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Maternal multimorbidity and adverse perinatal outcomes: The Japan Environment and Children's Study

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Title: Maternal multimorbidity and adverse perinatal outcomes: The Japan Environment and Children's Study

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ABSTRACT

Objectives: Multimorbidity is defined as the coexistence of two or more chronic physical or psychological conditions within an individual. The association between maternal multimorbidity and adverse perinatal outcomes such as preterm delivery and low birth weight has not been well studied. Therefore, this study aimed to investigate this association.

Methods: We conducted a prospective cohort study using data from the Japan Environment and Children's Study of pregnant women between 2011 and 2014. Those with data on chronic maternal conditions were included in the study and categorized as having no chronic condition, one chronic condition, or multimorbidities. The primary outcomes were the incidence of preterm birth (PTB), low birth weight (LBW), and small for gestational age (SGA). Adjusted logistic regression was performed to estimate odds ratios (aORs) and 95% confidence intervals (CIs).

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^2, respectively. The prevalence of pregnant women with one or more chronic conditions was 34.6%. The prevalence of maternal multimorbidity was 3.7%, 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 maternal obesity in 10.9%. Maternal multimorbidity was significantly associated with PTB (aOR, 1.76; 95% CI, 1.53-2.03), LBW (aOR, 1.58; 95% CI, 1.41-1.77), and SGA (aOR, 1.30; 95% CI, 1.15-1.47).

Conclusion: Maternal multimorbidity was associated with adverse perinatal outcomes, including PTB, LBW, and SGA. The risk of adverse perinatal outcomes increases with an increase in the number of chronic maternal conditions. Multimorbidity is becoming more prevalent among pregnant women, making our findings important for preconception counseling.

Keywords: chronic diseases, Japan, low birth weight, multimorbidity, preterm birth, small for gestational age.

Word counts: 3,514

Strengths and limitations of this study

- Maternal multimorbidity in this study included 23 chronic conditions including physical, psychological, and social morbidities to reduce the chance of missing pregnant women at a potential risk of adverse perinatal outcomes.

- This study included 100,000 Japanese mothers and neonates, which made it possible to study multimorbidity. A sufficient number of participants was needed to conduct the study on multimorbidity because of the low frequency of each chronic condition.

- The definition of multimorbidity varies among studies. The strict definition of maternal chronic condition in our study may be responsible for the lower prevalence of maternal multimorbidity than in previous studies.

- The details of the differences in risk by the combination of chronic conditions were not identified. The risk of adverse perinatal outcomes may vary depending on the combination of the chronic conditions.

INTRODUCTION

Multimorbidity is usually defined as the coexistence of two or more chronic physical or psychological conditions within an individual.[1, 2] Multimorbidity has attracted worldwide attention because of the increased complexity of treatment, consumption of medical care, and health care costs compared to a single disease.[1, 3-5] Multimorbidity is also associated with high mortality, functional disability, and diminished quality of life.[6-8] For many countries, there is evidence that a significant proportion of the adult population suffers from multiple chronic diseases, and the rates are increasing.[2, 9] However, the lack of uniform definitions and classifications of multimorbidity makes it difficult to ascertain their actual status. Consequently, the existing evidence is fragmented and often difficult to interpret.[2]

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 from 8.7 to 18.8%.[3, 4, 10, 11] Regarding pregnant women, the prevalence of multimorbidity has varied from 0.83 to 24.2%.[12-14] Although the prevalence of maternal multimorbidity has not been investigated in Japan, the number of pregnant women with multimorbidity is expected to increase as with maternal population ages.

The association between certain specific single maternal chronic diseases and related perinatal outcomes has been well studied; however, there are only a few studies on maternal multimorbidity and perinatal outcomes.[12, 13, 15] The 2020 systematic review in low- and middle-income countries by McCauley et al. classified maternal multimorbidity into three categories: physical morbidity (such as medical, infectious, and obstetrical conditions), psychological morbidity (such as depression and suicidal ideation), and social morbidity (such as domestic violence and substance abuse).[15] The World Health Organization Maternal Morbidity Working Group also considered physical, psychological, and social morbidity to measure maternal morbidity.[16] Domestic violence against pregnant women has also been a social issue in Japan,[17] not only in low- and middle-income countries.

It has been widely known that maternal physical morbidity such as hypertension, kidney disease, and systemic lupus erythematosus increase the risk of preterm births (PTB) and low birth weight infants (LBW).[18-21] Moreover, maternal psychological and social morbidity has been also associated with PTB and LBW.[22-27] In their review, McCauley et al. were trying to assess the impact of each type of morbidity on women's health and well-being during pregnancy and after childbirth, however, a meta-analysis of the associations between multimorbidity and obstetrical complications could not be

performed because of the heterogeneity of each study.[15] The evidence of maternal multimorbidity has been insufficient because only a few studies reported the association between maternal multimorbidity and adverse perinatal outcomes.[12, 13] Additionally, a previous study in the United States by Admon et al. underestimated the prevalence of maternal multimorbidity because only eight chronic conditions were included.[13] There is a need to conduct a study covering a broad range of maternal chronic conditions to avoid overlooking pregnant women at risk of potentially adverse perinatal outcomes. Therefore, we hypothesized that the risk of adverse perinatal outcomes, such as PTB, LBW, and small for gestational age (SGA), would increase with the number of chronic maternal conditions present in a woman, including physical, psychological, and social conditions.

In Japan, the association between maternal multimorbidity and adverse perinatal outcomes has not yet been investigated. The present study aimed to determine the association between maternal multimorbidity and adverse perinatal outcomes, such as PTB, LBW, and SGA, using a Japanese nationwide prospective cohort study.

METHODS

Study design and participants

This prospective cohort study used the dataset jecs-ta-20190930 from the Japan Environment and Children's Study (JECS). The JECS is an ongoing nationwide birth cohort study in Japan, the details of which have already been reported.[28, 29] Its main aim of the JECS was to investigate the association between environmental factors and children's health and development. The JECS recruited pregnant women from 15 regional centers selected to cover the Japanese geographical areas: Hokkaido, Miyagi, Fukushima, Chiba, Kanagawa, Koshin, Toyama, Aichi, Kyoto, Osaka, Hyogo, Tottori, Kochi, Fukuoka, and South Kyusyu/Okinawa, between January 2011 and March 2014.

During the study period, 104,062 fetal records were included in the baseline survey of the JECS. Miscarriages (n = 1,254), stillbirths (n = 382), and unknown birth outcomes (n = 2,123) were excluded, leaving 100,303 live births in the present study. After excluding pregnancies in the same mothers, there were 94,753 participants. Finally, patients with multiple pregnancies (n = 1,809), pregnancies with chromosomal abnormalities (n = 207), missing values of gestational age at delivery (n = 286), missing values of neonatal birth weight (n = 69), missing values of medication information (n = 2,166), missing values of domestic violence from intimate partners (n = 880), missing

values of maternal infection (n = 2,418), and missing values of maternal pre-pregnancy body mass index (BMI) (n = 33) were excluded and the final number of study participants was 86,885 singleton pregnant women (Figure 1). In the SGA analyses, the number of participants decreased to 86,674 because 211 deliveries at a gestational age of < 22 or > 41 weeks were excluded (Figure 1).

Ethics

The study protocol was approved by the Ministry of the Environment's Institutional Review Board on Epidemiological Studies and by the Ethics Committees of all participating institutions (No. 100910001).[28] The JECS was performed in accordance with the Declaration of Helsinki. All the participants provided written informed consent.

Maternal and neonatal baseline information

Baseline information on the mothers, including educational level, smoking status, and alcohol consumption, was collected from self-administered questionnaires applied to the enrolled pregnant women during the second or third trimesters. Maternal medical history was obtained using self-administered questionnaires and medical record transcripts during the first trimester of pregnancy. A history of domestic violence from an intimate

partner was obtained from self-administered questionnaires applied to the enrolled pregnant women during the first trimester. The following maternal information was obtained from the medical record transcripts: maternal infection, neonate's date of birth, parity, and gestational period. Although maternal pre-pregnancy height and weight were collected from medical record transcripts, in instances where the above information was missing, the values were obtained from mothers' self-reports. Maternal age at delivery was calculated from the birth dates of mothers and neonates. Parity was categorized as 0, 1, 2, or higher. The categories of maternal smoking status were defined as follows: never; previously did, but quit before recognizing the current pregnancy; previously did, but quit after identifying the current pregnancy; and current smoker. The categories of maternal alcohol consumption were defined as follows: never consumed; previously consumed, but quit before identifying current pregnancy; previously consumed, but quit after identifying current pregnancy; and current drinker. The highest educational level of the mother was defined as follows: junior high school, high school, technical junior college, technical/vocational college or associate degree, bachelor's degree, or graduate degree (master/doctor). Maternal and neonatal medical information, such as maternal age at delivery, gestational age at delivery, neonatal birth weight, and neonatal sex, were collected from the medical record transcripts at birth.

Exposure: Maternal Multimorbidity

In our study, multimorbidity was defined as the coexistence of two or more physical, psychological, or social conditions in an individual according to previous reports.[13-16] Maternal chronic conditions included in multimorbidity were defined as the conditions with high prevalence among reproductive-age women or that had the potential to affect perinatal outcomes. The chronic conditions in this study were heterogeneous because the JECS lacked information regarding the disease severity. However, the definition of multimorbidity varies among studies.[16, 30] To identify pregnant women with chronic conditions more rigorously, a maternal chronic condition was defined as a condition that was medically treated at the time of pregnancy. This information was collected from self-reports, medical record transcripts, and medication interviews. Maternal chronic conditions included allergic diseases such as asthma, anemia, diabetes mellitus, dyslipidemia, epilepsy, gastric or duodenal ulcer, heart disease, hepatitis, human immunodeficiency virus (HIV) infection, hypertension, inflammatory bowel disease, kidney disease, malignancy, migraine, neurologic disease, other sexually transmitted diseases (*Chlamydia trachomatis* and syphilis), psychiatric disorders, rheumatic or collagen diseases, and thyroid disease.

Additionally, abnormal pre-pregnancy BMI, including underweight and obesity, physical or verbal domestic violence from intimate partners, and substance abuse, were included in the maternal chronic conditions.[16, 31] Maternal pre-pregnancy BMI was calculated from the maternal pre-pregnancy weight divided by the square of maternal height collected from medical record transcripts or self-reports. Pregnant women were categorized according to their pre-pregnancy BMI as follows: underweight (BMI < 18.5 kg/m^2), normal weight (18.5 $kg/m^2 \leq$ BMI < 25.0 kg/m^2), and obesity (BMI $\geq$ 25.0 kg/m^2). Information on domestic violence from intimate partners was obtained from a questionnaire administered during the first trimester: "Have you been verbally insulted or yelled at by your partner during pregnancy?" and "Have you been physically abused, such as being slapped or beaten, resulting in injury because of a quarrel between you and your partner during pregnancy?"[32] Each response was selected from one of four predefined categories: never, rarely, sometimes, and often. If the response "sometimes" or "often" was chosen, it was considered as presence of domestic violence. Medication information was obtained from interviews. Medication was considered relevant from pregnancy diagnosis to 12 weeks of gestation. The types of medication in early pregnancy included antiallergic drugs, lipid-lowering drugs, antimigraine drugs, anti-parkinsonian drugs, anti-rheumatic drugs, antithyroid drugs, antiviral drugs, anti-cancer drugs, cardiovascular

drugs, corticosteroids, gastrointestinal drugs, illegal drugs including marijuana, psychostimulant, ecstasy, thinner, and toluene, insulin preparations, iron preparations, psychoactive drugs, respiratory drugs, and thyroid hormone preparations.[33]

Outcomes

The primary outcome of this study was the incidence of adverse perinatal outcomes, including PTB, LBW, and SGA. The secondary outcomes were the incidences of very preterm birth (VPTB), very low birth weight (VLBW), and extremely low birth weight (ELBW). PTB was defined as a gestational age of less than 37 weeks at delivery. VPTB was defined as a gestational age of less than 34 weeks at delivery. LBW, VLBW, and ELBW were defined as neonatal birth weights of less than 2,500 g, 1,500 g, and 1,000 g, respectively. SGA was defined as birth weight below the 10th percentile, accounting for parity, gestational age, and neonatal sex according to the Japan Pediatric Society guidelines,[34] and percentiles were calculated using Excel-based clinical tools for growth evaluation of children distributed by the Japanese Society for Pediatric Endocrinology.[35]

Statistical analysis

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, parity, maternal smoking status, maternal alcohol consumption, maternal educational level, and neonatal sex. In the SGA analyses, parity and neonatal sex were removed from the covariates. These covariates were selected based on previous studies on multimorbidity. Statistical analyses were used to compare pregnant women with multimorbidity or with one chronic condition, to those without chronic conditions as a reference group.

