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Reviewers' comments:

Reviewer #1 (Remarks to the Author):

Overall comments to the authors

In this study, the authors examined the association between three different measures of lactation duration and incident IHD among Chinese parous postmenopausal women from the China Kadoorie Biobank Study, using appropriate statistical analyses. The authors also examined several scenarios using PAF and PIF to prevent IHD cases in Chinese parous postmenopausal women.

The study provides interesting insights as to the associations of different measures of lactation duration and incident IHD and explores the nature of the dose-response relationship. However, to strengthen the manuscript and further highlight its novelty and unique contributions to the literature, the manuscript would benefit from further discussion of findings in relation to previous studies and public health implications.

Specific comments to the authors

TITLE Please include the study design in the title.

INTRODUCTION

Lines 88-89 Please include any references to studies that have previously examined a dose-response relationship between lactation duration and IHD.

METHODS

Lines 136-137 What were the actual questions used to assess lactation duration? Please include these in the paper.

Lines 167-177 Besides alcohol intake, were there other relevant dietary variables that were asked about in the questionnaire and that could have been included as covariates? If yes, why weren't these included in the study?

Lines 240-242 This sentence on its own is unclear, please reword it.

RESULTS

Lines 273-285 Please provide a brief description of other main characteristics of the

sample at baseline as this is missing.

DISCUSSION

General comments

- To further highlight this study's key findings, authors may want to summarise optimal lactation duration periods for different measures of lactation duration and discuss findings in relation to current breastfeeding recommendations/guidelines. What are the main public health implications that can be derived from this study?
- In the introduction, the importance of assessing the effects of lactation duration for one child versus lifetime cumulative lactation duration was raised (lines 90-94). Please discuss findings related to this point in the discussion.

Lines 361-368 Authors may want to highlight the novel and unique contributions of this study in this paragraph

Lines 369-377 Although findings from two other studies are mentioned, a more substantial discussion of how this study's findings compare with those from other studies would have been appreciated, for example, in terms of the magnitude of effect. The authors may also want to refer to findings from a recent systematic review and meta-analysis by Tschiderer et al. (Breastfeeding Is Associated With a Reduced Maternal Cardiovascular Risk: Systematic Review and Meta-Analysis Involving Data From 8 Studies and 1 192 700 Parous Women. *J Am Heart Assoc.* 2022 Jan 18;11(2):e022746. doi: 10.1161/JAHA.121.022746).

Lines 409-410 To increase clarity, please provide examples of "other factors".

Lines 415-416 Can the authors clarify what they mean by "scaling up breastfeeding practices"?

Lines 419-420 Authors should consider tempering the language in "These findings... offer a comprehensive understanding of lactation's role in preventing IHD..." as the findings do not help us to fully understand the role of lactation in preventing IHD in parous postmenopausal women.

Lines 433-439 Limitations: did the questionnaire ask about conditions that these parous women may have experienced during pregnancy (e.g. pre-eclampsia, gestational diabetes) that may have affected breastfeeding practice?

Reviewer #2 (Remarks to the Author):

Dear authors,

Thank you for undertaking this important work. You have done a tremendous job of thoroughly assessing the relationship between lactation duration and future risk of ischemic heart disease (IHD). Your research has yielded important results for the field by defining a U-shaped curve between lactation duration and IHD risk. These results, as you point out, have significant repercussions for how we advocate for breastfeeding.

Although I am convinced by many of the results in your paper, and there certainly is an association between lactation duration and subsequent IHD risk, I am not fully convinced about causation. You suggest that increasing the prevalence of breastfeeding can reduce IHD burden - that more breastfeeding would lead to less IHD. Though you have adjusted for many variables, and offer comprehensive suggestions for why this relationship may exist, I still think there are too many variables that contribute to IHD risk for us to find causation based on your results alone. I agree with your conclusion that lactation duration should be considered in thinking about future IHD risk, but to suggest that promoting breastfeeding alone will reduce IHD incidence is a step further than I am willing to take it.

Overall, however, I think the results you have presented are important and rigorously help address a gap in the literature regarding reproductive history and IHD risk. You should be commended on undertaking this work and the meaningful outcomes you have shown.

