

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Association between maternal multimorbidity and preterm birth, low birth weight, and small for gestational age: a prospective birth cohort study from the Japan Environment Children's Study
<b>AUTHORS</b>	Nakanishi, Kentaro; Saijo, Yasuaki; Yoshioka, Eiji; Sato, Yukihiro; Kato, Yasuhito; Nagaya, Ken; Takahashi, Satoru; Ito, Yoshiya; Kobayashi, Sumitaka; Miyashita, Chihiro; Araki, Atsuko; Kishi, Reiko; group, The Japan Environment

### VERSION 1 – REVIEW

<b>REVIEWER</b>	CHINIEN CHEN National Taiwan University Hospital Hsin-Chu Branch, Pediatrics
<b>REVIEW RETURNED</b>	29-Nov-2022

<b>GENERAL COMMENTS</b>	<p>Regarding the association of chronic diseases and perinatal prognosis, and the inference of the research results, it is recommended to add some relevant information to discuss about the mediator effect or direct impact from the chronic illness on perinatal outcomes, and the definition of outcomes and exposures should be revised.</p> <p>Introduction</p> <ol style="list-style-type: none"><li>1. Although there is a lack of studies about multimorbidity during pregnancy in Japan, it is recommended to provide research on the prevalence of individual chronic diseases in pregnant women to help support the accuracy of this study.</li><li>2. It is necessary to consider whether maternal prepregnancy (early pregnancy) obesity and underweight directly lead to GDM or preeclampsia during pregnancy, which in turn leads to poor perinatal prognosis later.</li><li>3. In addition to the impact of chronic disease, drug use may also significantly affect perinatal outcomes. A discussion of drug use studies was suggested to be added to the content.</li></ol> <p>(Reference suggestion: Medicine (Baltimore). 2015 Jan;94(1):e386. Exposure of drugs for hypertension, diabetes, and autoimmune disease during pregnancy and perinatal outcomes: an investigation of the regulator in Japan)</p> <p>Method</p> <ol style="list-style-type: none"><li>1. p 10. The probability of neonatal survival at &lt;22 weeks is relatively low. Is it meaningful to include this study in the analysis?</li><li>2. P 12. The questionnaire survey collected domestic violence information, will there be any underestimation or overestimation (bias), and is there a validation study to prove it</li></ol>
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	<p>3. p 12. Pregnant women's weight is collected through questionnaires or self-reports. There may be errors or bias. It is recommended to explain the differences and accuracy for the body weight measurement (exposure).</p> <p>4. p 13. About the definition of obesity, the international standard regards BMI&gt;30 as obesity and BMI:25~30 as overweight. Please revise the definition of obesity. Or if there is a Japanese BMI standard definition that can be cited.</p> <p>5. P 14. About the very preterm definition, in the literature review, infants born very preterm are defined as &lt;32 weeks gestation. (Clin Perinatol. 2018 Sep; 45(3): 565–577.) Is there any reference to define VPTB as less than 34 weeks? It is recommended to add references to the source.</p> <p>6. p 15. "These covariates were selected based on previous studies on multimorbidity." Please add the citation references.</p> <p>7. P 15. The k-nearest neighbor imputation method is used in the study, but the manuscript does not mention whether there is an imputation for discussing the differences in the research. It is recommended to discuss the importance of using this imputation method for research analysis.</p> <p>8. In addition to the mother's education level, are there other socioeconomic background data that can be used for adjustment model, such as the job, family income, and urbanization of the place of residence?</p> <p><b>Result</b></p> <p>The descriptions in the SGA analysis on page 10 and figure 1 should be consistent. One is &gt;41, and the other is ≥ 42. It is suggested to revise to the same description.</p> <p><b>Discussion</b></p> <ol style="list-style-type: none"> <li>1. Research limitation should be added to the description of bias, e.g., self-report body weight, etc.</li> <li>2. Please consider adding more discussion of drug use on perinatal outcomes.</li> <li>3. An important consideration is the complications during pregnancy, such as the interaction between GDM or preeclampsia and maternal obesity. How to distinguish which is a mediator or directly affects the perinatal outcomes? Please discuss this consideration.</li> </ol>
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<b>REVIEWER</b>	Sarka Lisonkova University of British Columbia, Canada, Obstetrics and Gynaecology
<b>REVIEW RETURNED</b>	30-Dec-2022