We used the k-nearest neighbor imputation method in the R package "VIM" (version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria),[36] introducing all outcomes and adjusted variables because the dataset had some missing values. We performed an additional analysis to test the robustness of our findings using a complete dataset, which excluded all missing values. Sensitivity analyses focusing on underweight, obesity, psychiatric disorders, and domestic violence were performed. Each of these chronic conditions was categorized separately as included or not included in the multimorbidity category. The results of these analyses are shown in Supplementary Tables 1 and 2. Statistical significance was defined as a two-tailed P-value < 0.05. All analyses, except k-nearest neighbor imputation, were performed using STATA version 16.1, for Windows (Stata Corporation, College Station, TX, USA). K-nearest neighbor

imputation was conducted using R (version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The maternal characteristics are shown in Table 1. The median maternal age was 31 years (range, 14-48), and the median pre-pregnancy BMI was 20.5 kg/m^2 (range, 13.2-52.8). In the present study, 34.6% of pregnant women had one or more chronic conditions (Table 1). The prevalence of maternal multimorbidity was 3.7% (3,237/86,885). Regarding perinatal outcomes, the prevalences of PTB and VPTB were 4.6% and 1.0%, respectively. The prevalences of LBW, VLBW, ELBW, and SGA were 8.1 %, 0.6%, 0.2%, and 7.5 %, respectively (Table 2). The details of the maternal chronic conditions are shown in Table 3. Maternal underweight (15.6%) was the most frequently observed in chronic conditions, followed by maternal obesity (10.9%). The prevalence of domestic violence was 4.6%. The other most frequent chronic conditions were allergic diseases (3.1%), other sexually transmitted diseases (1.4%), anemia (0.7%), psychiatric disorders (0.7%), and thyroid disease (0.7%).

Maternal multimorbidity was significantly associated with PTB (aOR, 1.76; 95% CI, 1.53-2.03), VPTB (aOR, 1.49; 95% CI, 1.09-2.05), LBW (aOR, 1.58; 95% CI, 1.41-1.77), VLBW (aOR, 1.53; 95% CI, 1.01-2.34), and SGA (aOR, 1.30; 95% CI, 1.15-1.47) (Table 4). Adjusted odds ratios of PTB, LBW, and SGA tended to increase with multimorbidity rather than with one chronic condition. ELBW was not significantly

associated with maternal multimorbidities (Table 4).

The association between maternal multimorbidity and adverse perinatal outcomes, using the complete dataset, is shown in Supplementary Table 1. Maternal multimorbidity was also significantly associated with PTB, LBW, and SGA, however, it was not associated with VPTB and VLBW. Additionally, the aORs of PTB, LBW, and SGA also tended to increase with multimorbidity rather than with one chronic condition.

Supplementary Table 2 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 2A-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 2A-D). However, multimorbidity without underweight and that with obesity and psychiatric disorders did not show significant differences (Supplementary Tables 2A, B, and C).

DISCUSSION

In this study, one-third of pregnant women had one or more chronic conditions, and the prevalence of maternal multimorbidity was lower than that in previous studies.[3, 4] Among maternal chronic conditions, pre-pregnancy underweight was the most common, followed by pre-pregnancy obesity and domestic violence. This study showed that maternal multimorbidity was significantly associated with adverse perinatal outcomes including PTB, LBW, and SGA. The risk of adverse perinatal outcomes increases with the number of chronic conditions in the mother.

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. A sufficient number of participants was needed to conduct the study on multimorbidity because of the low frequency of each chronic condition.

However, this study has several limitations. First, the prevalence of maternal multimorbidity in this study was 3.7%, which was lower than the prevalence noted in reproductive-aged women in previous studies.[3, 4, 12, 14] The strict definition of a chronic condition in our study may be responsible for the lower prevalence of maternal

multimorbidity than in previous studies. However, there is no consensus on the definition of maternal multimorbidity or classification system for reporting.[2, 30] Second, the details of the differences in risk by the combination of chronic conditions were not identified. The risk of adverse perinatal outcomes may vary depending on the combination of the chronic conditions. Although sensitivity analyses focusing on underweight, obesity, psychiatric disorders, and domestic violence demonstrated the association of adverse perinatal outcomes with the presence or absence of each condition, no further detailed studies were conducted because the main aim of this study was not to examine the impact of each chronic condition. Third, the numbers of VPTB, VLBW, and ELBW cases were small. For VLBW and ELBW, although the risk of adverse perinatal outcomes was similar between chronic conditions and multimorbidity, a larger number of cases may show a significant difference between the two groups.

Conducting studies on maternal multimorbidity has been challenging because there is no agreed definition or uniform measurement tool for multimorbidity.[30] A systematic review of multimorbidity in 2012 by Fortin et al.[3] reported that the prevalence of multimorbidity seemed to be influenced by the operational definition of chronic conditions. Moreover, most studies on multimorbidity conducted in the general population predominantly used questionnaires. As this method was based on self-report,

it might present the disadvantage of assigning equal weight to both major and minor chronic conditions.[3] Although the present study also used self-report questionnaires, multimorbidity was defined as chronic conditions treated with medication to reduce the variability in the severity of chronic conditions in multimorbidity. However, our method may have decreased the prevalence of multimorbidities.

This study comprised 23 chronic conditions, which included not only physical morbidity, but also psychological and social morbidity. A systematic review of multimorbidity by Fortin et al.[3] suggested using a list of at least the 12 most prevalent chronic conditions to conduct studies on multimorbidity. In a previous study by Admon et al.[13] on maternal multimorbidity, only seven physical and one social morbidity were defined as chronic conditions, and the prevalence of one chronic condition and multimorbidity were 8.4% and 0.83%, respectively. These values are much lower than those of our results. Although it has been controversial which chronic conditions should be included in maternal multimorbidity, our study may have reduced the chance of missing pregnant women at a potential risk of adverse perinatal outcomes.

The present study confirmed that an increase in the number of chronic maternal conditions increases the risk of PTB, LBW, and SGA. In a study on chronic diseases in pregnant women in Germany, pregnant women with at least one chronic condition had an

increased risk of PTB.[12] A study on maternal multimorbidity in the United States reported that the incidence of PTB less than 37 weeks of gestation, cesarean delivery, severe maternal morbidity, and mortality in pregnant women with multimorbidity was higher than those without chronic conditions.[13] These results were consistent with the present study, although the definition of maternal chronic conditions was different from our study.

Chronic physical conditions such as hypertension, kidney disease, systemic lupus erythematosus, and abnormal pre-pregnancy BMI are associated with adverse perinatal outcomes.[18-21, 37, 38] Our findings also indicated that multimorbidity might alter the risk of PTB, LBW, and SGA depending on whether multimorbidity included or did not include abnormal BMI. Additionally, maternal infections, such as HIV, malaria, syphilis, and tuberculosis, have been reported to be associated with adverse perinatal outcomes.[39-42] However, the influence of these infections may be small in the present study because the prevalence of these maternal infections was very low in Japan.

Although the prevalence of psychiatric disorders was 0.7% in the present study, which was very low compared to a previous systematic review of adult women,[43] maternal psychological morbidity was also associated with adverse perinatal outcomes.[23, 24, 44] The present study also showed that the risk of PTB and SGA might vary depending on the presence or absence of psychiatric disorders. In previous studies on depression during

pregnancy, depression was found to be associated with PTB, LBW, and SGA.[23, 24] In addition, common antenatal mental disorders also increased the risk of PTB and LBW.[44]

In the present study, domestic violence from intimate partners was the third most frequent chronic condition at 4.6%. Multimorbidity with and without domestic violence was significantly associated with PTB, LBW, and SGA, although the point estimate of the aOR for multimorbidity with domestic violence was slightly smaller than the aOR for those without domestic violence in this study. Social morbidity, including domestic violence, has been highlighted as a risk factor associated with adverse perinatal outcomes.[15, 26, 27] A cross-sectional study in Iran found a significant association between intimate partner violence during pregnancy and PTB.[26] A prospective cohort study in Tanzania reported that physical violence during pregnancy significantly increased the risk of PTB and LBW.[27] However, a population-based study in Canada reported no association between domestic violence before and during pregnancy and adverse perinatal outcomes, including PTB and SGA.[45] This previous study had the limitation that the prevalence of domestic violence was 10.9% and only 3.3% occurred during pregnancy.[45]

The mechanism by which maternal multimorbidity affected perinatal outcomes was not clear in the present study. Although previous studies reported that each chronic condition, including physical, psychological, and social conditions, increased the risk of

adverse perinatal outcomes, evidence on maternal multimorbidity is lacking.[2] Based on the results of our study, we hypothesized that each chronic condition that composes multimorbidity, such as underweight, obesity, psychiatric disorder, and domestic violence, provides a risk for PTB, and the combination of these chronic conditions might further increase the risk of adverse perinatal outcomes.

CONCLUSIONS

The present study reported an association between maternal multimorbidity and adverse perinatal outcomes including PTB, LBW, and SGA. The risk of adverse perinatal outcomes increases with an increase in the number of chronic maternal conditions. Since the number of reproductive-aged women with multimorbidity has been increasing as the maternal population ages, preconception care for maternal multimorbidity is becoming increasingly important. Our findings provide essential information for preconception counseling in women with multimorbidities.

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Contributors

KN and YaS designed the study. YaS, EY, KN, ST, YI, SK, CM, AA, and RK collected data. KN and YaS conducted the data analysis. KN, YaS, EY, YuS, YK, KN, ST, YI, SK, CM, AA, and RK contributed to the data interpretation. YaS, EY, YuS, YK, KN, ST, YI, SK, CM, AA, and RK conducted the critical reviews. KN drafted the manuscript. YaS made critical revisions. All authors reviewed and commented on the manuscript. All authors approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or

dissemination plans of this research.

Patient consent for publication

Not applicable.

Ethics approval

The study protocol was approved by the Ministry of the Environment's Institutional Review Board on Epidemiological Studies and by the Ethics Committees of all participating institutions (No. 100910001). The JECS was performed in accordance with the Declaration of Helsinki. All the participants provided written informed consent.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

Data are unsuitable for public deposition because of ethical restrictions and Japan's legal framework. The Act on the Protection of Personal Information (Act No. 57 of May 30, 2003, amended on September 9, 2015) prohibits making data containing personal

information publicly available. The Ethical Guidelines for Medical and Health Research Involving Human Subjects enforced by the Japan Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare also restrict the open sharing of epidemiological data. All inquiries about access to data were sent to jecs-en@nies.go.jp. The person responsible for handling inquiries sent to this e-mail address is Dr. Shoji F. Nakayama, JECS Program Office, National Institute for Environmental Studies.

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Figure legends

Figure 1. Flow diagram of the study participants.

Table 1. Maternal characteristics (n = 86,885)

Characteristics	The number of chronic conditions			
	Total	0 (n = 56,843)	1 (n = 26,805)	≥2 (n = 3,237)
Maternal age (years)				
≤ 24	8,599 (9.9)	5,020 (8.8)	3,086 (11.5)	493 (15.2)
25-29	23,873 (27.5)	15,563 (27.4)	7,492 (28.0)	818 (25.3)
30-34	30,686 (35.3)	20,369 (35.8)	9,281 (34.6)	1,036 (32.0)
35-39	19,703 (22.7)	13,241 (23.3)	5,728 (21.4)	734 (22.7)
≥ 40	4,018 (4.6)	2,648 (4.7)	1,215 (4.5)	155 (4.8)
Missing	6 (0.01)	2 (0.00)	3 (0.01)	1 (0.03)
Body mass index (kg/m^2)	20.5 (13.2–52.8)	20.7 (18.5-24.9)	19.5 (13.2-48.8)	20.0 (13.3-52.8)
Parity				
0	35,973 (41.4)	23,690 (41.7)	10,997 (41.0)	1,286 (39.7)

1	31,810 (36.6)	20,848 (36.7)	9,825 (36.7)	1,137 (35.1)
≥ 2	17,040 (19.6)	10.914 (19.2)	5,368 (20.0)	758 (23.4)
Missing	2,062 (2.4)	1,391 (2.5)	615 (2.3)	56 (1.7)
Smoking during pregnancy				
No	49,414 (56.9)	33,392 (58.7)	14,613 (54.5)	1,409 (43.5)
Quit before pregnancy	20,152 (23.2)	13,268 (23.3)	6,124 (22.9)	760 (23.5)
Quit after pregnancy	12,042 (13.9)	7,230 (12.7)	4,139 (15.4)	673 (20.8)
Yes	3,859 (4.4)	2,086 (3.7)	1,460 (5.5)	313 (9.7)
Missing	1,418 (1.6)	867 (1.5)	469 (1.8)	82 (2.5)
Drinking during pregnancy				
No	28,652 (33.0)	18,367 (32.3)	9,223 (34.4)	1,062 (32.8)
Quit before pregnancy	14,108	9,143	4,388 (16.4)	577 (17.8)

	(16.2)	(16.1)		
Quit after pregnancy	40,354 (46.5)	26,921 (47.4)	12,021 (44.9)	1,412 (43.6)
Yes	2,370 (2.7)	1,546 (2.7)	704 (2.6)	120 (3.7)
Missing	1,401 (1.6)	866 (1.5)	469 (1.8)	66 (2.0)
Maternal educational background				
Junior high school	4,089 (4.7)	2,127 (3.7)	1,625 (6.1)	337 (10.4)
High school	27,106 (31.2)	16,881 (29.7)	8,968 (33.5)	1,257 (38.8)
Technical junior college or technical/vocational college	36,123 (41.6)	24,192 (42.6)	10,772 (40.2)	1,159 (35.8)
University or above	18,415 (21.2)	12,922 (22.7)	5,073 (18.9)	420 (13.0)
Missing	1,152 (1.3)	721 (1.3)	367 (1.4)	64 (2.0)