Reviewer #3 (Remarks to the Author):

This is a very interesting article and points to the importance of public health to support breast feeding initiation and continuation to reduce the risk of future IHD. The authors limit their study to postmenopausal women in a large and what appears to be robust database.

There have been a number of recent articles published on this topic including a meta-analysis (J Am Heart Assoc. Jan 18 2022;11(2):e022746. doi:10.1161/jaha.121.022746) and an editorial (Eur J Prev Cardiol. 2023 Nov 28:zwad366. doi: 0.1093/eurjpc/zwad366. Online ahead of print.

PMID: 38015661) that should be considered.

The authors found that there was a reduction in IHD for those women who had lifetime breast feeding up to 24 months. However, beyond that, there was a reduction in benefit. The authors make no attempt to explain this but the finding is troubling as it doesn't perfectly align with the "reset hypothesis". Line 277-279 essentially says that the longer you breast feed, the greater your risk of IHD!

One of the potential confounders that they haven't considered, and they may have information in their database, relates to pregnancy complications. The recent editorial identified that the recent meta analysis couldn't differentiate those individuals with uncomplicated pregnancies and those with complicated pregnancies. We know that about 20% of individuals have a pregnancy complicated by one or more of hypertensive disorder of pregnancy, gestational diabetes, preterm birth, fetal growth restriction, etc.....all of which increase the risk of CVD including IHD. There is at least one study looking at the impact of breastfeeding duration following "high risk" pregnancies within the first year of metabolic parameters that demonstrated benefit. If the authors have data relating to pregnancy outcomes in their datasets, they should include them in the modelling. If they don't have such data, they at least need to comment on this limitation as it is a group that is at higher risk of future CVD and should be supported/encouraged to breast feed to reduce their risks.

I like the theoretical calculations to determine what would happen if all women breast fed in terms of risk reduction but there is no comment in the Discussion about how that might be attained.

The authors have focussed on postmenopausal women but it would also be worthwhile looking at premenopausal women....while the prevalence of IHD will be lower, these are the individuals who are at greater risk of CVD and cardiovascular death if they already have IHD before menopause.

"Response to referees" letter

COMMSMED-23-0591-T

Response to Reviewer #1 Comments

Reviewer #1 Comments to the Author:

Overall comments to the authors

In this study, the authors examined the association between three different measures of lactation duration and incident IHD among Chinese parous postmenopausal women from the China Kadoorie Biobank Study, using appropriate statistical analyses. The authors also examined several scenarios using PAF and PIF to prevent IHD cases in Chinese parous postmenopausal women.

The study provides interesting insights as to the associations of different measures of lactation duration and incident IHD and explores the nature of the dose-response relationship. However, to strengthen the manuscript and further highlight its novelty and unique contributions to the literature, the manuscript would benefit from further discussion of findings in relation to previous studies and public health implications.

Specific comments to the authors

Comment 1: TITLE: Please include the study design in the title.

Response 1: Thanks for your comments. We have revised the title according to your suggestion. The new title now includes the study design and reads as follows: "Lactation duration and ischemic heart disease among parous postmenopausal females: findings from a prospective cohort study and the potential health gains from scaling up breastfeeding practices".

Comment 2: INTRODUCTION: Lines 88-89 Please include any references to studies that have previously examined a dose-response relationship between lactation duration and IHD.

Response 2: Thanks for your reminder. We have added references that have previously examined a dose-response relationship between lactation duration and IHD.

A systematic review and meta-analysis involving data from 8 studies and 1,192,700 parous women found a significantly decreased risk for maternal cardiovascular disease, coronary heart disease, stroke, and fatal cardiovascular disease for lifetime durations of breastfeeding for up to 12 months, and after this time, the effect on coronary heart

disease appeared to reach a plateau between 12 and 48 months (doi: 10.1161/JAHA.121.022746). The HUNT study found that there was some evidence of a U-shaped association, where women who reported lactating 7–12 months had a HR of 0.55 (95% CI: 0.27, 1.09) for cardiovascular mortality (doi: 10.1186/1471-2458-13-1070). A prospective study of 300 000 Chinese women found there was an inverse log-linear association between the duration of breastfeeding per child and the risk of several major cardiovascular disease, as well as coronary heart disease (doi: 10.1161/JAHA.117.006081).

