT)) should be spelled out at first mention in the abstract for clarity.

Response: *Suggestion applied*

4. **Comment:** Thirty two studies were included, but the breakdown provided (2 RCTs + 18 cohort + 13 case-control) equals 33 studies.

Response: *Suggestion applied, and study count revised.*

INTRODUCTION

5. **Comment:** The introduction opens with a strong, global perspective on dementia, and you provide a clear rationale for the study. Add supporting references for these sentences: "Women are at greater risk of developing dementia than men"

Response: *Suggestion applied.*

6. **Comment:** Add supporting references for these sentences: "Estrogens are thought to have neuroprotective effects" → While you cite Low & Anstey (2006), it would be stronger to add a more recent reference.

Response: *We considered citing this article because of its relevance for the topic and the limited amount of references that we have permitted in the manuscript submission.*

7. **Comment:** Add supporting references for these sentences: "Findings from clinical research suggest an increased cardiovascular morbidity with HRT use but effects on cognition remain inconsistent"

Response: *We modified this part of the introduction and now deepen further on the discussion section*

METHODS

8. **Comment:** The Methods section is well-structured. However there are few issues need corrections and clarifications:

   -"The criteria used to select papers was based on post-menopause women…" → should be corrected to "…were based on postmenopausal women…" because criteria is plural.

Response: *Suggestion applied*

   -"In persisting conflicts, a third independent reviewer makes a resolution." → should be corrected to "…resolved the conflict" for correct tense and clarity.

Response: *Suggestion applied*

9. **Comment:** Clarify whether only English-language studies were included or if studies in all languages were considered

Response: *Suggestion applied*

10. **Comment:** Specify the range of publication years included in the search.

Response: *Suggestion applied*

11. Comment: Clarify how multiple reports of the same cohort were handled to avoid data duplication.

Response: *We revised this part carefully for data analysis, on a first glance we did not found overlapping or duplicating cohorts. However, we state this more clearly in the manuscript now.*

12. Comment: Describe how studies with incomplete outcome data were treated (e.g., exclusion or sensitivity analyses).

Response: *From the studies included none had incomplete outcome data. One of the main challenges however, is the ascertainment of the diagnosis of dementia which we address in the limitations section.*

13. Comment: NOS scoring : You mentioned 9 points for cohort studies and 8 points for case-control studies. While it is not mandatory to detail which domains differ, it is good practice to clearly state the maximum points for each study type and how scores translate to good, fair, or poor quality, which you have already done.

Response: *We have this detailed information on the correspondent figure which is now highlighted.*

RESULTS

14. Comment: Ensure consistent use of uppercase and lowercase letters for proper nouns, study types, and abbreviations, and use correct punctuation—including commas, semicolons, and periods—to improve readability and maintain professional scientific style.

Examples:

"The present review included information from 14,574,096 subjects distributed in 33 studies from which 2 were randomized Controlled Trials"

"follow up time" follow-up time

Missing comma: "…18 prospective and retrospective cohort studies, and 13 case-control studies."

Response: *Suggestion applied.*

15. Comment: Use past tense consistently when describing study results.

Response: *Suggestion applied.*

16. **Comment:** Split overly long sentences to improve readability.

Response: *Suggestion applied.*

17. Comment: The population of interest were women- change to was.

Response: *Suggestion applied*

DISCUSSION

18. Comment: The Discussion acknowledges some limitations, but several critical points are not fully addressed. Most notably:

1. Residual confounding in observational studies: The majority of included studies are observational, and important confounders such as age at menopause, baseline cognitive function, education, cardiovascular health, comorbidities, and lifestyle factors may not have been fully measured or adjusted for. This could bias observed associations between HRT and dementia.
2. Follow-up duration variability: Dementia is a long-latency outcome, yet some studies had relatively short follow-up periods, potentially underestimating the true effect of HRT.

Response: *In this revised version we highlighted the sources of heterogeneity and the implications for the interpretability of the results.*

Reviewer 4:

1. **Comment:** This is a well-designed and timely review that contributes to the literature. Addressing the above comments — particularly heterogeneity exploration, evidence grading, and improved data presentation — will significantly strengthen the manuscript and its clinical relevance.

Response: *Thank you for the important insights and kind commentaries. In the following lines we address each one of the points.*

2. **Comment:** The authors conducted a systematic review and meta-analysis of 32–33 studies (RCTs, cohort, and case-control) to examine the relationship between HRT and dementia risk, with a focus on timing, duration, and formulation. They followed PRISMA guidelines and performed both qualitative synthesis and quantitative meta-analysis with subgroup and sensitivity analyses. The findings suggest no significant overall association between HRT and dementia risk, but early initiation of estrogen-only therapy may confer protective effects, whereas late initiation (especially after age 65) may increase risk.

Major Strengths

• Comprehensive literature search using MEDLINE and SCOPUS, with clear inclusion/exclusion criteria.
• It was mentioned key effect modifiers such as timing, formulation, and duration, which is clinically relevant.
• Robust statistical approach including random-effects models, heterogeneity assessment (I^2), subgroup and sensitivity analyses, and publication bias testing.
• Balanced discussion acknowledging the complexity and heterogeneity of evidence.

Major Comments and Recommendations

3. **Comment:** Clarify Study Numbers: The abstract mentions 32 studies while the results section refers to 33 studies. Please reconcile this inconsistency.

ABSTRACT

4. **Comment: Result section in the Abstract***: 32 studies (2 RCTs, 18 cohort, 13 case-control; published 1996–2024) were included, evaluating estrogen-only therapy (ERT) and combined hormone therapy (CHT) in relation to all-cause dementia and Alzheimer's disease (AD).*

Response: *We revised the study count and made it consistent throughout the text*

RESULTS

5. **Comment:** ***3.1- Description of the Studies***

   The present review included information from 14,574,096 subjects distributed in 33 studies from which 2 were randomized Controlled Trials, 18 prospective and retrospective cohort studies and 13 case-control studies

   Certainty of Evidence: Incorporate a GRADE assessment to summarize the strength of evidence for each outcome (all-cause dementia, Alzheimer's disease).

Response: *Even when adding a GRADE assessment would certainly enrich the review, the way the outcomes were ascertained represents a major limitation to guide practice. This issue is now further developed in the discussion section.*

6. **Comment:** Data Presentation: Present odds ratios (OR) or risk ratios instead of log OR for clinical interpretability and include key forest plots and funnel plots. It will be important to mentioned in the material and method section the statistical methods for the quantitative analysis and why using Log OR instead of OR.

Response: *Suggestion applied in the Forest plots and the text.*

7. **Comment:** Clinical Applicability: Expand discussion to include guidance on patient selection, particularly regarding early initiation of therapy, and outline potential harms for older women initiating HRT late.

Response: *Suggestion applied*

8. **Comment:** Reference Formatting: Ensure consistent style (e.g., journal names, DOI inclusion, author initials). Use of italics for journal names is inconsistent.

Response: *Suggestion applied*

9. **Comment:** Reference Redundancy: Moher et al. (2009) and Liberati et al. (2009) are both PRISMA papers — either consolidate them or clarify the distinction (one is the statement, the other is the elaboration).

Response: *Suggestion applied*

10. **Comment:** Terminology: Be consistent when referring to 'combined hormone therapy' (CHT) vs. 'mixed HRT' to avoid confusion.

Response: *Suggestion applied*

Overall Assessment

Comment: This is a well-designed and timely review that contributes to the literature. Addressing the above comments — particularly heterogeneity exploration, evidence grading, and improved data presentation — will significantly strengthen the manuscript and its clinical relevance.