<b>GENERAL COMMENTS</b>	<p>This study describes the association between maternal multimorbidity and preterm birth, low birthweight and SGA in a robust sample of Japanese women. The results provide important information about the prevalence of multimorbidity in women who gave birth in Japan, especially the prevalence of domestic violence, which may be underreported. The increased odds of adverse outcomes are not surprising. The risks of adverse birth outcomes likely differ widely depending on the underlying morbidity or specific combinations of morbidities, which limits the utility of the study findings for pre-pregnancy counselling.</p> <p><b>Main comments</b></p> <ol style="list-style-type: none"> <li>1. Abstract: the sentence 'The risk of adverse perinatal outcomes increases with...' is not really supported by your results, as you studied only 1 condition and 2+ conditions. You either adjust your</li> </ol>
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	<p>conclusion or provide more detailed results by number of conditions (for instance 1, 2, 3 and 4+ conditions). The same sentence appears in the Discussion (line 24) and in the Conclusion on page 13 (please correct those as well).</p> <p>2. Abstract: Similarly, the sentence 'Multimorbidity is becoming more prevalent...' is also not originating from your results (you have not studied trends); I suggest more general wording, eg, 'As multimorbidity becomes more prevalent...'</p> <p>3. I suggest rewording the strengths of the study, for instance</p> <ul style="list-style-type: none"> <li>- Including a wide variety of chronic conditions makes the study more comprehensive with respect to maternal health and wellbeing</li> <li>- The study size is robust --- I would not comment further as you still do not have enough power to study ELBW in some subgroups – ie, 2+ maternal conditions with obesity, etc.)</li> </ul> <p>And Limitations</p> <ul style="list-style-type: none"> <li>- The third point: lack of information on severity of maternal morbidity is a limitation</li> <li>- Some self-reported conditions including domestic violence and substance may be underreported</li> </ul> <p>2. Can you provide more information on how was the participation in the study determined (all women in 'regional centers' were approached? At what stage of pregnancy?) and how many women declined to participate? (I know there is a reference to another paper, but this is important information that should be available, at least in the Appendix.)</p> <p>3. Please, clarify the inclusion/exclusion of subsequent pregnancies: if there were more than 1 pregnancy to the same woman, only the first pregnancy was included?</p> <p>4. You should state what proportion of women was excluded overall (due to exclusion criteria and due to missing values after the exclusion criteria were applied).The numbers are presented in Figure, but the proportion should be stated in the results.</p> <p>5. It seems that 16.5% were excluded from the original dataset (104,062); what missing data were imputed? (those with missing values in the study population of 86,885? Or any of those with missing values on gestational age, birth weight etc.)</p> <p>6. I think the answer 'rarely' to a question 'physically abused such as being beaten' constitutes domestic abuse (and should not be categorized as 'no abuse' together with the answer 'never')</p> <p>7. Page 13, Line 21: Why did you choose these BMI categories (e.g., no 'overweight' category)? Was there a specific reason?</p> <p>8. Page 14, line 10: can you specify 'iron preparations' and 'thinners'? (an Appendix table with more details on all medications would be useful)</p> <p>9. Sentence: 'Medication was considered relevant from pregnancy diagnosis to 12 weeks of gestation.' Why this period? (To include only chronic/pre-pregnancy conditions?)</p> <p>10. Discussion, Line 39: the statistical power of your sample is more dictated by the incidence of the outcome. Your sample size is robust to study multimorbidity and PTB, low birthweight and SGA.</p> <p>11. Discussion: a possible underreporting due to self-report is a limitation (eg, some women may not report on domestic violence or substance use due to shame).</p> <p>12. Table 1 and 2 in the footnotes: by 'range' do you mean 'quartile range' (also in the Results section)?</p> <p>13. Table 2: infant sex is not your outcome --- you can move it to Table 1</p> <p>14. How was maternal age included in the regression analyses? As a categorical variable?</p> <p>Minor comments</p>
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	1. Page 7, Line 49: I suggest wording: ‘... those with multimorbidity, ranging from 8.7% to 18.8%.’ 2. Some editing is needed
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### VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. CHINIEN CHEN, National Taiwan University Hospital Hsin-Chu Branch

Comments to the Author:

Regarding the association of chronic diseases and perinatal prognosis, and the inference of the research results, it is recommended to add some relevant information to discuss about the mediator effect or direct impact from the chronic illness on perinatal outcomes, and the definition of outcomes and exposures should be revised.

**Response:** We think that maternal multimorbidity including obesity, underweight, hypertension, kidney disease, systemic lupus erythematosus, etc. has the mediator effect and the direct impact on perinatal outcomes. For example, maternal abnormal BMI such as underweight and obesity is known to an independent risk factor for preterm birth (PTB) (Shaw GM, et al. 2014). Maternal obesity is also a risk factor for preeclampsia (Paré E, et al. 2014). Moreover, preeclampsia is contributed to develop PTB. Both maternal obesity and preeclampsia are regarded as the risk for PTB. PTB is thought to be a syndrome initiated by multiple mechanism, including infection or inflammation, uteroplacental ischemia or hemorrhage, uterine overdistension, stress, and other immunologically mediated processes (Goldenberg RL, et al. 2008).

In addition, the association between other chronic diseases such as hypertension, kidney disease, and autoimmune disease and PTB is similar to the association between obesity and PTB. Maternal hypertension is also related to develop preeclampsia and PTB. Therefore, we believe that maternal multimorbidity has the mediator effect and directly impact on perinatal outcomes. We have explained it in the Discussion section. (p.25-26, Line 376-391)