Values are presented as n (%) or median (range)

Table 2. Perinatal outcomes (n = 86,885)

Outcomes		The number of chronic conditions		
	Total	0 (n = 56,843)	1 (n = 26,805)	≥2 (n = 3,237)
Gestational age at delivery (weeks)	39 (22–43)	39 (23–42)	39 (22–42)	39 (23–43)
Birth weight (grams)	3,028 (312–5,214)	3,040 (312–4,906)	3,010 (350–5,214)	2,994 (398–4,554)
Neonatal sex				
Male	44,628 (51.4)	29,101 (51.2)	13,847 (51.7)	1,680 (51.9)
Female	42,252 (48.6)	27,740 (48.8)	12,956 (48.3)	1,556 (48.1)
Missing	5 (0.01)	2 (0.00)	2 (0.01)	1 (0.03)
Preterm birth (< 37 weeks' gestation)	3,963 (4.6)	2,302 (4.1)	1,430 (5.3)	231 (7.1)
Very preterm birth (< 34 weeks' gestation)	834 (1.0)	479 (0.8)	312 (1.2)	43 (1.3)
Low birth weight (< 2,500 g)	7,013 (8.1)	4,122 (7.3)	2,528 (9.4)	363 (11.2)
Very low birth weight (< 1,500 g)	483 (0.6)	269 (0.5)	190 (0.7)	24 (0.7)

Extremely low birth weight (< 1,000 g)	205 (0.2)	118 (0.2)	75 (0.3)	12 (0.4)
Small for gestational age				
No	78,138 (89.9)	51,407 (90.4)	23,873 (89.1)	2,858 (88.3)
Yes	6,474 (7.5)	3,909 (6.9)	2,251 (8.4)	314 (9.7)
Missing	2,273 (2.6)	1, 527 (2.7)	681 (2.5)	65 (2.0)

Values are presented as n (%) or median (range).

Table 3. Prevalence of 23 maternal chronic conditions (n = 86,885)

Condition	n (%)
Abnormal pre-pregnancy BMI	
Underweight (BMI < 18.5 kg/m^2)	13,533 (15.6)
Obesity (BMI ≥ 25.0 kg/m^2)	9,461 (10.9)
Allergic disease	2,680 (3.1)
Anemia	628 (0.7)
Diabetes mellitus	128 (0.2)
Domestic violence	3,949 (4.6)
Dyslipidemia	6 (0.01)
Epilepsy	133 (0.2)
Gastric or duodenal ulcer	298 (0.3)
Heart disease	7 (0.01)
Hepatitis	5 (0.01)
Human immunodeficiency virus infection	7 (0.01)
Hypertension	96 (0.1)
Inflammatory bowel disease	16 (0.02)
Kidney disease	17 (0.02)
Malignancy	0 (0)
Migraine	44 (0.1)
Neurologic disease	0 (0)
Other sexually transmitted disease	1,193 (1.4)
Psychiatric disorder	604 (0.7)

Rheumatic or collagen disease	94 (0.1)
Substance abuse	1 (0.0)
Thyroid disease	638 (0.7)

BMI, body mass index.

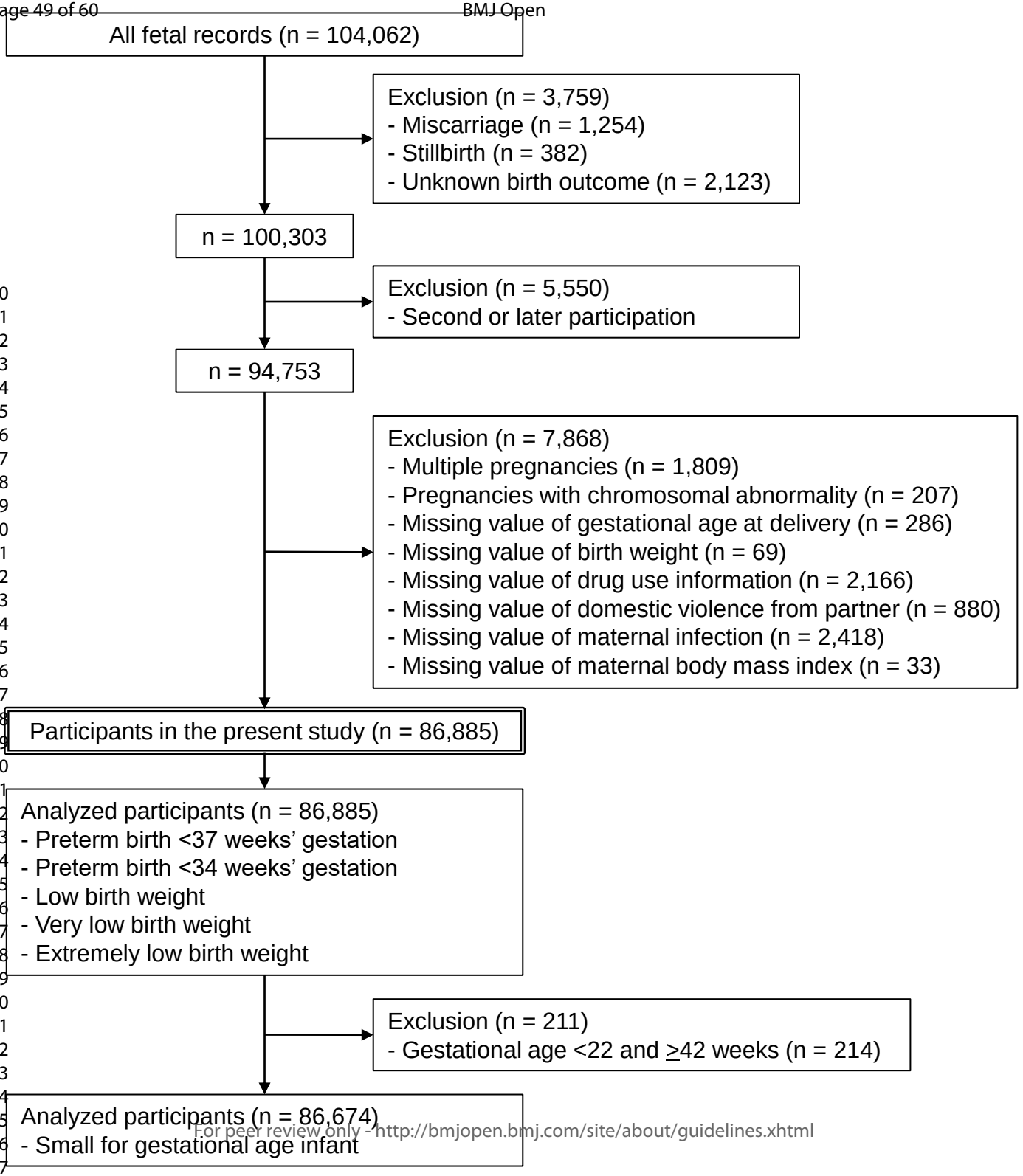
Table 4. Crude and adjusted odds ratios of maternal chronic conditions for adverse perinatal outcomes (n = 86,885)

Outcome	The number of chronic conditions		
	0	1	≥2
PTB			
N (%)	2,302 (4.1)	1,430 (5.3)	231 (7.1)
Crude OR (95% CI)	reference	1.34 (1.25-1.43)	1.82 (1.58-2.09)
Adjusted OR (95% CI)	reference	**1.33 (1.24-1.42)**	**1.76 (1.53-2.03)**
VPTB			
N (%)	479 (0.8)	312 (1.2)	43 (1.3)
Crude OR (95% CI)	reference	1.39 (1.20-1.60)	1.58 (1.16-2.17)
Adjusted OR (95% CI)	reference	**1.37 (1.19-1.58)**	**1.49 (1.09-2.05)**
LBW			
N (%)	4,122 (7.3)	2,528 (9.4)	363 (11.2)
Crude OR (95% CI)	reference	1.33 (1.26-1.40)	1.62 (1.44-1.81)
Adjusted OR (95% CI)	reference	**1.33 (1.26-1.40)**	**1.58 (1.41-1.77)**
VLBW			
N (%)	269 (0.5)	190 (0.7)	24 (0.7)
Crude OR (95% CI)	reference	1.50 (1.25-1.81)	1.57 (1.03-2.39)
Adjusted OR (95% CI)	reference	**1.51 (1.25-1.82)**	**1.53 (1.01-2.34)**
ELBW			
N (%)	118 (0.2)	75 (0.3)	12 (0.4)
Crude OR (95% CI)	reference	1.35 (1.01-1.80)	1.79 (0.99-3.24)

Adjusted OR (95% CI)	reference	**1.34 (1.00-1.80)**	1.68 (0.92-3.05)
SGA†			
N (%)	4,291 (7.6)	2,324 (8.7)	319 (9.9)
Crude OR (95% CI)	reference	1.16 (1.10-1.23)	1.34 (1.19-1.51)
Adjusted OR (95% CI)	reference	**1.15 (1.09-1.21)**	**1.30 (1.15-1.47)**

†The total number of participants was 86,674. Adjusted odds ratios with statistical significance are indicated in bold font.

CI, confidence interval; ELBW, extremely low birth weight (< 1,000 g); LBW, low birth weight (< 2,500 g); OR, odds ratio compared to that of infants of mothers without chronic conditions, adjusted for maternal age at delivery, parity (except for SGA analysis), maternal smoking status, maternal alcohol consumption, maternal educational background, and neonatal sex (except for SGA analysis); PTB, preterm birth before 37 weeks of gestation; SGA, small for gestational age; VLBW, very low birth weight (< 1,500 g); VPTB, preterm birth before 34 weeks of gestation.



Supplementary Table 1. Crude and adjusted odds ratios of maternal chronic conditions for adverse perinatal outcomes in the complete dataset (n = 82,393)

Outcome	The number of chronic conditions		
	0	1	≥2
PTB			
N (%)	2,110 (3.9)	1,309 (5.2)	208 (6.8)
Crude OR (95% CI)	reference	1.34 (1.25-1.43)	1.80 (1.55-2.08)
Adjusted OR (95% CI)	reference	**1.33 (1.24-1.43)**	**1.74 (1.50-2.02)**
VPTB			
N (%)	404 (0.8)	271 (1.1)	34 (1.1)
Crude OR (95% CI)	reference	1.43 (1.23-1.67)	1.49 (1.05-2.13)
Adjusted OR (95% CI)	reference	**1.41 (1.21-1.65)**	1.41 (0.99-2.01)
LBW			
N (%)	3,833 (7.1)	2,344 (9.2)	329 (10.8)
Crude OR (95% CI)	reference	1.33 (1.26-1.40)	1.58 (1.40-1.78)
Adjusted OR (95% CI)	reference	**1.33 (1.26-1.40)**	**1.54 (1.37-1.74)**
VLBW			
N (%)	217 (0.4)	155 (0.6)	17 (0.6)
Crude OR (95% CI)	reference	1.52 (1.24-1.87)	1.39 (0.85-2.28)
Adjusted OR (95% CI)	reference	**1.52 (1.23-1.87)**	1.34 (0.82-2.21)
ELBW			
N (%)	82 (0.2)	50 (0.2)	9 (0.3)
Crude OR (95% CI)	reference	1.30 (0.91-1.84)	1.95 (0.98-3.88)
Adjusted OR (95% CI)	reference	1.29 (0.90-1.83)	1.80 (0.90-3.61)
SGA†			

N (%)	3,784 (7.0)	2,171 (8.6)	299 (9.8)
Crude OR (95% CI)	reference	1.24 (1.17-1.31)	1.44 (1.27-1.63)
Adjusted OR (95% CI)	reference	**1.23 (1.16-1.29)**	**1.38 (1.22-1.57)**

†The total number of participants was 82,191. Adjusted odds ratios with statistical significance are indicated in bold font.

CI, confidence interval; ELBW, extremely low birth weight (< 1,000 g); LBW, low birth weight (< 2,500 g); OR, odds ratio compared to that of infants of mothers without chronic conditions, adjusted for maternal age at delivery, parity (except for SGA analysis), maternal smoking status, maternal alcohol consumption, maternal educational background, and neonatal sex (except for SGA analysis); PTB, preterm birth before 37 weeks of gestation; SGA, small-for-gestational age; VLBW, very low birth weight (< 1,500 g); VPTB, preterm birth before 34 weeks of gestation.

