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

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7 **Title: Maternal multimorbidity and adverse perinatal outcomes: The Japan**

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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/m², 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

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6 common, observed in 15.6% of multimorbidity cases, followed by maternal obesity in
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9 10.9%. Maternal multimorbidity was significantly associated with PTB (aOR, 1.76; 95%
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12 CI, 1.53-2.03), LBW (aOR, 1.58; 95% CI, 1.41-1.77), and SGA (aOR, 1.30; 95% CI,
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15 1.15-1.47).

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18 **Conclusion:** Maternal multimorbidity was associated with adverse perinatal outcomes,
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21 including PTB, LBW, and SGA. The risk of adverse perinatal outcomes increases with
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24 an increase in the number of chronic maternal conditions. Multimorbidity is becoming
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27 more prevalent among pregnant women, making our findings important for preconception
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30 counseling.
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36 **Keywords:** chronic diseases, Japan, low birth weight, multimorbidity, preterm birth,
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39 small for gestational age.
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45 **Word counts:** 3,514
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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.

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7 The association between certain specific single maternal chronic diseases and
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9 related perinatal outcomes has been well studied; however, there are only a few studies
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11 on maternal multimorbidity and perinatal outcomes.^{12, 13, 15} The 2020 systematic review
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13 in low- and middle-income countries by McCauley et al. classified maternal
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15 multimorbidity into three categories: physical morbidity (such as medical, infectious, and
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17 obstetrical conditions), psychological morbidity (such as depression and suicidal
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19 ideation), and social morbidity (such as domestic violence and substance abuse).¹⁵ The
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21 World Health Organization Maternal Morbidity Working Group also considered physical,
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23 psychological, and social morbidity to measure maternal morbidity.¹⁶ Domestic violence
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25 against pregnant women has also been a social issue in Japan,¹⁷ not only in low- and
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27 middle-income countries.
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39 It has been widely known that maternal physical morbidity such as hypertension,
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41 kidney disease, and systemic lupus erythematosus increase the risk of preterm births
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43 (PTB) and low birth weight infants (LBW).¹⁸⁻²¹ Moreover, maternal psychological and
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45 social morbidity has been also associated with PTB and LBW.²²⁻²⁷ In their review,
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47 McCauley et al. were trying to assess the impact of each type of morbidity on women's
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49 health and well-being during pregnancy and after childbirth, however, a meta-analysis of
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51 the associations between multimorbidity and obstetrical complications could not be
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6 performed because of the heterogeneity of each study.¹⁵ The evidence of maternal
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9 multimorbidity has been insufficient because only a few studies reported the association
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12 between maternal multimorbidity and adverse perinatal outcomes.^{12, 13} Additionally, a
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15 previous study in the United States by Admon et al. underestimated the prevalence of
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18 maternal multimorbidity because only eight chronic conditions were included.¹³ There is
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21 a need to conduct a study covering a broad range of maternal chronic conditions to avoid
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24 overlooking pregnant women at risk of potentially adverse perinatal outcomes. Therefore,
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27 we hypothesized that the risk of adverse perinatal outcomes, such as PTB, LBW, and
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30 small for gestational age (SGA), would increase with the number of chronic maternal
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33 conditions present in a woman, including physical, psychological, and social conditions.
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36 In Japan, the association between maternal multimorbidity and adverse perinatal
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39 outcomes has not yet been investigated. The present study aimed to determine the
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42 association between maternal multimorbidity and adverse perinatal outcomes, such as
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45 PTB, LBW, and SGA, using a Japanese nationwide prospective cohort study.
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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

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6 values of maternal infection (n = 2,418), and missing values of maternal pre-pregnancy
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9 body mass index (BMI) (n = 33) were excluded and the final number of study participants
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12 was 86,885 singleton pregnant women (Figure 1). In the SGA analyses, the number of
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15 participants decreased to 86,674 because 211 deliveries at a gestational age of < 22 or >
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18 41 weeks were excluded (Figure 1).
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20 21 22 23 24 ***Ethics***

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27 The study protocol was approved by the Ministry of the Environment's Institutional
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30 Review Board on Epidemiological Studies and by the Ethics Committees of all
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33 participating institutions (No. 100910001).²⁸ The JECS was performed in accordance
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36 with the Declaration of Helsinki. All the participants provided written informed consent.
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42 43 ***Maternal and neonatal baseline information***

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45 Baseline information on the mothers, including educational level, smoking status, and
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48 alcohol consumption, was collected from self-administered questionnaires applied to the
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51 enrolled pregnant women during the second or third trimesters. Maternal medical history
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54 was obtained using self-administered questionnaires and medical record transcripts
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57 during the first trimester of pregnancy. A history of domestic violence from an intimate
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6 partner was obtained from self-administered questionnaires applied to the enrolled
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9 pregnant women during the first trimester. The following maternal information was
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12 obtained from the medical record transcripts: maternal infection, neonate's date of birth,
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15 parity, and gestational period. Although maternal pre-pregnancy height and weight were
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18 collected from medical record transcripts, in instances where the above information was
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21 missing, the values were obtained from mothers' self-reports. Maternal age at delivery
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24 was calculated from the birth dates of mothers and neonates. Parity was categorized as 0,
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27 1, 2, or higher. The categories of maternal smoking status were defined as follows: never;
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30 previously did, but quit before recognizing the current pregnancy; previously did, but quit
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33 after identifying the current pregnancy; and current smoker. The categories of maternal
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36 alcohol consumption were defined as follows: never consumed; previously consumed,
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39 but quit before identifying current pregnancy; previously consumed, but quit after
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42 identifying current pregnancy; and current drinker. The highest educational level of the
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45 mother was defined as follows: junior high school, high school, technical junior college,
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48 technical/vocational college or associate degree, bachelor's degree, or graduate degree
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51 (master/doctor). Maternal and neonatal medical information, such as maternal age at
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54 delivery, gestational age at delivery, neonatal birth weight, and neonatal sex, were
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57 collected from the medical record transcripts at birth.
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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.