*The mechanism by which maternal multimorbidity affected perinatal outcomes was not clear in the present study. However, maternal multimorbidity appears to affect perinatal outcomes as both an intermediate and direct factor. For example, abnormal maternal BMI, such as underweight and obesity, is known to be an independent risk factor for PTB.<sup>55</sup> Maternal obesity is also a risk factor for preeclampsia.<sup>56</sup> Furthermore, preeclampsia promotes the development of PTB. After all, both maternal obesity and preeclampsia are regarded as risk factors for PTB. PTB is considered a syndrome initiated by multiple mechanism, including infection or inflammation, uteroplacental ischemia or hemorrhage, uterine overdistension, stress, and other immunologically mediated processes.<sup>57</sup> In addition, the associations between other chronic diseases such as hypertension, kidney disease, and autoimmune disease and PTB are similar to the association between obesity and PTB.<sup>20-23</sup> Therefore, we hypothesized that each chronic condition that composes multimorbidity, such as underweight, obesity, psychiatric disorder, and domestic violence, played an intermediate or direct role in perinatal outcomes, and that the combination of these chronic conditions might further increase the risk of adverse perinatal outcomes.<sup>2</sup>*

Ref. Shaw GM, et al. *Paediatr Perinat Epidemiol.* 2014 Jul;28(4):302-11.

Paré E, et al. *Obstet Gynecol.* 2014 Oct;124(4):763-770.

RL, et al. *Lancet*. 2008 Jan 5;371(9606):75-84.

## Introduction

1. Although there is a lack of studies about multimorbidity during pregnancy in Japan, it is recommended to provide research on the prevalence of individual chronic diseases in pregnant women to help support the accuracy of this study.

**Response:** The prevalence of individual chronic diseases among pregnant women has been added to the Introduction section. (p.6, Line 63-66) References on this prevalence also have been added. (p.33, Line 507-512)

*Although the prevalence of maternal multimorbidity in Japan has not been thoroughly studied, the prevalence of individual chronic conditions was 0.9% for chronic hypertension, 3.4% for diabetes mellitus, 10.6% for obesity, and 18.2% for underweight (Japanese Ministry of Health, Labour and Welfare. 2019: Enomoto K, et al. 2016).*

Ref. Japanese Ministry of Health, Labour and Welfare. 2019.  
[https://www.mhlw.go.jp/stf/newpage\\_03949.html](https://www.mhlw.go.jp/stf/newpage_03949.html). Accessed 24 Jan 2023.

Enomoto K, Aoki S, Toma R, Fujiwara K, Sakamaki K, Hirahara F. *PLoS One*. 2016;11:e0157081.

2. It is necessary to consider whether maternal prepregnancy (early pregnancy) obesity and underweight directly lead to GDM or preeclampsia during pregnancy, which in turn leads to poor perinatal prognosis later.

**Response:** Considering your comments, we have explained these contents in the Discussion section. (p.25-26, 376-391) Please see my reply to your first comment.

3. In addition to the impact of chronic disease, drug use may also significantly affect perinatal outcomes. A discussion of drug use studies was suggested to be added to the content. (Reference suggestion: *Medicine (Baltimore)*. 2015 Jan;94(1):e386. Exposure of drugs for hypertension, diabetes, and autoimmune disease during pregnancy and perinatal outcomes: an investigation of the regulator in Japan)

**Response:** In accordance with this suggestion, we have discussed the impact of drug use on perinatal outcomes in the Discussion section. (p.23, Line 340-347) This reference you suggested has been added to the Reference section. (p.39, Line 604-607)

*In maternal multimorbidity, medication during pregnancy may affect perinatal outcomes. The present study defined a physical or psychological condition as one that required medical attention during pregnancy. The study on the exposure to medication for hypertension, diabetes, and autoimmune disease during pregnancy reported that the ORs of PTB, LBW, and SGA were higher in the antihypertensives and corticosteroids exposed group compared with those in the unexposed group.*45

*However, it was also reported that chronic conditions, with or without medication exposure, may have affected perinatal outcomes. (Sato et al. 2015)*

Ref. Sato et al. *Medicine*. 2015 Jan;94(1):e386.

## Method

1. p 10. The probability of neonatal survival at <22 weeks is relatively low. Is it meaningful to include this study in the analysis?

**Response:** In all analyses of this study, deliveries at <22 weeks were excluded. However, the sentence “because 211 deliveries at a gestational age of < 22 or > 41 weeks were excluded” could lead to misinterpretation that our study includes pregnancies <22 weeks. Additionally, there is no reference to SGA at > 41 weeks of gestation in Japan. Therefore, we changed this sentence to “because 211 deliveries at a gestational age of > 41 weeks were excluded” (p.10, Line 123-124)

*In the SGA analyses, the number of participants decreased to 86,674 because 211 deliveries at a gestational age of > 41 weeks were excluded (Figure 1).*

2. P 12. The questionnaire survey collected domestic violence information, will there be any underestimation or overestimation (bias), and is there a validation study to prove it.

**Response:** The study on domestic violence has reported that the prevalence of domestic violence may be underestimated because of social desirability bias (Köksal S, et al. 2022). We have added this sentence and this reference to the limitation section. (p.21, Line 306-309, p.38, Line 600-602)

*Third, some self-reported biases may exist. Self-reported body weight may be underestimated for underweight and overestimated for obesity (Seijo M, et al. 2018; Okamoto N, et al. 2017). The prevalence of self-reported domestic violence may be underestimated due to social desirability bias (Köksal S. et al. 2022).*

Ref. Köksal S, et al. *Eur J Popul*. 2022 May 30;38(3):517-545.