For ease of review, we also list it below:

Page 3, Lines 71-72 (Introduction):

“Nonetheless, the dose-response relationship between lactation duration and the risk of IHD is poorly understood¹⁸⁻²⁰.”.

Reference 18-20:

- 18 Tschiderer, L. *et al.* Breastfeeding is associated with a reduced maternal cardiovascular risk: Systematic review and meta-analysis involving data from 8 studies and 1 192 700 parous women. *Journal of the American Heart Association* **11**, e022746 (2022).
- 19 Natland Fagerhaug, T. *et al.* A prospective population-based cohort study of lactation and cardiovascular disease mortality: the HUNT study. *BMC public health* **13**, 1070, doi:10.1186/1471-2458-13-1070 (2013).
- 20 Peters, S. A. *et al.* Breastfeeding and the risk of maternal cardiovascular disease: a prospective study of 300 000 Chinese women. *Journal of the American Heart Association* **6**, e006081 (2017)

Comment 3: METHODS: Lines 136-137 What were the actual questions used to assess lactation duration? Please include these in the paper.

Response 3: Thanks for your considerable suggestion. The specific question used to assess lactation duration was “Age and length of lactation at each live birth” in the China Kadoorie Biobank (CKB) questionnaire. We have included this question in the Methods section.

Page 4, Lines 118-120 (Methods):

“At baseline, females completed an interviewer-administered electronic questionnaire on lactation duration for each live birth using the specific question “Age and length of lactation at each live birth”. ”

Comment 4: METHODS: Lines 167-177 Besides alcohol intake, were there other relevant dietary variables that were asked about in the questionnaire and that could have been included as covariates? If yes, why weren’t these included in the study?

Response 4: Thanks for your insightful comments. In the CKB study, dietary variables were assessed using food frequency questionnaires. However, due to restrictions in those data, we were unable to include these dietary variables as covariates in the study. We acknowledge this limitation and have explicitly mentioned it in the limitations section of our study.

Page 13, Lines 451-454 (Methods):

“Third, although comprehensive adjustment has been made for a wide range of covariates, the influence of certain confounding factors, such as the family history of IHD, dietary variables were not taken into account, limiting our ability to establish causality.”

Comment 5: METHODS: Lines 240-242 This sentence on its own is unclear, please reword it.

Response 5: Thanks for your suggestions. We have revised it as follows:

Page 7, Lines 240-242 (Methods):

“In contrast to PAF, which is typically based on an impractical counterfactual scenario assuming a 100% reduction in the risk factor, PIF is estimated based on reasonably achievable theoretical counterfactual scenarios.”

Comment 6: RESULTS: Lines 273-285 Please provide a brief description of other main characteristics of the sample at baseline as this is missing.

Response 6: Thanks for your thoughtful suggestion. We have included a brief description of other main characteristics of the sample at baseline in the Results section. For ease of review, we also list it below:

Pages 8-9, Lines 274-290 (Results):

“A total of 130,147 parous postmenopausal females were finally included in our study (median age: 58.4 [IQR 54.0-64.8]), of whom 14,268 (11.0%) developed IHD during follow-up, showing an incidence density of 1276.2 per 100,000 person-years. The baseline characteristics of the 130,147 parous postmenopausal females are shown in **Table 1**. Generally, most participants were urban residents (55.4%), had an education level of primary school or below (74.5%), unemployed or retired (53.5%), belonging to middle-income households (51.0%). These participants with incident IHD tended to have gravidity of ≥ 5 (41.2% vs 30.3%), have parity of ≥ 4 (37.4% vs 26.1%), compared to non-IHD ones. While in non-IHD subgroup, the proportions of participants with age at first live birth between 20 and 24 (53.4%) or with age at menopause between 45 and 54 (84.4%) are larger. Compared with those who did not develop IHD, parous postmenopausal females who developed IHD have significantly longer lifetime lactation duration (44.0 [IQR 24.0-72.0] months vs. 36.0 [IQR 24.0-60.0] months) and per-child lactation duration (13.0 [IQR 12.0-19.5] months vs. 12.2 [IQR 12.0-19.3] months). While for the first-child lactation duration, this difference was not statistically significant. More baseline characteristics of females by SES or residence are shown in **Table S2-S3**.”