Supplementary Table 2A. Adjusted odds ratios of multimorbidity with underweight for adverse perinatal outcomes (n = 86,885)

Outcome	The number of chronic conditions			
	0	1	≥2 without underweight	≥2 with underweight
PTB				
N (%)	2,302 (4.1)	1,430 (5.3)	146 (8.3)	85 (5.7)
Adjusted OR (95% CI)	reference	**1.33 (1.24-1.42)**	**2.01 (1.69-2.40)**	**1.45 (1.16-1.81)**
VPTB				
N (%)	479 (0.8)	312 (1.2)	30 (1.7)	13 (0.9)
Adjusted OR (95% CI)	reference	**1.37 (1.19-1.58)**	**1.85 (1.27-2.68)**	1.04 (0.60-1.81)
LBW				
N (%)	4,122 (7.3)	2,528 (9.4)	181 (10.3)	182 (12.3)
Adjusted OR (95% CI)	reference	**1.33 (1.26-1.40)**	**1.41 (1.20-1.65)**	**1.79 (1.52-2.10)**
VLBW				
N (%)	269 (0.5)	190 (0.7)	17 (1.0)	7 (0.5)
Adjusted OR (95% CI)	reference	**1.51 (1.25-1.82)**	**1.93 (1.18-3.17)**	1.03 (0.48-2.18)
ELBW				
N (%)	118 (0.2)	75 (0.3)	8 (0.5)	4 (0.3)

Adjusted OR (95% CI)	reference	**1.34 (1.00-1.80)**	1.95 (0.94-4.01)	1.31 (0.48-3.57)
SGA†				
N (%)	4,291 (7.6)	2,324 (8.7)	128 (7.3)	191 (12.9)
Adjusted OR (95% CI)	reference	**1.15 (1.09-1.21)**	0.93 (0.77-1.12)	**1.78 (1.52-2.08)**

†The total number of participants was 86,674. Adjusted odds ratios with statistical significance are indicated in bold font.

CI, confidence interval; ELBW, extremely low birth weight (< 1,000 g); LBW, low birth weight (< 2,500 g); OR, odds ratio compared to that of infants of mothers without chronic conditions, adjusted for maternal age at delivery, parity (except for SGA analysis), maternal smoking status, maternal alcohol consumption, maternal educational background, and neonatal sex (except for SGA analysis); PTB, preterm birth before 37 weeks of gestation; SGA, small-for-gestational age; VLBW, very low birth weight (< 1,500 g); VPTB, preterm birth before 34 weeks of gestation.

Supplementary Table 2B. Adjusted odds ratios of multimorbidity with obesity for adverse perinatal outcomes (n = 86,885)

Outcome	The number of chronic conditions			
	0	1	≥2 without obesity	≥2 with obesity
PTB				
N (%)	2,302 (4.1)	1,430 (5.3)	123 (6.4)	108 (8.2)
Adjusted OR (95% CI)	reference	**1.33 (1.24-1.42)**	**1.60 (1.33-1.93)**	**1.98 (1.62-2.43)**
VPTB				
N (%)	479 (0.8)	312 (1.2)	17 (0.9)	26 (2.0)
Adjusted OR (95% CI)	reference	**1.37 (1.19-1.58)**	1.02 (0.63-1.67)	**2.13 (1.43-3.18)**
LBW				
N (%)	4,122 (7.3)	2,528 (9.4)	231 (12.0)	132 (10.1)
Adjusted OR (95% CI)	reference	**1.33 (1.26-1.40)**	**1.72 (1.49-1.99)**	**1.37 (1.14-1.65)**
VLBW				
N (%)	269 (0.5)	190 (0.7)	10 (0.5)	14 (1.1)
Adjusted OR (95% CI)	reference	**1.51 (1.25-1.82)**	1.11 (0.59-2.10)	**2.11 (1.23-3.63)**
ELBW				
N (%)	118 (0.2)	75 (0.3)	5 (0.3)	7 (0.5)

Adjusted OR (95% CI)	reference	**1.34 (1.00-1.80)**	1.23 (0.50-3.01)	**2.27 (1.05-4.91)**
SGA†				
N (%)	4,291 (7.6)	2,324 (8.7)	227 (11.8)	92 (7.0)
Adjusted OR (95% CI)	reference	**1.15 (1.09-1.21)**	**1.60 (1.38-1.84)**	0.89 (0.72-1.11)

†The total number of participants was 86,674. Adjusted odds ratios with statistical significance are indicated in bold font.

CI, confidence interval; ELBW, extremely low birth weight (< 1,000 g); LBW, low birth weight (< 2,500 g); OR, odds ratio compared to that of infants of mothers without chronic conditions, adjusted for maternal age at delivery, parity (except for SGA analysis), maternal smoking status, maternal alcohol consumption, maternal educational background, and neonatal sex (except for SGA analysis); PTB, preterm birth before 37 weeks of gestation; SGA, small-for-gestational age; VLBW, very low birth weight (< 1,500 g); VPTB, preterm birth before 34 weeks of gestation.

Supplementary Table 2C. Adjusted odds ratios of multimorbidity with psychiatric disorder for adverse perinatal outcomes (n = 86,885)

Outcome	The number of chronic conditions			
	0	1	≥2 without psychiatric disorder	≥2 with psychiatric disorder
PTB				
N (%)	2,302 (4.1)	1,430 (5.3)	201 (6.9)	30 (9.4)
Adjusted OR (95% CI)	reference	**1.33 (1.24-1.42)**	**1.71 (1.47-1.98)**	**2.22 (1.52-3.25)**
VPTB				
N (%)	479 (0.8)	312 (1.2)	40 (1.4)	3 (0.9)
Adjusted OR (95% CI)	reference	**1.37 (1.19-1.58)**	**1.56 (1.12-2.12)**	0.96 (0.30-3.00)
LBW				
N (%)	4,122 (7.3)	2,528 (9.4)	325 (11.1)	38 (11.9)
Adjusted OR (95% CI)	reference	**1.33 (1.26-1.40)**	**1.58 (1.40-1.78)**	**1.55 (1.10-2.18)**
VLBW				
N (%)	269 (0.5)	190 (0.7)	21 (0.7)	3 (0.9)
Adjusted OR (95% CI)	reference	**1.51 (1.25-1.82)**	1.50 (0.96-2.35)	1.78 (0.57-5.61)
ELBW				

N (%)	118 (0.2)	75 (0.3)	11 (0.4)	1 (0.3)
Adjusted OR (95% CI)	reference	**1.34 (1.00-1.80)**	1.73 (0.93-3.23)	1.24 (0.17-8.97)
SGA†				
N (%)	4,291 (7.6)	2,324 (8.7)	292 (10.0)	27 (8.5)
Adjusted OR (95% CI)	reference	**1.15 (1.09-1.21)**	**1.33 (1.17-1.51)**	1.06 (0.71-1.58)

†The total number of participants was 86,674. Adjusted odds ratios with statistical significance are indicated in bold font.

CI, confidence interval; ELBW, extremely low birth weight (< 1,000 g); LBW, low birth weight (< 2,500 g); OR, odds ratio compared to that of infants of mothers without chronic conditions, adjusted for maternal age at delivery, parity (except for SGA analysis), maternal smoking status, maternal alcohol consumption, maternal educational background, and neonatal sex (except for SGA analysis); PTB, preterm birth before 37 weeks of gestation; SGA, small-for-gestational age; VLBW, very low birth weight (< 1,500 g); VPTB, preterm birth before 34 weeks of gestation.

Supplementary Table 2D. Adjusted odds ratios of multimorbidity with domestic violence from intimate partner for adverse perinatal outcomes (n = 86,885)

Outcome	The number of chronic conditions			
	0	1	≥2 without domestic violence	≥2 with domestic violence
PTB				
N (%)	2,302 (4.1)	1,430 (5.3)	141 (7.6)	90 (6.5)
Adjusted OR (95% CI)	reference	**1.33 (1.24-1.42)**	**1.88 (1.58-2.25)**	**1.59 (1.28-1.98)**
VPTB				
N (%)	479 (0.8)	312 (1.2)	30 (1.6)	13 (0.9)
Adjusted OR (95% CI)	reference	**1.37 (1.19-1.58)**	**1.81 (1.25-2.63)**	1.05 (0.60-1.84)
LBW				
N (%)	4,122 (7.3)	2,528 (9.4)	219 (11.8)	144 (10.4)
Adjusted OR (95% CI)	reference	**1.33 (1.26-1.40)**	**1.66 (1.44-1.92)**	**1.46 (1.23-1.75)**
VLBW				
N (%)	269 (0.5)	190 (0.7)	16 (0.9)	8 (0.6)
Adjusted OR (95% CI)	reference	**1.51 (1.25-1.82)**	**1.74 (1.04-2.88)**	1.24 (0.61-2.52)
ELBW				

N (%)	118 (0.2)	75 (0.3)	8 (0.4)	4 (0.3)
Adjusted OR (95% CI)	reference	**1.34 (1.00-1.80)**	1.96 (0.95-4.02)	1.30 (0.48-3.55)
SGA†				
N (%)	4,291 (7.6)	2,324 (8.7)	188 (10.2)	131 (9.5)
Adjusted OR (95% CI)	reference	**1.15 (1.09-1.21)**	**1.36 (1.17-1.59)**	**1.22 (1.02-1.47)**

†The total number of participants was 86,674. Adjusted odds ratios with statistical significance are indicated in bold font.

CI, confidence interval; ELBW, extremely low birth weight (< 1,000 g); LBW, low birth weight (< 2,500 g); OR, odds ratio compared to that of infants of mothers without chronic conditions, adjusted for maternal age at delivery, parity (except for SGA analysis), maternal smoking status, maternal alcohol consumption, maternal educational background, and neonatal sex (except for SGA analysis); PTB, preterm birth before 37 weeks of gestation; SGA, small-for-gestational age; VLBW, very low birth weight (< 1,500 g); VPTB, preterm birth before 34 weeks of gestation.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6-8
Objectives	3	State specific objectives, including any prespecified hypotheses	8
Methods			
Study design	4	Present key elements of study design early in the paper	9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	9-10
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	9-10
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10-14
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	10-14
Bias	9	Describe any efforts to address potential sources of bias	15
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	12-14
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	15-16
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	17
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	17
Outcome data	15*	Report numbers of outcome events or summary measures over time	17-18

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	17-18
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	18
Discussion			
Key results	18	Summarise key results with reference to study objectives	19
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	19-20
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	20-24
Generalisability	21	Discuss the generalisability (external validity) of the study results	24
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	26

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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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

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Title: 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

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ABSTRACT

Objectives: Multimorbidity is defined as the coexistence of two or more chronic physical or psychological conditions within an individual. The association between maternal multimorbidity and adverse perinatal outcomes such as preterm delivery and low birth weight has not been well studied. Therefore, this study aimed to investigate this association.

Methods: We conducted a prospective cohort study using data from the Japan Environment and Children's Study of pregnant women between 2011 and 2014. Those with data on chronic maternal conditions were included in the study and categorized as having no chronic condition, one chronic condition, or multimorbidities. The primary outcomes were the incidence of preterm birth (PTB), low birth weight (LBW), and small for gestational age (SGA). Adjusted logistic regression was performed to estimate odds ratios (aORs) and 95% confidence intervals (CIs).

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^2, 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).

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

Keywords: chronic diseases, Japan, low birth weight, multimorbidity, preterm birth, small for gestational age.

Word counts: 3,934

Strengths and limitations of this study

- 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.

INTRODUCTION

Multimorbidity is usually defined as the coexistence of two or more chronic physical or psychological conditions within an individual.[1, 2] Multimorbidity has attracted worldwide attention because of the increased complexity of treatment, consumption of medical care, and health care costs compared to a single disease.[1, 3-5] Multimorbidity is also associated with high mortality, functional disability, and diminished quality of life.[6-8] For many countries, there is evidence that a significant proportion of the adult population suffers from multiple chronic diseases, and the rates are increasing.[2, 9] However, the lack of uniform definitions and classifications of multimorbidity makes it difficult to ascertain their actual status. Consequently, the existing evidence is fragmented and often difficult to interpret.[2]

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%.[3, 4, 10, 11] Regarding pregnant women, the prevalence of multimorbidity has varied from 0.83 to 24.2%.[12-14] 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.[15, 16] The number of pregnant women with multimorbidity is expected to increase as with maternal population ages.

The association between certain specific single maternal chronic diseases and related perinatal outcomes has been well studied; however, there are only a few studies on maternal multimorbidity and perinatal outcomes.[12, 13, 17] The 2020 systematic review in low- and middle-income countries by McCauley et al. classified maternal multimorbidity into three categories: physical morbidity (such as medical, infectious, and obstetrical conditions), psychological morbidity (such as depression and suicidal ideation), and social morbidity (such as domestic violence and substance abuse).[17] The World Health Organization Maternal Morbidity Working Group also considered physical, psychological, and social morbidity to measure maternal morbidity.[18] Domestic violence against pregnant women has also been a social issue in Japan,[19] not only in low- and middle-income countries.

It has been widely known that maternal physical morbidity such as hypertension, kidney disease, and systemic lupus erythematosus increase the risk of preterm births (PTB) and low birth weight infants (LBW).[20-23] Moreover, maternal psychological and social morbidity has been also associated with PTB and LBW.[24-29] In their review, McCauley et al. were trying to assess the impact of each type of morbidity on women's

health and well-being during pregnancy and after childbirth, however, a meta-analysis of the associations between multimorbidity and obstetrical complications could not be performed because of the heterogeneity of each study.[17] The evidence of maternal multimorbidity has been insufficient because only a few studies reported the association between maternal multimorbidity and adverse perinatal outcomes.[12, 13] Additionally, a previous study in the United States by Admon et al. underestimated the prevalence of maternal multimorbidity because only eight chronic conditions were included.[13] There is a need to conduct a study covering a broad range of maternal chronic conditions to avoid overlooking pregnant women at risk of potentially adverse perinatal outcomes. Therefore, we hypothesized that the risk of adverse perinatal outcomes, such as PTB, LBW, and small for gestational age (SGA), would increase with the number of chronic maternal conditions present in a woman, including physical, psychological, and social conditions.