3. p 12. Pregnant women's weight is collected through questionnaires or self-reports. There may be errors or bias. It is recommended to explain the differences and accuracy for the body weight measurement (exposure).

**Response:** The systematic review on self-reported body weight reported that self-reported body weight may be underestimated for underweight and overestimated for obesity (Seijo M, et al. 2018; Okamoto N, et al. 2017). Therefore, we have explained it in the limitation section. (p.21 Line 306-309; p.38, Line 593-599)

*Third, some self-reported biases may exist. Self-reported body weight may be underestimated for underweight and overestimated for obesity (Seijo M, et al. 2018; Okamoto N, et al. 2017). The*

prevalence of self-reported domestic violence may be underestimated due to social desirability bias (Köksal S. et al. 2022).

Ref. Seijo M, Minckas N, Cormick G, Comandé D, Ciapponi A, BelizÁN JM. *Acta Obstet Gynecol Scand.* 2018;97:429-39.

Okamoto N, Hosono A, Shibata K, Tsujimura S, Oka K, Fujita H, et al. *Obes Sci Pract.* 2017;3:417-24.

4. p 13. About the definition of obesity, the international standard regards BMI>30 as obesity and BMI:25~30 as overweight. Please revise the definition of obesity. Or if there is a Japanese BMI standard definition that can be cited.

**Response:** In Japan, BMI $\geq$ 25 is generally categorized as obesity (Suzuki S. et al. 2017; Nomura K. et al. 2020). We have added these references to support this evidence. (p.13, Line 185-186, p.37; Line 571-575)

*Pregnant women were categorized according to their pre-pregnancy BMI as follows: underweight (BMI < 18.5 kg/m<sup>2</sup>), normal weight (18.5 kg/m<sup>2</sup> < BMI < 25.0 kg/m<sup>2</sup>), and obesity (BMI > 25.0 kg/m<sup>2</sup>).<sup>34, 35</sup>*

Ref. Suzuki S. et al. *J Clin Med Res.* 2017 Feb;9(2):180-181

Nomura K. et al. *Nutrients.* 2020 Sep 2;12(9):2684

5. P 14. About the very preterm definition, in the literature review, infants born very preterm are defined as <32 weeks gestation. (Clin Perinatol. 2018 Sep; 45(3): 565–577.) Is there any reference to define VPTB as less than 34 weeks? It is recommended to add references to the source.

**Response:** Very preterm birth (VPTB) is generally defined as preterm birth from 28 to 31 weeks of gestation. In addition, preterm birth from 32 to 33 weeks of gestation is called moderately preterm birth, and preterm birth <28 weeks of gestation is called extremely preterm birth. The present study aimed to investigate the association between preterm birth <34 weeks and perinatal adverse outcomes because 34 weeks of gestation was an important time for the fetus when the incidence of neonatal complications changes. However, there was no appropriate term for preterm birth <34 weeks. Therefore, we defined preterm birth <34 weeks as VPTB because a previous study defined it as <34 weeks. (Clark CA, et al. *Child Dev.* 2008 Sep-Oct;79(5):1444-62.)

6. p 15. "These covariates were selected based on previous studies on multimorbidity." Please add the citation references.

**Response:** We have added the references to the Methods section. (p.15, Line 221-222)

*These covariates were selected based on previous studies on multimorbidity.<sup>13, 18, 33</sup>*

7. P 15. The k-nearest neighbor imputation method is used in the study, but the manuscript does not mention whether there is an imputation for discussing the differences in the research. It is recommended to discuss the importance of using this imputation method for research analysis.

**Response:** We used the k-nearest neighbor (kNN) imputation for all variables with missing values. We have explained the kNN imputation method in the Methods section (p.16, Line 228-231) The kNN imputation method is a widely accepted single imputation method and has been confirmed its validity (Jerez JM, et al. 2010). This reference has been added to the Reference section. (p.38, Line 589-592)

*We used the k-nearest neighbor (kNN) imputation method in the R package “VIM” (version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria),<sup>40</sup> introducing all outcomes and adjusted variables because the dataset had some missing values. The covariates such as maternal age, parity, smoking status during pregnancy, drinking status during pregnancy, maternal education, and household income, and neonatal sex, were among the imputed missing data. kNN is a widely accepted single imputation method whose validity has been established (Jerez JM, et al. 2010).*

Ref. Jerez JM, et al. *Artif Intell Med.* 2010;50(2):105–15

8. In addition to the mother's education level, are there other socioeconomic background data that can be used for adjustment model, such as the job, family income, and urbanization of the place of residence?

**Response:** We have added household income to maternal background and an adjustment model. (p.12, Line 156-158 and Supplementary Table 1) These maternal background are shown in Supplementary Table 1 because the BMJ open allows a maximum 2 pages for tables embedded in the main document. However, the results had not changed significantly after including household income. (p.16-17, Line 259-262 and Table 4)

#### *Methods*

*Annual household income was defined as follows: <2,000,000; 2,000,000–3,990,000; 4,000,000–5,990,000; 6,000,000–7,990,000; 8,000,000–9,990,000; and > 10,000,000 JPY.*

#### *Results*

*Maternal multimorbidity was significantly associated with PTB (aOR, 1.50; 95% CI, 1.33-1.69), VPTB (aOR, 1.34; 95% CI, 1.03-1.74), LBW (aOR, 1.49; 95% CI, 1.35-1.63), VLBW (aOR, 1.62; 95% CI, 1.16-2.25), ELBW (aOR, 1.81; 95% CI, 1.12-2.90), and SGA (aOR, 1.33; 95% CI, 1.20-1.46) (Table 4).*

#### Result

The descriptions in the SGA analysis on page 10 and figure 1 should be consistent. One is >41, and the other is  $\geq$  42. It is suggested to revise to the same description.