Comment 7: DISCUSSION: General comments:

- To further highlight this study's key findings, authors may want to summarize optimal

lactation duration periods for different measures of lactation duration and discuss findings in relation to current breastfeeding recommendations/guidelines. What are the main public health implications that can be derived from this study?

Response 7: Thanks for your comments. Our study suggests that lactation durations of at least six months may be protective against IHD among this population. This is consistent with the World Health Organization's recommendations of exclusive breastfeeding for six months, followed by continued breastfeeding along with appropriate complementary foods for up to two years or beyond. In light of those findings, we propose that lactation should be supported not only for its known benefits to the child but also as a significant modifiable protective factor for IHD in later life for the mother. This perspective aligns with a more holistic approach to public health, where the well-being of a mother is seen as closely linked to the health of her children and the wider community.

To address the public health implications more directly, we have revised the conclusion to include a summary of the optimal lactation durations and a discussion on how these findings could inform current breastfeeding practices and policies. We believe that by scaling up breastfeeding practices to meet these durations, significant health gains could be achieved for both mothers and children, especially within low SES communities in urban settings.

For ease of review, we also list it below:

Page 13, Lines 459-468 (Conclusion):

“In conclusion, our study indicates that lactation durations of at least six months may be beneficial in reducing the risk of IHD, especially for those with low SES and urban residence. These findings underscore the positive population-level impact achievable through the promotion of extended breastfeeding practices, aligning with the existing guidelines that advocate for prolonged optimal breastfeeding. Public health initiatives should prioritize the enhancement of breastfeeding support structures, particularly targeting urban women of low SES, to facilitate these recommended lactation durations. Such targeted strategies have the potential to a decrease in IHD burden, providing long-term health benefits and reducing economic burdens associated with cardiovascular diseases.”

Comment 8: DISCUSSION: General comments:

- In the introduction, the importance of assessing the effects of lactation duration for one child versus lifetime cumulative lactation duration was raised (lines 90-94). Please discuss findings related to this point in the discussion.

Response 8: Thank you for your valuable comments. Our intention was to emphasize that the effects of lifetime cumulative lactation duration, considering the number of live births, may differ from the effects of lactation duration for one child. Since separating lactation duration into three measures is a methodological consideration, we have

moved this section to discussion.

Regarding the findings of the three lactation duration measures in our study, we observed that both lifetime lactation duration and lactation duration for one child were associated with a lower risk of IHD compared to those who had never lactated. Specifically, all measures exhibited a U-shaped relationship, with the lowest risk observed at 24.06 months for lifetime lactation duration, 9.95 months for average lactation duration per child, and 10.85 months for lactation duration for the first child. Given these findings, lactation duration for one child could serve as a practical and easily communicated metric for public health professionals when counseling patients. This measure could be particularly beneficial for setting achievable breastfeeding goals for new mothers and for use in educational materials. However, it is essential to emphasize that the cumulative benefits of breastfeeding across multiple children may compound its protective effect against IHD, which supports the promotion of sustained breastfeeding practices with subsequent pregnancies. These insights could inform future public health strategies aimed at optimizing lactation practices to improve maternal cardiovascular health.

We have discussed these findings and their potential implications in the discussion section. For ease of review, we also list it below:

Page 12, Lines 415-420 (Discussion):

“Our findings reveal the positive impact of lactation duration, regardless of the measures employed (lifetime, average per child, or first-child). The findings regarding cumulative lactation duration across multiple children provide valuable insights into the promotion of sustained breastfeeding practices in subsequent pregnancies. While lactation duration for one child could serve as a practical and widely communicable measure in public health, making it suitable for setting achievable breastfeeding goals.”

Comment 9: DISCUSSION: Lines 361-368 Authors may want to highlight the novel and unique contributions of this study in this paragraph

Response 9: Thanks for your comments. We would like to clarify our intention in this paragraph is to summarize our findings. While the novel and unique contributions of this study have been clarified in the discussion section.