In Japan, the association between maternal multimorbidity and adverse perinatal outcomes has not yet been investigated. The present study aimed to determine the association between maternal multimorbidity and adverse perinatal outcomes, such as PTB, LBW, and SGA, using a Japanese nationwide prospective cohort study.

METHODS

Study design and participants

This prospective cohort study used the dataset jecs-ta-20190930 from the Japan Environment and Children's Study (JECS). The JECS is an ongoing nationwide birth cohort study in Japan, the details of which have already been reported.[30, 31] Its main aim of the JECS was to investigate the association between environmental factors and children's health and development. The JECS recruited pregnant women from 15 regional centers selected to cover the Japanese geographical areas: Hokkaido, Miyagi, Fukushima, Chiba, Kanagawa, Koshin, Toyama, Aichi, Kyoto, Osaka, Hyogo, Tottori, Kochi, Fukuoka, and South Kyusyu/Okinawa, between January 2011 and March 2014. The recruitment strategy in the JECS is shown in Supplementary Appendix 1.[30]

During the study period, 104,062 fetal records were included in the baseline survey of the JECS. Miscarriages (n = 1,254), stillbirths (n = 382), and unknown birth outcomes (n = 2,123) were excluded, leaving 100,303 live births in the present study. 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. Finally, patients with multiple pregnancies (n = 1,809), pregnancies with chromosomal abnormalities (n = 207), missing values of gestational age at delivery (n =

286), missing values of neonatal birth weight (n = 69), missing values of medication information (n = 2,166), missing values of domestic violence from intimate partners (n = 880), missing values of maternal infection (n = 2,418), and missing values of maternal pre-pregnancy body mass index (BMI) (n = 33) were excluded and the final number of study participants was 86,885 singleton pregnant women (Figure 1). 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).

Ethics

The study protocol was approved by the Ministry of the Environment's Institutional Review Board on Epidemiological Studies and by the Ethics Committees of all participating institutions (No. 100910001).[30] The JECS was performed in accordance with the Declaration of Helsinki. All the participants provided written informed consent.

Patient and Public Involvement statement

This study did not involve patients or public.

Maternal and neonatal baseline information

Baseline information on the mothers, including educational level, smoking status, and alcohol consumption, was collected from self-administered questionnaires applied to the enrolled pregnant women during the second or third trimesters. Maternal medical history was obtained using self-administered questionnaires and medical record transcripts during the first trimester of pregnancy. A history of domestic violence from an intimate partner was obtained from self-administered questionnaires applied to the enrolled pregnant women during the first trimester. The following maternal information was obtained from the medical record transcripts: maternal infection, neonate's date of birth, parity, and gestational period. Although maternal pre-pregnancy height and weight were collected from medical record transcripts, in instances where the above information was missing, the values were obtained from mothers' self-reports. Maternal age at delivery was calculated from the birth dates of mothers and neonates. Parity was categorized as 0, 1, 2, or higher. The categories of maternal smoking status were defined as follows: never; previously did, but quit before recognizing the current pregnancy; previously did, but quit after identifying the current pregnancy; and current smoker. The categories of maternal alcohol consumption were defined as follows: never consumed; previously consumed, but quit before identifying current pregnancy; previously consumed, but quit after identifying current pregnancy; and current drinker. The highest educational level of the

mother was defined as follows: junior high school, high school, technical junior college, technical/vocational college or associate degree, bachelor's degree, or graduate degree (master/doctor). Annual household income was categorized 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. Maternal and neonatal medical information, such as maternal age at delivery, gestational age at delivery, neonatal birth weight, and neonatal sex, were collected from the medical record transcripts at birth.

Exposure: Maternal Multimorbidity

In our study, multimorbidity was defined as the coexistence of two or more physical, psychological, or social conditions in an individual according to previous reports.[13, 14, 17, 18] Maternal chronic conditions included in multimorbidity were defined as the conditions with high prevalence among reproductive-age women or that had the potential to affect perinatal outcomes. The chronic conditions in this study were heterogeneous because the JECS lacked information regarding the disease severity. However, the definition of multimorbidity varies among studies.[18, 32] To identify pregnant women with chronic conditions more rigorously, a maternal chronic condition was defined as a condition that was medically treated at the time of pregnancy. This information was collected from self-

reports, medical record transcripts, and medication interviews. Maternal chronic conditions included allergic diseases such as asthma, anemia, diabetes mellitus, dyslipidemia, epilepsy, gastric or duodenal ulcer, heart disease, hepatitis, human immunodeficiency virus (HIV) infection, hypertension, inflammatory bowel disease, kidney disease, malignancy, migraine, neurologic disease, other sexually transmitted diseases (*Chlamydia trachomatis* and syphilis), psychiatric disorders, rheumatic or collagen diseases, and thyroid disease.

Additionally, abnormal pre-pregnancy BMI, including underweight and obesity, physical or verbal domestic violence from intimate partners, and substance abuse, were included in the maternal chronic conditions.[18, 33] Maternal pre-pregnancy BMI was calculated from the maternal pre-pregnancy weight divided by the square of maternal height collected from medical record transcripts or self-reports. Pregnant women were categorized according to their pre-pregnancy BMI as follows: underweight (BMI < 18.5 kg/m^2), normal weight (18.5 $kg/m^2 \leq$ BMI < 25.0 kg/m^2), and obesity (BMI $\geq$ 25.0 kg/m^2).[34, 35] Information on domestic violence from intimate partners was obtained from a questionnaire administered during the first trimester: “Have you been verbally insulted or yelled at by your partner during pregnancy?” and “Have you been physically abused, such as being slapped or beaten, resulting in injury because of a quarrel between you and

your partner during pregnancy?"[36] Each response was selected from one of four predefined categories: never, rarely, sometimes, and often. If the response "rarely" or "sometimes" or "often" was chosen, it was considered as presence of domestic violence. Medication information was obtained from interviews (Supplementary Appendix 2).[37] 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. The types of medication in early pregnancy included antiallergic drugs, lipid-lowering drugs, antimigraine drugs, anti-parkinsonian drugs, anti-rheumatic drugs, antithyroid drugs, antiviral drugs, anti-cancer drugs, cardiovascular drugs, corticosteroids, gastrointestinal drugs, illegal drugs including marijuana, psychostimulant, ecstasy, thinner, and toluene, insulin preparations, iron preparations, psychoactive drugs, respiratory drugs, and thyroid hormone preparations.[37]

Outcomes

The primary outcome of this study was the incidence of adverse perinatal outcomes, including PTB, LBW, and SGA. The secondary outcomes were the incidences of very preterm birth (VPTB), very low birth weight (VLBW), and extremely low birth weight (ELBW). PTB was defined as a gestational age of less than 37 weeks at delivery. VPTB

was defined as a gestational age of less than 34 weeks at delivery. LBW, VLBW, and ELBW were defined as neonatal birth weights of less than 2,500 g, 1,500 g, and 1,000 g, respectively. SGA was defined as birth weight below the 10th percentile, accounting for parity, gestational age, and neonatal sex according to the Japan Pediatric Society guidelines,[38] and percentiles were calculated using Excel-based clinical tools for growth evaluation of children distributed by the Japanese Society for Pediatric Endocrinology.[39]

Statistical analysis

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, household income, and neonatal sex. In the SGA analyses, parity and neonatal sex were removed from the covariates. These covariates were selected based on previous studies on multimorbidity.[13, 18, 33] Statistical analyses were used to compare pregnant women with multimorbidity or with one chronic condition, to those without chronic conditions as a reference group.

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),[40] 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.[41] We performed an additional analysis to test the robustness of our findings using a complete dataset, which excluded all missing values. 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. Sensitivity analyses focusing on underweight, obesity, psychiatric disorders, and domestic violence were performed. Each of these chronic conditions was categorized separately as included or not included in the multimorbidity category. The results of these analyses are shown in Supplementary Tables 1, 2 and 3. Statistical significance was defined as a two-tailed *P*-value < 0.05. All analyses, except kNN imputation, were performed using STATA version 16.1, for Windows (Stata Corporation, College Station, TX, USA). kNN imputation was conducted using R (version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

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). The main and all maternal characteristics are shown in Table 1 and Supplementary Table 1, respectively. The median maternal age was 31 years (range, 14-48), and the median pre-pregnancy BMI was 20.5 kg/m^2 (range, 13.2-52.8). 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). Regarding perinatal outcomes, the prevalences of PTB and VPTB were 4.6% and 1.0%, respectively. The prevalences of LBW, VLBW, ELBW, and SGA were 8.1 %, 0.6%, 0.2%, and 7.5 %, respectively (Table 2). The details of the maternal chronic conditions are shown in Table 3. Maternal underweight (15.6%) was the most frequently observed in chronic conditions, followed by domestic violence (13.0%). The prevalence of maternal obesity was 10.9%. The other most frequent chronic conditions were allergic diseases (3.1%), other sexually transmitted diseases (1.4%), anemia (0.7%), psychiatric disorders (0.7%), and thyroid disease (0.7%).

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 3 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.

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 4A-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

In this study, one-third of pregnant women had one or more chronic conditions, and the prevalence of maternal multimorbidity was lower than that in previous studies.[3, 4] Among maternal chronic conditions, pre-pregnancy underweight was the most common, followed by domestic violence and pre-pregnancy obesity. This study showed that maternal multimorbidity was significantly associated with PTB, LBW, and SGA. The number of chronic conditions in the mother tends to increase the risk of adverse perinatal outcomes.

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.

However, this study has several limitations. First, the prevalence of maternal multimorbidity in this study was 6.3%, which was lower than the prevalence noted in reproductive-aged women in previous studies.[3, 4, 14] The strict definition of a chronic condition in our study may be responsible for the lower prevalence of maternal multimorbidity than in previous studies. However, there is no consensus on the definition

of maternal multimorbidity or classification system for reporting.[2, 32] Second, the details of the differences in risk by the combination of chronic conditions were not identified. The risk of adverse perinatal outcomes may vary depending on the combination of the chronic conditions. Although sensitivity analyses focusing on underweight, obesity, psychiatric disorders, and domestic violence demonstrated the association of adverse perinatal outcomes with the presence or absence of each condition, no further detailed studies were conducted because the main aim of this study was not to examine the impact of each chronic condition. Third, some self-reported biases may exist. Self-reported body weight may be underestimated for underweight and overestimated for obesity.[42, 43] The prevalence of self-reported domestic violence may be underestimated due to social desirability bias.[44] Forth, the numbers of VPTB, VLBW, and ELBW cases were small. This study was insufficient to investigate these severe adverse outcomes.

Conducting studies on maternal multimorbidity has been challenging because there is no agreed definition or uniform measurement tool for multimorbidity.[32] A systematic review of multimorbidity in 2012 by Fortin et al.[3] reported that the prevalence of multimorbidity seemed to be influenced by the operational definition of chronic conditions. Moreover, most studies on multimorbidity conducted in the general population predominantly used questionnaires. As this method was based on self-report,

it might present the disadvantage of assigning equal weight to both major and minor chronic conditions.[3] Although the present study also used self-report questionnaires, multimorbidity was defined as chronic conditions treated with medication to reduce the variability in the severity of chronic conditions in multimorbidity. However, our method may have decreased the prevalence of multimorbidities.

This study comprised 23 chronic conditions, which included not only physical morbidity, but also psychological and social morbidity. A systematic review of multimorbidity by Fortin et al.[3] suggested using a list of at least the 12 most prevalent chronic conditions to conduct studies on multimorbidity. In a previous study by Admon et al.[13] on maternal multimorbidity, only seven physical and one social morbidity were defined as chronic conditions, and the prevalence of one chronic condition and multimorbidity were 8.4% and 0.83%, respectively. These values are much lower than those of our results. Although it has been controversial which chronic conditions should be included in maternal multimorbidity, our study may have reduced the chance of missing pregnant women at a potential risk of adverse perinatal outcomes.

The present study confirmed that an increase in the number of chronic maternal conditions increases the risk of PTB, LBW, and SGA. In a study on chronic diseases in pregnant women in Germany, pregnant women with at least one chronic condition had an

increased risk of PTB.[12] A study on maternal multimorbidity in the United States reported that the incidence of PTB less than 37 weeks of gestation, cesarean delivery, severe maternal morbidity, and mortality in pregnant women with multimorbidity was higher than those without chronic conditions.[13] These results were consistent with the present study, although the definition of maternal chronic conditions was different from our study.

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.

Chronic physical conditions such as hypertension, kidney disease, systemic lupus erythematosus, and abnormal pre-pregnancy BMI are associated with adverse perinatal outcomes.[20-23, 46, 47] Our findings also indicated that multimorbidity might alter the risk of PTB, LBW, and SGA depending on whether multimorbidity included or did not include abnormal BMI. Additionally, maternal infections, such as HIV, malaria,

syphilis, and tuberculosis, have been reported to be associated with adverse perinatal outcomes.[48-51] However, the influence of these infections may be small in the present study because the prevalence of these maternal infections was very low in Japan.