**Response:** We have changed “ $\geq 42$ ” to “ $> 41$ .” (Figure 1)

## Discussion

1. Research limitation should be added to the description of bias, e.g., self-report body weight, etc.

**Response:** The description of bias such as self-reported body weight and domestic violence has been added to the limitation section. (p.21, Line 306-309)

*Third, some self-reported biases may exist. Self-reported body weight may be underestimated for underweight and overestimated for obesity (Seijo M, et al. 2018; Okamoto N, et al. 2017). The prevalence of self-reported domestic violence may be underestimated due to social desirability bias (Köksal S. et al. 2022).*

Ref. Seijo M, Minckas N, Cormick G, Comandé D, Ciapponi A, BelizÁN JM. Acta Obstet Gynecol Scand. 2018;97:429-39.

Okamoto N, Hosono A, Shibata K, Tsujimura S, Oka K, Fujita H, et al. Obes Sci Pract. 2017;3:417-24.

Köksal S, et al. Eur J Popul. 2022 May 30;38(3):517-545.

2. Please consider adding more discussion of drug use on perinatal outcomes.

**Response:** We have discussed the effects of medication during pregnancy on perinatal outcomes. (p.23, Line 340-347) This reference you suggested has been added to the Reference section. (p.39, Line 604-607)

*In maternal multimorbidity, medication during pregnancy may affect perinatal outcomes. The present study defined a physical or psychological condition as one that required medical attention during pregnancy. The study on the exposure to medication for hypertension, diabetes, and autoimmune disease during pregnancy reported that the ORs of PTB, LBW, and SGA were higher in the antihypertensives and corticosteroids exposed group compared with those in the unexposed group.45 However, it was also reported that chronic conditions, with or without medication exposure, may have affected perinatal outcomes. (Sato et al. 2015)*

Ref. Sato et al. Medicine. 2015 Jan;94(1):e386.

3. An important consideration is the complications during pregnancy, such as the interaction between GDM or preeclampsia and maternal obesity. How to distinguish which is a mediator or directly affects the perinatal outcomes? Please discuss this consideration.

**Response:** As mentioned above, we have added this important discussion about the mechanism to the Discussion section. (p.25-26, Line 376-391)

*The mechanism by which maternal multimorbidity affected perinatal outcomes was not clear in the present study. However, maternal multimorbidity appears to affect perinatal outcomes as both an intermediate and direct factor. For example, abnormal maternal BMI, such as underweight and obesity, is known to be an independent risk factor for PTB (Shaw GM, et al. 2014). Maternal obesity is also a risk factor for preeclampsia (Paré E, et al. 2014). Furthermore, preeclampsia promotes the development of PTB. After all, both maternal obesity and preeclampsia are regarded as risk factors for PTB. PTB is considered a syndrome initiated by multiple mechanism, including infection or inflammation, uteroplacental ischemia or hemorrhage, uterine overdistension, stress, and other immunologically mediated processes (Goldenberg RL, et al. 2008). In addition, the associations between other chronic diseases such as hypertension, kidney disease, and autoimmune disease and PTB are similar to the association between obesity and PTB.<sup>20-23</sup> Therefore, we hypothesized that each chronic condition that composes multimorbidity, such as underweight, obesity, psychiatric disorder, and domestic violence, played an intermediate or direct role in perinatal outcomes, and the combination of these chronic conditions might further increase the risk of adverse perinatal outcomes.<sup>2</sup>*

Ref. Shaw GM, et al. *Paediatr Perinat Epidemiol.* 2014 Jul;28(4):302-11.

Paré E, et al. *Obstet Gynecol.* 2014 Oct;124(4):763-770.

RL, et al. *Lancet.* 2008 Jan 5;371(9606):75-84.

## RESPONSE TO REVIEWER 2:

Thank you for your valuable comments. Our answers to your points are as follows.

Reviewer: 2

Dr. Sarka Lisonkova, University of British Columbia, Canada

Comments to the Author:

This study describes the association between maternal multimorbidity and preterm birth, low birthweight and SGA in a robust sample of Japanese women. The results provide important information about the prevalence of multimorbidity in women who gave birth in Japan, especially the prevalence of domestic violence, which may be underreported. The increased odds of adverse outcomes are not surprising. The risks of adverse birth outcomes likely differ widely depending on the underlying morbidity or specific combinations of morbidities, which limits the utility of the study findings for pre-pregnancy counselling.

Main comments

1. Abstract: the sentence 'The risk of adverse perinatal outcomes increases with...' is not really supported by your results, as you studied only 1 condition and 2+ conditions. You either adjust your conclusion or provide more detailed results by number of conditions (for instance 1, 2, 3 and 4+ conditions). The same sentence appears in the Discussion (line 24) and in the Conclusion on page 13 (please correct those as well).