For ease of review, we also list it below:

Page 12, Lines 421-426 (Discussion):

“With the application of PAF and PIF, this study successfully revealed that by scaling up lactation to adequate durations, there is potential for a notable reduction in IHD events. Scaling up breastfeeding practices by promoting and encouraging women to lactate for adequate duration could be recommended in reducing IHD events. These insights could inform future public health strategies aimed at advocating for integrating lactation optimization into IHD preventive strategies from a maternal health standpoint.”

Page 12, Lines 434-447 (Discussion):

“Our study represents a considerable advancement in the exploration of lactation's protective effects against ischemic heart disease (IHD) in parous postmenopausal women, within the Chinese demographic. This study, to our knowledge, is the first large-scale prospective cohort study examining the associations of lactation duration with the risk of IHD, among parous postmenopausal females in China. The robustness of our findings is supported by the extensive follow-up period, the high follow-up rate from the CKB study. Our use of ICD-10 diagnosis, made by trained healthcare professionals, rather than self-reporting, enhances the accuracy of our diagnosis of IHD. Stratification and sensitivity analyses have been employed to confirm the credibility of our primary outcomes. Furthermore, the novel application of PAF and PIF in our study not only underscores the preventive potential of prolonged lactation but also provides a quantifiable framework for public health initiatives aimed at elevating breastfeeding practices to reduce the burden of IHD among postmenopausal women.”

Page 13, Lines 459-468 (Discussion):

“In conclusion, our study indicates that lactation durations of at least six months may be beneficial in reducing the risk of IHD, especially for those with low SES and urban residence. These findings underscore the positive population-level impact achievable through the promotion of extended breastfeeding practices, aligning with the existing guidelines that advocate for prolonged optimal breastfeeding. Public health initiatives should prioritize the enhancement of breastfeeding support structures, particularly targeting urban women of low SES, to facilitate these recommended lactation durations. Such targeted strategies have the potential to a decrease in IHD burden, providing long-term health benefits and reducing economic burdens associated with cardiovascular diseases.”

Comment 10: DISCUSSION: Lines 369-377 Although findings from two other studies are mentioned, a more substantial discussion of how this study's findings compare with those from other studies would have been appreciated, for example, in terms of the magnitude of effect. The authors may also want to refer to findings from a recent systematic review and meta-analysis by Tschiderer et al. (Breastfeeding Is Associated with a Reduced Maternal Cardiovascular Risk: Systematic Review and Meta-Analysis Involving Data From 8 Studies and 1 192 700 Parous Women. J Am Heart Assoc. 2022 Jan 18;11(2): e022746. doi: 10.1161/JAHA.121.022746).

Response 10: Thank you for your insightful suggestions. We acknowledge the importance of a more substantial discussion comparing our study's findings with those from other studies. We have addressed this concern in our revised discussion section. Furthermore, we have incorporated the recent systematic review and meta-analysis you mentioned into our revised manuscript.

For ease of review, we also list it below:

Page 10, Lines 351-353 (Discussion):

“In a random-effects meta-analysis involving data from over a million parous women found an 11% risk reduction for CVD and a 14% reduction for CHD among those who breastfed compared to those who did not¹⁸.”

Page 10, Lines 357-359 (Discussion):

“Consistent with these findings, our study further revealed a risk reductions between 8% and 30% across various lactation subgroups, underscoring the importance of lactation for cardiovascular health.”

Comment 11: DISCUSSION: Lines 409-410 To increase clarity, please provide examples of “other factors”.

Response 11: Thank you. We have clarified and provide specific examples of the "other factors" in our revised manuscript.

For ease of review, we also list it below:

Page 11, Lines 390-401 (Discussion):

“This association may be also influenced by CVD risk factors such as parity and pregnancy complications^{17,62,63}. Notably, our study found that the beneficial effects of lactation on IHD were most significant among females with parity of ≤ 3 , indicating that the increased cardiovascular risk associated with multiparity may diminish lactation's benefits, then appearing in U-shaped associations between lactation and the risk of IHD. Besides, longer lifetime lactation duration, commonly accompanied by multiparity, often correlates with a higher risk of pregnancy complications, including gestational diabetes, hypertensive disorders of pregnancy, and preeclampsia⁶⁴. These pregnancy complications, in turn, can increase the overall risk of cardiovascular diseases, including IHD¹⁶. Therefore, the protective effect of longer lactation duration on IHD risk may be diluted by the potential adverse impact of pregnancy complications.”