Although the prevalence of psychiatric disorders was 0.7% in the present study, which was very low compared to a previous systematic review of adult women,[52] maternal psychological morbidity was also associated with adverse perinatal outcomes.[25, 26, 52] The present study also showed that the risk of PTB and SGA might vary depending on the presence or absence of psychiatric disorders. In previous studies on depression during pregnancy, depression was found to be associated with PTB, LBW, and SGA.[25, 26] In addition, common antenatal mental disorders also increased the risk of PTB and LBW.[53]

In the present study, domestic violence from intimate partners was the second most frequent chronic condition at 13.0%. Multimorbidity with and without domestic violence was significantly associated with PTB, LBW, and SGA, although the point estimate of the aOR for multimorbidity with domestic violence was slightly smaller than the aOR for those without domestic violence in this study. Social morbidity, including domestic violence, has been highlighted as a risk factor associated with adverse perinatal outcomes.[17, 28, 29] A cross-sectional study in Iran found a significant association between intimate partner violence during pregnancy and PTB.[28] A prospective cohort study in

Tanzania reported that physical violence during pregnancy significantly increased the risk of PTB and LBW.[29] However, a population-based study in Canada reported no association between domestic violence before and during pregnancy and adverse perinatal outcomes, including PTB and SGA.[54] This previous study had the limitation that the prevalence of domestic violence was 10.9% and only 3.3% occurred during pregnancy.[54]

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.[55] Maternal obesity is also a risk factor for preeclampsia.[56] 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.[57] 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.[20-23] 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.[2]

CONCLUSIONS

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. Since the number of reproductive-aged women with multimorbidity has been increasing as the maternal population ages, preconception care for maternal multimorbidity is becoming increasingly important. Our findings provide essential information for preconception counseling in women with multimorbidities.

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Contributors

KN and YaS designed the study. YaS, EY, KN, ST, YI, SK, CM, AA, RK, and the JECS Group collected data. KN and YaS conducted the data analysis. KN, YaS, EY, YuS, YK, KN, ST, YI, SK, CM, AA, and RK contributed to the data interpretation. YaS, EY, YuS, YK, KN, ST, YI, SK, CM, AA, RK, and the JECS Group conducted the critical reviews. KN drafted the manuscript. YaS made critical revisions. All authors reviewed and commented on the manuscript. All authors approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

Patient consent for publication

Not applicable.

Ethics approval

The study protocol was approved by the Ministry of the Environment's Institutional Review Board on Epidemiological Studies and by the Ethics Committees of all participating institutions (No. 100910001). The JECS was performed in accordance with the Declaration of Helsinki. All the participants provided written informed consent.

Provenance and peer review

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Data availability statement

Data are unsuitable for public deposition because of ethical restrictions and Japan's legal framework. The Act on the Protection of Personal Information (Act No. 57 of May 30, 2003, amended on September 9, 2015) prohibits making data containing personal information publicly available. The Ethical Guidelines for Medical and Health Research Involving Human Subjects enforced by the Japan Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare also restrict the open sharing of epidemiological data. All inquiries about access to data were sent to jecs-

en@nies.go.jp. The person responsible for handling inquiries sent to this e-mail address is Dr. Shoji F. Nakayama, JECS Program Office, National Institute for Environmental Studies.

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Figure legends

Figure 1. Flow diagram of the study participants.

654 **Table 1. Main maternal characteristics (n = 86,885)**

Characteristics		The number of chronic conditions		
	Total	0 (n = 51,964)	1 (n = 29,459)	≥2 (n = 5,462)
Maternal age (years)				
≤ 24	8,599 (9.9)	4,451 (8.6)	3,342 (11.3)	806 (14.8)
25-29	23,873 (27.5)	14,205 (27.3)	8,232 (27.9)	1,436 (26.3)
30-34	30,686 (35.3)	18,776 (36.1)	10,142 (34.4)	1,768 (32.4)
35-39	19,703 (22.7)	12,121 (23.3)	6,381 (21.7)	1,201 (22.0)
≥ 40	4,018 (4.6)	2,409 (4.6)	1,359 (4.6)	250 (4.6)
Missing	6 (0.01)	2 (0.00)	3 (0.01)	1 (0.02)
Body mass index (kg/m^2)	20.5 (13.2–52.8)	20.7 (18.5–24.9)	20.0 (13.2–48.8)	19.5 (13.3–52.8)
Parity				
0	35,973 (41.4)	21,952 (42.2)	11,972 (40.6)	2,049 (37.5)
1	31,810 (36.6)	19,030 (36.6)	10,750 (36.5)	2,030 (37.2)
≥ 2	17,040 (19.6)	9,691 (18.7)	6,059 (20.6)	1,290 (23.6)
Missing	2,062 (2.4)	1,291 (2.5)	678 (2.3)	93 (1.7)
Smoking during pregnancy				
No	49,414 (56.9)	31,028 (59.7)	15,937 (54.1)	2,449 (44.8)
Quit before	20,152 (23.2)	12,094 (23.3)	6,777 (23.0)	1,281 (23.5)

pregnancy				
Quit after pregnancy	12,042 (13.9)	6,320 (12.2)	4,613 (15.7)	1,109 (20.3)
Yes	3,859 (4.4)	1,757 (3.4)	1,604 (5.4)	498 (9.1)
Missing	1,418 (1.6)	765 (1.5)	528 (1.8)	125 (2.3)
Drinking during pregnancy				
No	28,652 (33.0)	16,928 (32.6)	9,957 (33.8)	1,767 (32.4)
Quit before pregnancy	14,108 (16.2)	8,321 (16.0)	4,832 (16.4)	955 (17.5)
Quit after pregnancy	40,354 (46.5)	24,554 (47.3)	13,378 (45.4)	2,422 (44.3)
Yes	2,370 (2.7)	1,386 (2.7)	771 (2.6)	213 (3.9)
Missing	1,401 (1.6)	775 (1.5)	521 (1.8)	105 (1.9)

655 Values are presented as n (%) or median (range: min–max)

656 **Table 2. Perinatal characteristics (n = 86,885)**

Outcomes		The number of chronic conditions		
	Total	0 (n = 51,964)	1 (n = 29,459)	≥2 (n = 5,462)
Gestational age at delivery (weeks)	39 (22–43)	39 (23–42)	39 (22–42)	39 (23–43)
Birth weight (grams)	3,028 (312–5,214)	3,038 (312–4,700)	3,016 (350–5,214)	2,998 (398–4,568)
Neonatal sex				
Male	44,628 (51.4)	26,577 (51.2)	15,225 (51.7)	2,826 (51.7)
Female	42,252 (48.6)	25,385 (48.8)	14,233 (48.3)	2,634 (48.2)
Missing	5 (0.01)	2 (0.00)	1 (0.00)	2 (0.04)
Preterm birth (< 37 weeks' gestation)	3,963 (4.6)	2,125 (4.1)	1,498 (5.1)	340 (6.2)
Very preterm birth (< 34 weeks' gestation)	834 (1.0)	441 (098)	328 (1.1)	65 (1.2)
Low birth weight (< 2,500 g)	7,013 (8.1)	3,775 (7.3)	2,661 (9.0)	577 (10.6)
Very low birth weight (< 1,500 g)	483 (0.6)	248 (0.5)	193 (0.7)	42 (0.8)

Extremely low birth weight (< 1,000 g)	205 (0.2)	108 (0.2)	76 (0.3)	21 (0.4)
Small for gestational age				
No	78,138 (89.9)	46,975 (90.4)	26,322 (89.4)	4,841 (88.6)
Yes	6,474 (7.5)	3,574 (6.9)	2,388 (8.1)	512 (9.4)
Missing	2,273 (2.6)	1, 415 (2.7)	749 (2.5)	109 (2.0)

657 Values are presented as n (%) or median (range: min–max).

Table 3. Prevalence of 23 maternal chronic conditions (n = 86,885)

Condition	n (%)
Abnormal pre-pregnancy BMI	
Underweight (BMI < 18.5 kg/m^2)	13,533 (15.6)
Obesity (BMI ≥ 25.0 kg/m^2)	9,461 (10.9)
Allergic disease	2,680 (3.1)
Anemia	628 (0.7)
Diabetes mellitus	128 (0.2)
Domestic violence	11,261 (13.0)
Dyslipidemia	6 (0.01)
Epilepsy	133 (0.2)
Gastric or duodenal ulcer	298 (0.3)
Heart disease	7 (0.01)
Hepatitis	5 (0.01)
Human immunodeficiency virus infection	7 (0.01)
Hypertension	96 (0.1)
Inflammatory bowel disease	16 (0.02)
Kidney disease	17 (0.02)
Malignancy	0 (0)
Migraine	44 (0.1)
Neurologic disease	0 (0)
Other sexually transmitted disease	1,193 (1.4)
Psychiatric disorder	604 (0.7)

Rheumatic or collagen disease	94 (0.1)
Substance abuse	1 (0.0)
Thyroid disease	638 (0.7)

659 BMI, body mass index.

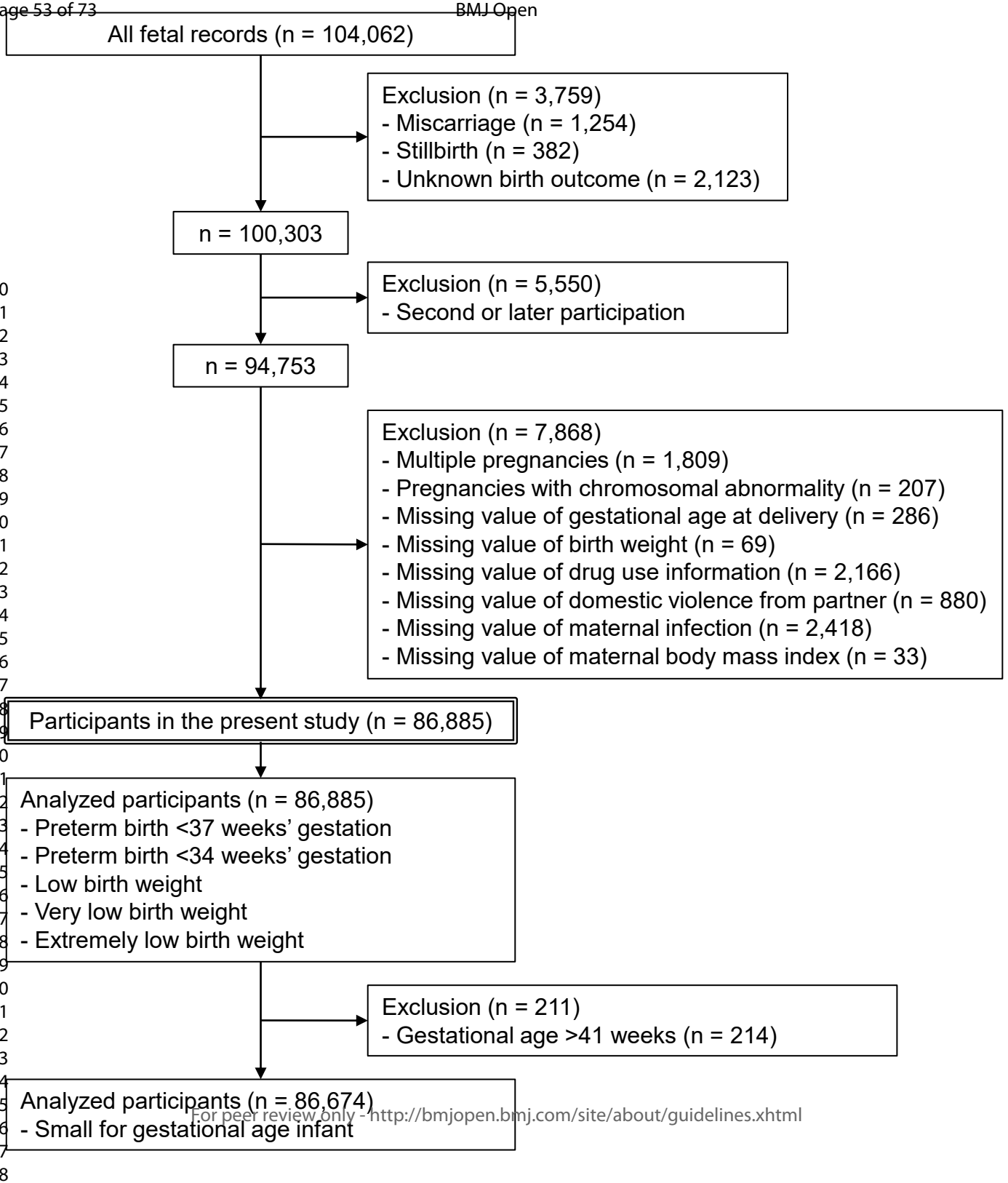
Table 4. Crude and adjusted odds ratios of maternal chronic conditions for adverse perinatal outcomes (n = 86,885)

Outcome	The number of chronic conditions		
	0	1	≥2
PTB			
N (%)	2,125 (4.1)	1,498 (5.1)	340 (6.2)
Crude OR (95% CI)	reference	1.26 (1.17-1.34)	1.56 (1.38-1.75)
Adjusted OR (95% CI)	reference	**1.24 (1.16-1.33)**	**1.50 (1.33-1.69)**
VPTB			
N (%)	441 (0.9)	328 (1.1)	65 (1.2)
Crude OR (95% CI)	reference	1.32 (1.14-1.52)	1.41 (1.08-1.83)
Adjusted OR (95% CI)	reference	**1.29 (1.12-1.49)**	**1.34 (1.03-1.74)**
LBW			
N (%)	3,775 (7.3)	2,661 (9.0)	577 (10.6)
Crude OR (95% CI)	reference	1.27 (1.20-1.33)	1.51 (1.37-1.65)
Adjusted OR (95% CI)	reference	**1.27 (1.20-1.34)**	**1.49 (1.35-1.63)**
VLBW			
N (%)	248 (0.5)	193 (0.7)	42 (0.8)
Crude OR (95% CI)	reference	1.38 (1.14-1.66)	1.61 (1.16-2.24)
Adjusted OR (95% CI)	reference	**1.39 (1.15-1.67)**	**1.62 (1.16-2.25)**
ELBW			
N (%)	108 (0.2)	76 (0.3)	21 (0.4)

Crude OR (95% CI)	reference	1.24 (0.93-1.67)	1.85 (1.16-2.96)
Adjusted OR (95% CI)	reference	1.24 (0.92-1.67)	**1.81 (1.12-2.90)**
SGA†			
N (%)	3,685 (7.1)	2,443 (8.3)	522 (9.6)
Crude OR (95% CI)	reference	1.18 (1.12-1.25)	1.39 (1.26-1.52)
Adjusted OR (95% CI)	reference	**1.17 (1.11-1.23)**	**1.33 (1.20-1.46)**

†The total number of participants was 86,674. Adjusted odds ratios with statistical significance are indicated in bold font.