**Response:** To evaluate the dose response relationship between the number of chronic conditions and perinatal adverse outcomes, we have added the additional analyses using a detailed classification of the number of chronic conditions (0, 1, 2, 3, and 4+) and a test for trend. (p.16, Line 233-235) This analysis shows that the odds ratio for adverse outcomes increases in the number of chronic conditions and *P* value for trend (Supplementary Table 2). However, there were no significant differences in 4+ chronic conditions because of the small number of the 4+ chronic condition group. Therefore, we have revised these sentences as follow: The risk of adverse perinatal outcomes "tends" to increase in the number of chronic maternal conditions. (p.4, Line 24-25: p.18, Line 270-272: p.25, Line 395-396)

*Abstract (p.4, Line 24-25)*

*Maternal multimorbidity was associated with adverse perinatal outcomes, including PTB, LBW, and SGA. The risk of adverse perinatal outcomes tends to increase with a rise in the number of chronic maternal conditions.*

*Methods (p.16, Line 233-235)*

*We also analytically evaluated the dose-response relationship between the number of chronic conditions and perinatal adverse outcomes using a detailed classification of the number of chronic conditions (0, 1, 2, 3, and >4) and a test for trend.*

*Results (p.18, Line 269-271)*

*Supplementary Table 2 shows the additional analysis for PTB, LBW, and SGA using exposure as the number of chronic conditions (0, 1, 2, 3, and >4). All of the trend *P* values were statistically significant.*

*Conclusion (p.25, Line 395-396)*

*The present study reported an association between maternal multimorbidity and adverse perinatal outcomes including PTB, LBW, and SGA. The risk of adverse perinatal outcomes tends to increase as the number of chronic maternal conditions increases.*

2. Abstract: Similarly, the sentence ‘Multimorbidity is becoming more prevalent...’ is also not originating from your results (you have not studied trends); I suggest more general wording, eg, ‘As multimorbidity becomes more prevalent...’

**Response:** We have changed this sentence to “As multimorbidity becomes more prevalent...” in Abstract. (p.4, Line 25-27)

*As multimorbidity becomes more prevalent among pregnant women, making our findings important for preconception counseling.*

3. I suggest rewording the strengths of the study, for instance
- Including a wide variety of chronic conditions makes the study more comprehensive with respect to maternal health and wellbeing
  - The study size is robust --- I would not comment further as you still do not have enough power to study ELBW in some subgroups – ie, 2+ maternal conditions with obesity, etc.)

And Limitations

- The third point: lack of information on severity of maternal morbidity is a limitation
- Some self-reported conditions including domestic violence and substance may be underreported

**Response:** Following suggestions, we have revised the strengths and limitations of this study as follow. (p.5, Line 33-46)

- *Including a wide variety of chronic conditions makes the study more comprehensive concerning to maternal health and wellbeing.*
- *The study size is robust enough to investigate preterm birth, low birth weight, and small gestational age; however, the numbers of secondary outcomes such as very preterm birth, very low birth weight, and extremely low birth weight are too small to have enough statistical power.*
- *Lack of information on the severity of maternal morbidity is a limitation.*
- *Some self-reported maternal conditions including, such as domestic and substance abuse, may be underreported.*

4. Can you provide more information on how was the participation in the study determined (all women in 'regional centers' were approached? At what stage of pregnancy?) and how many women declined to participate? (I know there is a reference to another paper, but this is important information that should be available, at least in the Appendix.)

**Response:** The recruitment strategy in the Japan Environment and Children’s Study (JECS) on which this study was based has been provided as the Supplementary Appendix because of the limitation words of the manuscript. (p.9, Line 109-110) (Supplementary Appendix 1)

*The recruitment strategy in the JECS is shown in Supplementary Appendix 1.<sup>30</sup>*

Ref. Kawamoto T, Nitta H, Murata K, Toda E, Tsukamoto N, Hasegawa M, et al. Rationale and study design of the Japan environment and children's study (JECS). BMC Public Health. 2014;14:25.

5. Please, clarify the inclusion/exclusion of subsequent pregnancies: if there were more than 1 pregnancy to the same woman, only the first pregnancy was included?

**Response:** When there were more than one pregnancy in the same mother, only the first pregnancy was included in this study. We have clarified the inclusion/exclusion of subsequent pregnancies. (p.9, Line 114-115)

*When a mother had more than one pregnancy, only the first pregnancy was included in this study. After excluding pregnancies in the same mothers, there were 94,753 participants.*

6. You should state what proportion of women was excluded overall (due to exclusion criteria and due to missing values after the exclusion criteria were applied). The numbers are presented in Figure, but the proportion should be stated in the results.

**Response:** The proportion of women who were excluded has been added to the Results section. (p.17, Line 245-246)

*Of the 104,062 fetal records included in this study, 17,177 (16.5%) were excluded, leaving a final number of 86,885 singleton pregnant women (Figure 1).*

7. It seems that 16.5% were excluded from the original dataset (104,062); what missing data were imputed? (those with missing values in the study population of 86,885? Or any of those with missing values on gestational age, birth weight etc.)