Comment 12: DISCUSSION: Lines 415-416 Can the authors clarify what they mean by “scaling up breastfeeding practices”?

Response 12: Thanks for your comments. We apologize for any confusion caused by our previous wording. We have further clarified in the discussion.

For ease of review, we also list it below:

Page 12, Lines 423-424 (Discussion):

“Scaling up breastfeeding practices by promoting and encouraging women to lactate for adequate duration could be recommended in reducing IHD events.”

Comment 13: DISCUSSION: Lines 419-420 Authors should consider tempering the language in “These findings... offer a comprehensive understanding of lactation’s role in preventing IHD...” as the findings do not help us to fully understand the role of lactation in preventing IHD in parous postmenopausal women.

Response 13: Thanks for pointing this out. We have rectified accordingly in the

discussion.

For ease of review, we also list it below:

Page 12, Lines 424-426 (Discussion):

“These insights could inform future public health strategies aimed at advocating for integrating lactation optimization into IHD preventive strategies from a maternal health standpoint. ”

Comment 14: DISCUSSION: Lines 433-439 Limitations: did the questionnaire ask about conditions that these parous women may have experienced during pregnancy (e.g. pre-eclampsia, gestational diabetes) that may have affected breastfeeding practice?

Response 14: Thanks for your valuable comments. Since the CKB questionnaire did not specifically collect information on pregnancy complications, such as pre-eclampsia or gestational diabetes, we were unable to account for these factors in our analysis. However, we have now added this limitation in our revised manuscript.

Response to Reviewer #2 Comments

Reviewer #2 Comments to the Author:

Thank you for undertaking this important work. You have done a tremendous job of thoroughly assessing the relationship between lactation duration and future risk of ischemic heart disease (IHD). Your research has yielded important results for the field by defining a U-shaped curve between lactation duration and IHD risk. These results, as you point out, have significant repercussions for how we advocate for breastfeeding.

Although I am convinced by many of the results in your paper, and there certainly is an association between lactation duration and subsequent IHD risk, I am not fully convinced about causation. You suggest that increasing the prevalence of breastfeeding can reduce IHD burden - that more breastfeeding would lead to less IHD. Though you have adjusted for many variables, and offer comprehensive suggestions for why this relationship may exist, I still think there are too many variables that contribute to IHD risk for us to find causation based on your results alone. I agree with your conclusion that lactation duration should be considered in thinking about future IHD risk, but to suggest that promoting breastfeeding alone will reduce IHD incidence is a step further than I am willing to take it.

Overall, however, I think the results you have presented are important and rigorously help address a gap in the literature regarding reproductive history and IHD risk. You should be commended on undertaking this work and the meaningful outcomes you have shown.

Response: Thanks for your constructive comments on our manuscript. We appreciate your overall positive assessment of our work.

Regarding your concern about causation, we appreciate your perspective. While our study demonstrates an association between lactation duration and subsequent IHD risk, we recognize that even after controlling for numerous confounders, residual confounding may still exist. Our study design and the observational nature of the data inherently limit our ability to establish a causal relationship. We agree that the promotion of breastfeeding, while potentially beneficial, is not a panacea for IHD prevention and should be integrated into a comprehensive cardiovascular risk reduction strategy that includes lifestyle modification, genetic risk assessment, and management of traditional IHD risk factors.

In light of your comments, we have revised our manuscript throughout to avoid the implications of our findings regarding causation. We now emphasize that lactation duration should be considered a potential modifiable risk factor within the broader context of IHD risk and that our findings warrant further investigation, particularly through interventional studies which could better elucidate causality.

Response to Reviewer #3 Comments

Reviewer #3 Comments to the Author:

This is a very interesting article and points to the importance of public health to support breast feeding initiation and continuation to reduce the risk of future IHD. The authors limit their study to postmenopausal women in a large and what appears to be robust database.