CI, confidence interval; ELBW, extremely low birth weight (< 1,000 g); LBW, low birth weight (< 2,500 g); OR, odds ratio compared to that of infants of mothers without chronic conditions, adjusted for maternal age at delivery, parity (except for SGA analysis), maternal smoking status, maternal alcohol consumption, maternal educational background, and neonatal sex (except for SGA analysis); PTB, preterm birth before 37 weeks of gestation; SGA, small for gestational age; VLBW, very low birth weight (< 1,500 g); VPTB, preterm birth before 34 weeks of gestation.



Supplementary Appendix 1. Recruitment strategies in the Japan Environment and Children's Study

We attempted to contact as many expected mothers living in study areas as possible. The recruitment rate was targeted more than 50% of all eligible mothers. Either or both of the following two recruitment protocols were applied: 1) recruitment at cooperating health care providers, such as obstetric facilities, at the time of the first prenatal examination (provider-mediated community-based recruitment); 2) recruitment at local government offices issuing pregnancy journals, namely Mother-Child Health Handbooks (the Mother-Child Health Handbook was an official booklet provided complimentary to all expecting mothers in Japan when they became pregnant to receive municipal services for pregnancy, delivery, and childcare). Written informed consent for participation in the study was obtained from individual mothers and their partners, and for children, from their parents or guardian. The study participants were free to withdraw at any moment. Women who refused their consent to study protocol and those who were unreachable during pregnancy, were excluded. In Japan, expecting mothers usually return to their parents' homes to give birth. Those who planned to return to their parents' homes were not eligible unless they were near one of the regional centers. Though we carefully planned the sampling, the recruitment was not entirely random. Both health care providers and local government facilities participated in the recruitment activities. We made every effort to reach out to as many eligible women in the study areas as possible. The representativeness of the JECS samples would be evaluated when the birth data were fixed. (Reference No. 30: Kawamoto T, et al. Rationale and study design of the Japan environment and children's study (JECS). BMC Public Health. 2014;14:25.)

Supplementary Appendix 2. Medication list in the Japan Environment and Children's Study (Nishigori H, et al. Drug use before and during pregnancy in Japan: the Japan environment and children's study. Pharmacy (Basel). 2017;5.)

Antibacterial, Antiviral, Antifungal, Carcinostatic drugs

0 Antimicrobial

1 Antiviral

2 Antifungal

3 Carcinostatic

Corticosteroids

4 Corticosteroids: oral administration, inhalation, infusion

5 Corticosteroids: external use, enema

Antipyretic, Analgesic drugs

6 Antipyretic, Analgesic, Medicine for common cold: prescription

7 Antipyretic, Analgesic, Medicine for common cold: over the counter

8 Poultice which the analgesic is included in

Antirheumatic drugs

9 Immunosuppressant, Immunoregulation

10 Infliximab, Etanercept

11 Antirheumatic drug unidentified in detail

Antiallergy drugs

12 Antiallergic drug (oral administration, inhalation, nasal drip, tape, Antihistaminic)

Respiratory drugs

13 β stimulative (oral administration, inhalation)

14 Nontypeable inhalant

15 Antitussive, Expectorant

16 Theophylline

17 Other respiratory drug

Antidiabetic drugs, Antihyperlipidemic drugs

21 Insulin preparation

22 Hypoglycemic tablet

23 Antihyperlipidemic

24 Antigout

Hormone-related drugs

25 Thyroid hormone preparation/levothyroxine sodium

26 Antithyroid/Thiamazole

27 Other hormone drugs

Blood-related drugs

28 Iron preparation

29 Other blood-related

Cardiovascular drugs

31 Antihypertensive (including diuretic)

32 Pressor

33 Antiarrhythmic, Antianginal

34 Heart failure therapeutic

35 Other cardiovascular drugs

Gastrointestinal drugs

36 Antiulcer (Proton pump inhibitor, H2 blocker)

37 General gastrointestinal agents

38 Other gastrointestinal agents

Psychoactive drugs

41 Selective serotonin reuptake inhibitors (SSRI)

42 Antidepressant drug except the SSRI

43 Antianxiety

44 Sleeping pill

45 Antipsychotic

46 Valproic acid

47 Antiepileptic except the above

48 Lithium carbonate

49 Other psychoactive drugs

Perinatal drugs

51 Utero relaxants

52 Utero-tonic

53 Ovulation inducing

54 Other perinatal related drugs

Other drugs

61 Anesthetic, pain block injection

62 Chinese herbal medicines

63 External application (non-identified contents)

64 Injection, Drip infusion (non-identified contents)

65 Bone and Calcium metabolism

66 Antimigraine headache

67 Muscle relaxant

68 Antiemetic drug

69 AntiParkinson

70 Hemorrhoids

Supplements, vitamins/minerals

71 Vitamin A

72 Vitamin B

73 Vitamin C

74 Vitamin D

75 Vitamin E

76 Folic acid

77 Minerals

78 Multi vitamins supplement

79 Total supplement

Illegal drugs

80 Marijuana

81 Psychostimulant

82 Ecstasy

83 Thinner

84 Toluene

85 Other illegal drugs

90 Vaccines

98 Drugs not included in the list mentioned above

99 Forgot the drug name

Supplementary Table 1. All maternal characteristics (n = 86,885)

Characteristics		The number of chronic conditions		
	Total	0 (n = 51,964)	1 (n = 29,459)	≥2 (n = 5,462)
Maternal age (years)				
≤ 24	8,599 (9.9)	4,451 (8.6)	3,342 (11.3)	806 (14.8)
25-29	23,873 (27.5)	14,205 (27.3)	8,232 (27.9)	1,436 (26.3)
30-34	30,686 (35.3)	18,776 (36.1)	10,142 (34.4)	1,768 (32.4)
35-39	19,703 (22.7)	12,121 (23.3)	6,381 (21.7)	1,201 (22.0)
≥ 40	4,018 (4.6)	2,409 (4.6)	1,359 (4.6)	250 (4.6)
Missing	6 (0.01)	2 (0.00)	3 (0.01)	1 (0.02)
Body mass index (kg/m^2)	20.5 (13.2–52.8)	20.7 (18.5–24.9)	20.0 (13.2–48.8)	19.5 (13.3–52.8)
Parity				
0	35,973 (41.4)	21,952 (42.2)	11,972 (40.6)	2,049 (37.5)
1	31,810 (36.6)	19,030 (36.6)	10,750 (36.5)	2,030 (37.2)
≥ 2	17,040 (19.6)	9,691 (18.7)	6,059 (20.6)	1,290 (23.6)
Missing	2,062 (2.4)	1,291 (2.5)	678 (2.3)	93 (1.7)
Smoking during pregnancy				
No	49,414 (56.9)	31,028 (59.7)	15,937 (54.1)	2,449 (44.8)

Quit before pregnancy	20,152 (23.2)	12,094 (23.3)	6,777 (23.0)	1,281 (23.5)
Quit after pregnancy	12,042 (13.9)	6,320 (12.2)	4,613 (15.7)	1,109 (20.3)
Yes	3,859 (4.4)	1,757 (3.4)	1,604 (5.4)	498 (9.1)
Missing	1,418 (1.6)	765 (1.5)	528 (1.8)	125 (2.3)
Drinking during pregnancy				
No	28,652 (33.0)	16,928 (32.6)	9,957 (33.8)	1,767 (32.4)
Quit before pregnancy	14,108 (16.2)	8,321 (16.0)	4,832 (16.4)	955 (17.5)
Quit after pregnancy	40,354 (46.5)	24,554 (47.3)	13,378 (45.4)	2,422 (44.3)
Yes	2,370 (2.7)	1,386 (2.7)	771 (2.6)	213 (3.9)
Missing	1,401 (1.6)	775 (1.5)	521 (1.8)	105 (1.9)
Maternal educational background				
Junior high school	4,089 (4.7)	1,814 (3.5)	1,730 (5.9)	545 (10.0)
High school	27,106 (31.2)	15,266 (29.4)	9,738 (33.1)	2,102 (38.5)
Technical junior college or	36,123 (41.6)	22,182 (42.7)	11,949 (40.6)	1,992 (36.5)

technical/ vocational college				
University or above	18,415 (21.2)	12,062 (23.2)	5,626 (19.1)	727 (13.3)
Missing	1,152 (1.3)	640 (1.2)	416 (1.4)	96 (1.8)
Household income (JPY)				
< 2,000,000	4,538 (5.2)	2,176 (4.2)	1,838 (6.2)	524 (9.6)
2,000,000–3,990,000	27,625 (31.8)	15,817 (30.4)	9,815 (33.3)	1,993 (36.5)
4,000,000–5,990,000	26,440 (30.4)	16,369 (31.5)	8,587 (29.2)	1,484 (27.2)
6,000,000–7,990,000	12,757 (14.7)	8,188 (15.8)	4,019 (13.6)	550 (10.1)
8,000,000–9,990,000	5,298 (6.1)	3,384 (6.5)	1,675 (5.7)	239 (4.4)
≥ 10,000,000	3,400 (3.9)	2,174 (4.2)	1,043 (3.5)	183 (3.4)
Missing	6,827 (7.9)	3,856 (7.4)	2,482 (8.4)	489 (9.0)

Values are presented as n (%) or median (range: min–max)

Supplementary Table 2. Crude and adjusted odds ratios of maternal chronic conditions for adverse perinatal outcomes in the complete dataset (n = 76,931)

Outcome	The number of chronic conditions		
	0	1	≥2
PTB			
N (%)	1,838 (4.0)	1,253 (4.8)	290 (6.0)
Crude OR (95% CI)	reference	1.23 (1.14-1.32)	1.55 (1.37-1.77)
Adjusted OR (95% CI)	reference	**1.21 (1.13-1.31)**	**1.49 (1.31-1.70)**
VPTB			
N (%)	354 (0.8)	259 (1.0)	48 (1.0)
Crude OR (95% CI)	reference	1.31 (1.11-1.54)	1.31 (0.97-1.77)
Adjusted OR (95% CI)	reference	**1.28 (1.09-1.50)**	1.23 (0.91-1.67)
LBW			
N (%)	3,307 (7.2)	2,247 (8.7)	491 (10.2)
Crude OR (95% CI)	reference	1.23 (1.17-1.30)	1.48 (1.34-1.64)
Adjusted OR (95% CI)	reference	**1.23 (1.16-1.30)**	**1.45 (1.31-1.61)**
VLBW			
N (%)	193 (0.4)	141 (0.5)	29 (0.6)
Crude OR (95% CI)	reference	1.31 (1.05-1.62)	1.45 (0.98-2.15)
Adjusted OR (95% CI)	reference	**1.30 (1.04-1.61)**	1.41 (0.95-2.10)
ELBW			
N (%)	71 (0.2)	43 (0.2)	13 (0.3)
Crude OR (95% CI)	reference	1.08 (0.74-1.58)	1.77 (0.98-3.19)
Adjusted OR (95% CI)	reference	1.06 (0.72-1.55)	1.61 (0.89-2.95)

SGA†			
N (%)	3,249 (7.0)	2,100 (8.1)	455 (9.5)
Crude OR (95% CI)	reference	1.17 (1.10-1.24)	1.39 (1.25-1.54)
Adjusted OR (95% CI)	reference	**1.15 (1.09-1.22)**	**1.33 (1.20-1.47)**

†The total number of participants was 76,740. Adjusted odds ratios with statistical significance are indicated in bold font.