**Response:** We performed kNN imputation after exclusion. The imputed missing data were covariates such as maternal age, parity, smoking status during pregnancy, drinking status during pregnancy, maternal education, and household income (this variable is newly added). We have explained it in the Methods section. (p.16, Line 228-231)

*We used the k-nearest neighbor (kNN) imputation method in the R package "VIM" (version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria),<sup>40</sup> introducing all outcomes and adjusted variables because the dataset had some missing values. The covariates such as maternal age, parity, smoking status during pregnancy, drinking status during pregnancy, maternal education, and household income, and neonatal sex, were among the imputed missing data. kNN is a widely accepted single imputation method whose validity has been established.<sup>41</sup>*

8. I think the answer 'rarely' to a question 'physically abused such as being beaten' constitutes domestic abuse (and should not be categorized as 'no abuse' together with the answer 'never')

**Response:** We agree with this suggestion. We re-categorized "rarely" as a domestic violence group and reanalyzed the data of this study. (p.14, Line 191) The prevalence of domestic violence has changed from 4.6% to 13.0%. Following maternal underweight, domestic violence has become the second highest prevalence among maternal morbidities. (p.17, Line 254-255 and Table 3) The odds ratios in the results also have changed a little bit because the prevalence of maternal multimorbidity

has increased to 6.3%. (Table 4, Supplementary Table 2, and Supplementary Table 4A-D) We have revised the results and discussion about domestic violence. (p.17-18, Lines 249-250 and 259-262; p.24, Line 363-364)

Abstract (p.3-4, Line 16-22)

**Results:** *Of the 104,062 fetal records, 86,885 singleton pregnant women were analyzed. The median maternal age and body mass index were 31 years and 20.5 kg/m<sup>2</sup>, respectively. The prevalence of pregnant women with one or more chronic conditions was 40.2%. The prevalence of maternal multimorbidity was 6.3%, and that of PTB, LBW, and SGA were 4.6%, 8.1%, and 7.5%, respectively. Pre-pregnancy underweight women were the most common, observed in 15.6% of multimorbidity cases, followed by domestic violence from intimate partner in 13.0%. Maternal multimorbidity was significantly associated with PTB (aOR, 1.50; 95% CI, 1.33-1.69), LBW (aOR, 1.49; 95% CI, 1.35-1.63), and SGA (aOR, 1.33; 95% CI, 1.20-1.46).*

Methods (p.14, Line 191-192)

*If the response “rarely” or “sometimes” or “often” was chosen, it was considered as presence of domestic violence.*

Results (p.17, Line 248-250)

*In the present study, 40.2% of pregnant women had one or more chronic conditions (Table 1). The prevalence of maternal multimorbidity was 6.3% (5,462/86,885).*

(p.17, Line 254-255)

*Maternal underweight (15.6%) was the most frequently observed in chronic conditions, followed by domestic violence (13.0%).*

(p.17-19, Line 259-269, 273-280)

*Maternal multimorbidity was significantly associated with PTB (aOR, 1.50; 95% CI, 1.33-1.69), VPTB (aOR, 1.34; 95% CI, 1.03-1.74), LBW (aOR, 1.49; 95% CI, 1.35-1.63), VLBW (aOR, 1.62; 95% CI, 1.16-2.25), ELBW (aOR, 1.81; 95% CI, 1.12-2.90), and SGA (aOR, 1.33; 95% CI, 1.20-1.46) (Table 4). Adjusted odds ratios of PTB, LBW, and SGA tended to increase with multimorbidity rather than with one chronic condition.*

*The association between maternal multimorbidity and adverse perinatal outcomes, using the complete dataset, is shown in Supplementary Table 2. Maternal multimorbidity was also significantly associated with PTB, LBW, and SGA, however, it was not associated with VPTB, VLBW and ELBW. Additionally, the aORs of PTB, LBW, and SGA also tended to increase with multimorbidity rather than with one chronic condition.*

*Supplementary Table 4 demonstrates the aOR for adverse perinatal outcomes, focusing on each disease, including underweight, obesity, psychiatric disorders, and domestic violence. Regarding PTB and LBW, significant differences were found between maternal multimorbidity and no chronic conditions, regardless of the presence or absence of specific chronic conditions (Supplementary Table 3A-D). For SGA, maternal multimorbidity with underweight, without obesity,*

*without psychiatric disorder, and with and without domestic violence showed significant differences compared to no chronic conditions (Supplementary Table 4A-D).*

Discussion (p.24, Line 363-364)

*In the present study, domestic violence from intimate partners was the second most frequent chronic condition at 13.0%.*

9. Page 13, Line 21: Why did you choose these BMI categories (e.g., no 'overweight' category)? Was there a specific reason?