Comment 1: There have been a number of recent articles published on this topic including a meta-analysis (J Am Heart Assoc. Jan 18 2022;11(2): e022746. doi:10.1161/jaha.121.022746) and an editorial (Eur J Prev Cardiol. 2023 Nov 28: zwad366. doi: 0.1093/eurjpc/zwad366. Online ahead of print. PMID: 38015661) that should be considered.

Response 1: Thank you for providing us with the information about the recent articles published on this topic. We have carefully reviewed these articles and their relevance to our study. We have incorporated the meta-analysis and editorial in our revised manuscript.

For ease of review, we also list it below:

Page 3, Lines 66-69 (Introduction):

“Previous studies have revealed that lactation is associated with a reduced risk of coronary artery heart disease (CHD), coronary artery and aortic calcification, stroke, metabolic syndrome, hypertension, and diabetes^{15,16}.”

Page 11, Lines 398-399 (Discussion):

“These pregnancy complications, in turn, can increase the overall risk of cardiovascular diseases, including IHD¹⁶.”

Page 11, Lines 351-353 (Discussion):

“In a random-effects meta-analysis involving data from over a million parous women found an 11% risk reduction for CVD and a 14% reduction for CHD among those who breastfed compared to those who did not¹⁸.”

Page 11, Lines 378-382 (Discussion):

“For instance, a comprehensive systematic review and meta-analysis encompassing data from over one million parous women reported a substantially decreased risk of maternal cardiovascular disease and coronary heart disease (CHD) with lactation durations of up to 12 months, with the effect on CHD appearing to plateau between 12 and 48 months¹⁸.”

Reference:

- 15 Victora, C. G. *et al.* Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. *Lancet (London, England)* **387**, 475-490, doi:10.1016/s0140-6736(15)01024-7 (2016).
- 16 Smith, G. N. & Dayan, N. Management of cardiac and cardiovascular dysfunction postpartum should include support to initiate and continue breastfeeding. *European journal of preventive cardiology*, zwad366 (2023).

18 Tschiderer, L. *et al.* Breastfeeding is associated with a reduced maternal cardiovascular risk: Systematic review and meta-analysis involving data from 8 studies and 1 192 700 parous women. *Journal of the American Heart Association* **11**, e022746 (2022).

Comment 2: The authors found that there was a reduction in IHD for those women who had lifetime breast feeding up to 24 months. However, beyond that, there was a reduction in benefit. The authors make no attempt to explain this but the finding is troubling as it doesn't perfectly align with the "reset hypothesis". Line 277-279 essentially says that the longer you breast feed, the greater your risk of IHD!

Response 2:

Thank you for your insightful comment. Our study indeed suggests a U-shaped association between lactation duration and the risk of IHD, with an observed reduction in risk up to a lifetime lactation duration of approximately 24 months followed by a plateau and subsequent increase beyond this point. The "reset hypothesis" posits that lactation has a long-term protective effect on maternal metabolic health, potentially "resetting" the mother's risk of cardiovascular disease to pre-pregnancy levels. However, our findings suggest that there may be diminishing returns or even potential risks associated with extended periods of lactation. To address the unexpected findings that challenge this "reset hypothesis," we have considered several potential explanations that could account for the observed U-shaped curve. Multiparity may increase CVD incidence and mortality, the beneficial effects of lactation may not be enough to outweigh the adverse effects of multiparity, then appearing in U-shaped associations between lactation and the risk of IHD. Besides, longer lifetime lactation duration, commonly accompanied by multiparity, often correlates with a higher risk of pregnancy complications, including gestational diabetes, hypertensive disorders of pregnancy, and preeclampsia. These pregnancy complications, in turn, can increase the overall risk of cardiovascular diseases, including IHD. Therefore, the protective effect of longer lactation duration on IHD risk may be diluted by the potential adverse impact of pregnancy complications.

We therefore hypothesize that while moderate lactation may confer a cardioprotective effect, excessive cumulative lactation, particularly in the context of other risk factors, may not provide additional IHD risk reduction and may even reflect an increased underlying risk associated with other health and lifestyle factors.