CI, confidence interval; ELBW, extremely low birth weight (< 1,000 g); LBW, low birth weight (< 2,500 g); OR, odds ratio compared to that of infants of mothers without chronic conditions, adjusted for maternal age at delivery, parity (except for SGA analysis), maternal smoking status, maternal alcohol consumption, maternal educational background, and neonatal sex (except for SGA analysis); PTB, preterm birth before 37 weeks of gestation; SGA, small for gestational age; VLBW, very low birth weight (< 1,500 g); VPTB, preterm birth before 34 weeks of gestation.

Supplementary Table 3. Adverse perinatal outcomes in maternal multimorbidity categorized in detail (n = 86,885)

Outcome	The number of chronic conditions					
	0 (n = 51,964)	1 (n = 29,459)	2 (n = 5,039)	3 (n = 385)	≥4 (n = 38)	*P* value for trend
PTB						
N (%)	2,125 (4.1)	1,498 (5.1)	301 (6.0)	36 (9.4)	3 (7.9)	
Crude OR (95% CI)	reference	1.26 (1.17-1.34)	1.49 (1.32-1.69)	2.42 (1.71-3.42)	2.01 (0.62-6.54)	
Adjusted OR (95% CI)	reference	**1.24 (1.16-1.33)**	**1.44 (1.27-1.64)**	**2.30 (1.62-3.26)**	1.72 (0.53-5.62)	< 0.001
LBW						
N (%)	3,775 (7.3)	2,661 (9.0)	525 (10.4)	46 (12.0)	6 (15.8)	
Crude OR (95% CI)	reference	1.27 (1.20-1.33)	1.48 (1.35-1.63)	1.73 (1.27-2.36)	2.39 (1.00-5.73)	
Adjusted OR (95% CI)	reference	**1.26 (1.20-1.34)**	**1.47 (1.33-1.62)**	**1.66 (1.22-2.27)**	2.09 (0.86-5.05)	< 0.001
SGA†						
N (%)	3,685 (7.1)	2,443 (8.3)	483 (9.6)	33 (8.6)	6 (15.8)	
Crude OR (95% CI)	reference	1.18 (1.12-1.25)	1.39 (1.26-1.54)	1.23 (0.86-1.76)	2.45 (1.02-5.86)	

Adjusted OR (95% CI)	reference	**1.17 (1.10-1.23)**	**1.33 (1.21-1.48)**	1.14 (0.80-1.63)	2.19 (0.91-5.27)	< 0.001

†The total number of participants was 86,674. Adjusted odds ratios with statistical significance are indicated in bold font.

CI, confidence interval; LBW, low birth weight (< 2,500 g); OR, odds ratio compared to that of infants of mothers without chronic conditions, adjusted for maternal age at delivery, parity (except for SGA analysis), maternal smoking status, maternal alcohol consumption, maternal educational background, and neonatal sex (except for SGA analysis); PTB, preterm birth before 37 weeks of gestation; SGA, small for gestational age.

Supplementary Table 4A. Adjusted odds ratios of multimorbidity with underweight for adverse perinatal outcomes (n = 86,885)

Outcome	The number of chronic conditions			
	0	1	≥2 without underweight	≥2 with underweight
PTB				
N (%)	2,125 (4.1)	1,498 (5.1)	207 (7.1)	133 (5.2)
Adjusted OR (95% CI)	reference	**1.24 (1.16-1.33)**	**1.69 (1.46-1.96)**	**1.28 (1.07-1.54)**
VPTB				
N (%)	441 (0.9)	328 (1.1)	44 (1.5)	21 (0.8)
Adjusted OR (95% CI)	reference	**1.29 (1.12-1.49)**	**1.64 (1.20-2.25)**	0.97 (0.62-1.50)
LBW				
N (%)	3,775 (7.3)	2,661 (9.0)	266 (9.1)	311 (12.2)
Adjusted OR (95% CI)	reference	**1.27 (1.20-1.33)**	**1.25 (1.09-1.42)**	**1.78 (1.57-2.01)**
VLBW				
N (%)	248 (0.5)	193 (0.7)	27 (0.9)	15 (0.6)
Adjusted OR (95% CI)	reference	**1.39 (1.15-1.67)**	**1.89 (1.27-2.84)**	1.28 (0.76-2.16)
ELBW				

N (%)	108 (0.2)	76 (0.3)	13 (0.5)	8 (0.3)
Adjusted OR (95% CI)	reference	1.24 (0.92-1.67)	**2.03 (1.13-3.63)**	1.54 (0.75-3.12)
SGA†				
N (%)	3,685 (7.1)	2,443 (8.3)	205 (7.1)	317 (12.5)
Adjusted OR (95% CI)	reference	**1.17 (1.10-1.23)**	0.94 (0.81-1.09)	**1.80 (1.59-2.04)**

†The total number of participants was 86,674. Adjusted odds ratios with statistical significance are indicated in bold font.

CI, confidence interval; ELBW, extremely low birth weight (< 1,000 g); LBW, low birth weight (< 2,500 g); OR, odds ratio compared to that of infants of mothers without chronic conditions, adjusted for maternal age at delivery, parity (except for SGA analysis), maternal smoking status, maternal alcohol consumption, maternal educational background, and neonatal sex (except for SGA analysis); PTB, preterm birth before 37 weeks of gestation; SGA, small for gestational age; VLBW, very low birth weight (< 1,500 g); VPTB, preterm birth before 34 weeks of gestation.

Supplementary Table 4B. Adjusted odds ratios of multimorbidity with obesity for adverse perinatal outcomes (n = 86,885)

Outcome	The number of chronic conditions			
	0	1	≥2 without obesity	≥2 with obesity
PTB				
N (%)	2,125 (4.1)	1,498 (5.1)	185 (5.4)	155 (7.5)
Adjusted OR (95% CI)	reference	**1.24 (1.16-1.33)**	**1.33 (1.14-1.56)**	**1.78 (1.50-2.11)**
VPTB				
N (%)	441 (0.9)	328 (1.1)	28 (0.8)	37 (1.8)
Adjusted OR (95% CI)	reference	**1.29 (1.12-1.49)**	0.95 (0.65-1.40)	**1.93 (1.37-2.72)**
LBW				
N (%)	3,775 (7.3)	2,661 (9.0)	383 (11.3)	194 (9.4)
Adjusted OR (95% CI)	reference	**1.27 (1.20-1.34)**	**1.61 (1.44-1.80)**	**1.29 (1.10-1.50)**
VLBW				
N (%)	248 (0.5)	193 (0.7)	20 (0.6)	22 (1.1)
Adjusted OR (95% CI)	reference	**1.39 (1.15-1.68)**	1.27 (0.80-2.00)	**2.16 (1.39-3.36)**
ELBW				

N (%)	108 (0.2)	76 (0.3)	9 (0.3)	12 (0.6)
Adjusted OR (95% CI)	reference	1.24 (0.92-1.67)	1.28 (0.64-2.53)	**2.64 (1.44-4.83)**
SGA†				
N (%)	3,685 (7.1)	2,443 (8.3)	380 (11.2)	142 (6.9)
Adjusted OR (95% CI)	reference	**1.17 (1.10-1.23)**	**1.59 (1.42-1.78)**	0.92 (0.77-1.09)

†The total number of participants was 86,674. Adjusted odds ratios with statistical significance are indicated in bold font.

CI, confidence interval; ELBW, extremely low birth weight (< 1,000 g); LBW, low birth weight (< 2,500 g); OR, odds ratio compared to that of infants of mothers without chronic conditions, adjusted for maternal age at delivery, parity (except for SGA analysis), maternal smoking status, maternal alcohol consumption, maternal educational background, and neonatal sex (except for SGA analysis); PTB, preterm birth before 37 weeks of gestation; SGA, small for gestational age; VLBW, very low birth weight (< 1,500 g); VPTB, preterm birth before 34 weeks of gestation.

Supplementary Table 4C. Adjusted odds ratios of multimorbidity with psychiatric disorder for adverse perinatal outcomes (n = 86,885)

Outcome	The number of chronic conditions			
	0	1	≥2 without psychiatric disorder	≥2 with psychiatric disorder
PTB				
N (%)	2,125 (4.1)	1,498 (5.1)	309 (6.1)	31 (8.6)
Adjusted OR (95% CI)	reference	**1.24 (1.16-1.33)**	**1.47 (1.30-1.66)**	**1.99 (1.36-2.89)**
VPTB				
N (%)	441 (0.9)	328 (1.1)	62 (1.2)	3 (0.8)
Adjusted OR (95% CI)	reference	**1.29 (1.11-1.49)**	**1.38 (1.05-1.81)**	0.84 (0.27-2.63)
LBW				
N (%)	3,775 (7.3)	2,661 (9.0)	536 (10.5)	41 (11.4)
Adjusted OR (95% CI)	reference	**1.27 (1.20-1.34)**	**1.49 (1.35-1.64)**	**1.45 (1.04-2.02)**
VLBW				
N (%)	248 (0.5)	193 (0.7)	39 (0.8)	3 (0.8)
Adjusted OR (95% CI)	reference	**1.39 (1.15-1.67)**	**1.62 (1.15-2.28)**	1.58 (0.50-4.96)

ELBW				
N (%)	108 (0.2)	76 (0.3)	20 (0.4)	1 (0.3)
Adjusted OR (95% CI)	reference	1.24 (0.92-1.67)	**1.86 (1.15-3.02)**	1.14 (0.16-8.25)
SGA†				
N (%)	3,685 (7.1)	2,443 (8.3)	492 (9.7)	30 (8.3)
Adjusted OR (95% CI)	reference	**1.17 (1.10-1.23)**	**1.34 (1.22-1.49)**	1.08 (0.74-1.57)

†The total number of participants was 86,674. Adjusted odds ratios with statistical significance are indicated in bold font.

CI, confidence interval; ELBW, extremely low birth weight (< 1,000 g); LBW, low birth weight (< 2,500 g); OR, odds ratio compared to that of infants of mothers without chronic conditions, adjusted for maternal age at delivery, parity (except for SGA analysis), maternal smoking status, maternal alcohol consumption, maternal educational background, and neonatal sex (except for SGA analysis); PTB, preterm birth before 37 weeks of gestation; SGA, small for gestational age; VLBW, very low birth weight (< 1,500 g); VPTB, preterm birth before 34 weeks of gestation.

Supplementary Table 4D. Adjusted odds ratios of multimorbidity with domestic violence from intimate partner for adverse perinatal outcomes (n = 86,885)

Outcome	The number of chronic conditions			
	0	1	≥2 without domestic violence	≥2 with domestic violence
PTB				
N (%)	2,125 (4.1)	1,498 (5.1)	122 (7.4)	218 (5.7)
Adjusted OR (95% CI)	reference	**1.24 (1.16-1.33)**	**1.79 (1.48-2.17)**	**1.38 (1.19-1.59)**
VPTB				
N (%)	441 (0.9)	328 (1.1)	28 (1.7)	37 (1.0)
Adjusted OR (95% CI)	reference	**1.29 (1.12-1.49)**	**1.88 (1.28-2.77)**	1.10 (0.78-1.54)
LBW				
N (%)	3,775 (7.3)	2,661 (9.0)	198 (12.0)	379 (9.9)
Adjusted OR (95% CI)	reference	**1.27 (1.20-1.33)**	**1.69 (1.45-1.97)**	**1.40 (1.25-1.57)**
VLBW				
N (%)	248 (0.5)	193 (0.7)	14 (0.9)	28 (0.7)
Adjusted OR (95% CI)	reference	**1.38 (1.15-1.67)**	**1.69 (0.98-2.90)**	**1.58 (1.06-2.35)**

ELBW				
N (%)	108 (0.2)	76 (0.3)	7 (0.4)	14 (0.4)
Adjusted OR (95% CI)	reference	1.24 (0.92-1.67)	1.95 (0.90-4.20)	1.74 (0.99-3.06)
SGA†				
N (%)	3,685 (7.1)	2,443 (8.3)	169 (10.3)	353 (9.3)
Adjusted OR (95% CI)	reference	**1.17 (1.10-1.23)**	**1.46 (1.24-1.72)**	**1.27 (1.13-1.43)**

†The total number of participants was 86,674. Adjusted odds ratios with statistical significance are indicated in bold font.

CI, confidence interval; ELBW, extremely low birth weight (< 1,000 g); LBW, low birth weight (< 2,500 g); OR, odds ratio compared to that of infants of mothers without chronic conditions, adjusted for maternal age at delivery, parity (except for SGA analysis), maternal smoking status, maternal alcohol consumption, maternal educational background, and neonatal sex (except for SGA analysis); PTB, preterm birth before 37 weeks of gestation; SGA, small for gestational age; VLBW, very low birth weight (< 1,500 g); VPTB, preterm birth before 34 weeks of gestation.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6-8
Objectives	3	State specific objectives, including any prespecified hypotheses	8
Methods			
Study design	4	Present key elements of study design early in the paper	9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	9-10
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	9-10
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10-15
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	10-15
Bias	9	Describe any efforts to address potential sources of bias	15-16
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	13-15
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	15-16
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	17
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	17
Outcome data	15*	Report numbers of outcome events or summary measures over time	17-18

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	17-18
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	18
Discussion			
Key results	18	Summarise key results with reference to study objectives	20
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	20-21
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	21-26
Generalisability	21	Discuss the generalisability (external validity) of the study results	26
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	28

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.