**Response:** In Japan, BMI $\geq$ 25 is generally categorized as obesity (Suzuki S, et al. 2017; Nomura K, et al. 2020). We have added the references to support this evidence. (p.13, Line 185-186, p.37; Line 571-575)

*Pregnant women were categorized according to their pre-pregnancy BMI as follows: underweight (BMI < 18.5 kg/m<sup>2</sup>), normal weight (18.5 kg/m<sup>2</sup> < BMI < 25.0 kg/m<sup>2</sup>), and obesity (BMI > 25.0 kg/m<sup>2</sup>).<sup>34, 35</sup>*

Ref. Suzuki S. et al. *J Clin Med Res.* 2017 Feb;9(2):180-181

Nomura K. et al. *Nutrients.* 2020 Sep 2;12(9):2684

10. Page 14, line 10: can you specify 'iron preparations' and 'thinners'? (an Appendix table with more details on all medications would be useful)

**Response:** This study was based on the JECS, and the drug interviews of this study have included "iron preparation" and "thinners." Therefore, we have added the list of all medications as the Appendix. (Supplementary Appendix 2)

11. Sentence: 'Medication was considered relevant from pregnancy diagnosis to 12 weeks of gestation.' Why this period? (To include only chronic/pre-pregnancy conditions?)

**Response:** We aimed to investigate the impact of maternal pre-pregnant chronic conditions on perinatal outcomes. Therefore, the medication was considered relevant from pregnancy diagnosis to 12 weeks of gestation. We have explained this reason in the Methods section. (p.14, Line 193-196)

*Medication information was obtained from interviews (Supplementary Appendix 2).<sup>37</sup> Medication was considered relevant from pregnancy diagnosis to 12 weeks of gestation to investigate the impact of maternal pre-pregnancy chronic conditions on perinatal outcomes.*

12. Discussion, Line 39: the statistical power of your sample is more dictated by the incidence of the outcome. Your sample size is robust to study multimorbidity and PTB, low birthweight and SGA.

**Response:** This study has enough sample size to study associations between multimorbidity and PTB, LBW, and SGA. However, the sample size is not enough to study other severe outcomes such

as very PTB, very LBW, and extremely LBW due to their lower incidence. Therefore, we have revised the limitation about sample size as below. (p.20, Line 292-293: p.21, Line 310)

*To our knowledge, the present study is the first to investigate the association between maternal multimorbidity, including physical, psychological, and social morbidities, with perinatal outcomes. In the present study, the use of data from the JECS, including 100,000 Japanese mothers and neonates, made it possible to study multimorbidities. The incidence of adverse perinatal outcomes was sufficient to investigate the influence of maternal multimorbidity on PTB, LBW, and SGA.*

Forth, the numbers of VPTB, VLBW, and ELBW cases were small. This study was insufficient to investigate these severe adverse outcomes.

13. Discussion: a possible underreporting due to self-report is a limitation (eg, some women may not report on domestic violence or substance use due to shame).

**Response:** The prevalence of domestic violence and substance use may be underreported because of social desirability bias (Köksal S, et al. 2022). We have added this sentence and this reference to the limitation section. (p.21, Line 306-309, p.38, Line 600-602)

*Third, some self-reported biases may exist. Self-reported body weight may be underestimated for underweight and overestimated for obesity (Seijo M, et al. 2018; Okamoto N, et al. 2017). The prevalence of self-reported domestic violence may be underestimated due to social desirability bias (Köksal S. et al. 2022).*

Ref. Köksal S, et al. *Eur J Popul.* 2022 May 30;38(3):517-545.

14. Table 1 and 2 in the footnotes: by 'range' do you mean 'quartile range' (also in the Results section)?

**Response:** The ranges in Tables present from minimum number to max number. We have changed "range" to "range: min to max." (Tables 1 and 2)

15. Table 2: infant sex is not your outcome --- you can move it to Table 1

**Response:** We have presented the perinatal information in Table 2. Therefore, we have changed "Perinatal outcomes" to "Perinatal characteristics" in Table 2.

16. How was maternal age included in the regression analyses? As a categorical variable?

**Response:** Maternal age was included in the regression analysis as a categorical variable. We revised this sentence in the Methods section. (p.15, Line 218-219)



*In the main analyses, adjusted odds ratios (aORs) and 95% confidence intervals (CIs) for adverse perinatal outcomes were estimated using a multivariable logistic regression model adjusted for maternal age at delivery (<20, 20-24, 25-29, 30-34, 35-39, and ≥40 years), parity, maternal smoking status, maternal alcohol consumption, maternal educational level, and neonatal sex.*

Minor comments

1. Page 7, Line 49: I suggest wording: ‘... those with multimorbidity, ranging from 8.7% to 18.8%.’  
**Response:** We have changed “...those with multimorbidity from 8.7% to 18.8%” to “...those with multimorbidity, ranging from 8.7% to 18.8%.” (p.6, Line 61)

*Although the prevalence of multimorbidity is highest in those aged 65 years or older, younger persons, including reproductive-age women, also represent a large proportion of those with multimorbidity, ranging from 8.7 to 18.8%.*

2. Some editing is needed

**Response:** This manuscript has been edited by professional English proofreading (Editage, [www.editage.com](http://www.editage.com)) before this re-submission.

**VERSION 2 – REVIEW**

<b>REVIEWER</b>	CHINIEN CHEN National Taiwan University Hospital Hsin-Chu Branch, Pediatrics
<b>REVIEW RETURNED</b>	02-Mar-2023
<b>GENERAL COMMENTS</b>	The authors have responded to my questions and comments satisfactorily.