Comment 3: One of the potential confounders that they haven't considered, and they may have information in their database, relates to pregnancy complications. The recent editorial identified that the recent meta-analysis couldn't differentiate those individuals with uncomplicated pregnancies and those with complicated pregnancies. We know that about 20% of individuals have a pregnancy complicated by one or more of hypertensive disorder of pregnancy, gestational diabetes, preterm birth, fetal growth restriction,

etc.....all of which increase the risk of CVD including IHD. There is at least one study looking at the impact of breastfeeding duration following "high risk" pregnancies within the first year of metabolic parameters that demonstrated benefit. If the authors have data relating to pregnancy outcomes in their datasets, they should include them in the modelling. If they don't have such data, they at least need to comment on this limitation as it is a group that is at higher risk of future CVD and should be supported/encouraged to breast feed to reduce their risks.

Response 3: Thanks for your insightful comments. We acknowledge the importance of considering pregnancy complications, such as pre-eclampsia or gestational diabetes, in our analysis. Unfortunately, the CKB questionnaire did not specifically collect information on pregnancy complications, we were unable to account for these factors in our study. However, we have now added this limitation in our revised manuscript. By acknowledging this limitation, we agree to emphasize the importance of considering pregnancy complications as a significant factor in understanding future CVD risk and individuals who have experienced complicated pregnancies should be supported and encouraged to breastfeed.

For ease of review, we also list it below:

Page 13, Lines 452-458 (Discussion):

“Third, although comprehensive adjustment has been made for a wide range of covariates, the influence of certain confounding factors, such as the family history of IHD, dietary variables were not taken into account, limiting our ability to establish causality. Important data on pregnancy complications, such as pre-eclampsia or gestational diabetes, that may affect lactation success, were not captured either. Fourth, our study is also unable to assess the risk of IHD during the childbearing years, restricting our findings to a postmenopausal cohort.”

Comment 4: I like the theoretical calculations to determine what would happen if all women breast fed in terms of risk reduction but there is no comment in the Discussion about how that might be attained.

Response 4: Thank you for your comment. It is indeed crucial to move from theoretical calculations to practical applications in public health policy and intervention design. The potential reduction in IHD risk through widespread breastfeeding is significant, but realizing this benefit requires a comprehensive strategy to support lactation across diverse populations. To address this gap, we have incorporated a detailed discussion on the strategies for promoting breastfeeding in the revised manuscript. We propose a multi-tiered approach that involves healthcare policy reform, community support systems, and education campaigns.

For ease of review, we also list it below:

Page 12, Lines 427-433 (Discussion):

“Several strategies may be effective to promote breastfeeding practice according to

previous studies , e.g. ensuring stable funding and resources for a successful national strategy for protection, promotion, and support of breastfeeding, calling for strong governmental commitment to develop an effective national breastfeeding program⁶⁵. This study thereby provides a foundation for policy initiatives that prioritize maternal lactation as a modifiable risk factor for IHD, with significant implications for public health outcomes. ”

Comment 5: The authors have focused on postmenopausal women but it would also be worthwhile looking at premenopausal women....while the prevalence of IHD will be lower, these are the individuals who are at greater risk of CVD and cardiovascular death if they already have IHD before menopause.

Response 5: We appreciate your suggestion to include premenopausal women in our analysis. We have conducted a stratified analysis by menopausal status to explore the association between lactation duration and IHD among premenopausal women. Our findings reveal nuanced associations of longer lactation duration (lifetime: ≥ 37 months; first-child: ≥ 13 months) with IHD tended to be attenuated among premenopausal females. While the associations of per-child lactation duration with IHD remained significant in both premenopausal and postmenopausal females. These additional analysis highlights the need for further research to elucidate the protective effects of lactation against IHD in younger women and to determine the optimal duration of breastfeeding that confers the greatest long-term cardiovascular benefit.

REVIEWERS' COMMENTS:

Reviewer #2 (Remarks to the Author):

This manuscript is much improved, both with reference to my earlier comments about highlighting the differences between causation/correlation as well as in reference to suggested changes from the other reviewers.

Reviewer #3 (Remarks to the Author):

The authors have adequately and appropriately responded to all the questions posed.