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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/m²), normal weight (18.5 kg/m² ≤ BMI < 25.0 kg/m²), and obesity (BMI ≥ 25.0 kg/m²). 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

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6 drugs, corticosteroids, gastrointestinal drugs, illegal drugs including marijuana,
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9 psychostimulant, ecstasy, thinner, and toluene, insulin preparations, iron preparations,
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12 psychoactive drugs, respiratory drugs, and thyroid hormone preparations.³³
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18 ***Outcomes***

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

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57 In the main analyses, adjusted odds ratios (aORs) and 95% confidence intervals (CIs) for
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6 adverse perinatal outcomes were estimated using a multivariable logistic regression
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9 model adjusted for maternal age at delivery, parity, maternal smoking status, maternal
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12 alcohol consumption, maternal educational level, and neonatal sex. In the SGA analyses,
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15 parity and neonatal sex were removed from the covariates. These covariates were selected
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18 based on previous studies on multimorbidity. Statistical analyses were used to compare
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21 pregnant women with multimorbidity or with one chronic condition, to those without
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24 chronic conditions as a reference group.
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27 We used the k-nearest neighbor imputation method in the R package “VIM”
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30 (version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria),³⁶ introducing
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33 all outcomes and adjusted variables because the dataset had some missing values. We
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36 performed an additional analysis to test the robustness of our findings using a complete
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39 dataset, which excluded all missing values. Sensitivity analyses focusing on underweight,
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42 obesity, psychiatric disorders, and domestic violence were performed. Each of these
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45 chronic conditions was categorized separately as included or not included in the
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48 multimorbidity category. The results of these analyses are shown in Supplementary
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51 Tables 1 and 2. Statistical significance was defined as a two-tailed *P*-value < 0.05. All
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54 analyses, except k-nearest neighbor imputation, were performed using STATA version
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57 16.1, for Windows (Stata Corporation, College Station, TX, USA). K-nearest neighbor
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imputation was conducted using R (version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria).

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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/m² (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

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6 associated with maternal multimorbidities (Table 4).
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9 The association between maternal multimorbidity and adverse perinatal
10 outcomes, using the complete dataset, is shown in Supplementary Table 1. Maternal
11 multimorbidity was also significantly associated with PTB, LBW, and SGA, however, it
12 was not associated with VPTB and VLBW. Additionally, the aORs of PTB, LBW, and
13 SGA also tended to increase with multimorbidity rather than with one chronic condition.
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24 Supplementary Table 2 demonstrates the aOR for adverse perinatal outcomes,
25 focusing on each disease, including underweight, obesity, psychiatric disorders, and
26 domestic violence. Regarding PTB and LBW, significant differences were found between
27 maternal multimorbidity and no chronic conditions, regardless of the presence or absence
28 of specific chronic conditions (Supplementary Table 2A-D). For SGA, maternal
29 multimorbidity with underweight, without obesity, without psychiatric disorder, and with
30 and without domestic violence showed significant differences compared to no chronic
31 conditions (Supplementary Table 2A-D). However, multimorbidity without underweight
32 and that with obesity and psychiatric disorders did not show significant differences
33 (Supplementary Tables 2A, B, and C).
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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

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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,

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

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21 This study comprised 23 chronic conditions, which included not only physical
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23 morbidity, but also psychological and social morbidity. A systematic review of
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25 multimorbidity by Fortin et al.³ suggested using a list of at least the 12 most prevalent
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27 chronic conditions to conduct studies on multimorbidity. In a previous study by Admon
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29 et al.¹³ on maternal multimorbidity, only seven physical and one social morbidity were
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31 defined as chronic conditions, and the prevalence of one chronic condition and
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33 multimorbidity were 8.4% and 0.83%, respectively. These values are much lower than
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35 those of our results. Although it has been controversial which chronic conditions should
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37 be included in maternal multimorbidity, our study may have reduced the chance of
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39 missing pregnant women at a potential risk of adverse perinatal outcomes.
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51 The present study confirmed that an increase in the number of chronic maternal
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53 conditions increases the risk of PTB, LBW, and SGA. In a study on chronic diseases in
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55 pregnant women in Germany, pregnant women with at least one chronic condition had an
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6 increased risk of PTB.¹² A study on maternal multimorbidity in the United States reported
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9 that the incidence of PTB less than 37 weeks of gestation, cesarean delivery, severe
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12 maternal morbidity, and mortality in pregnant women with multimorbidity was higher
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15 than those without chronic conditions.¹³ These results were consistent with the present
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18 study, although the definition of maternal chronic conditions was different from our study.
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22 Chronic physical conditions such as hypertension, kidney disease, systemic
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24 lupus erythematosus, and abnormal pre-pregnancy BMI are associated with adverse
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26 perinatal outcomes.^{18-21, 37, 38} Our findings also indicated that multimorbidity might alter
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28 the risk of PTB, LBW, and SGA depending on whether multimorbidity included or did
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30 not include abnormal BMI. Additionally, maternal infections, such as HIV, malaria,
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32 syphilis, and tuberculosis, have been reported to be associated with adverse perinatal
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34 outcomes.³⁹⁻⁴² However, the influence of these infections may be small in the present
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37 study because the prevalence of these maternal infections was very low in Japan.
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46 Although the prevalence of psychiatric disorders was 0.7% in the present study,
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48 which was very low compared to a previous systematic review of adult women,⁴³ maternal
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50 psychological morbidity was also associated with adverse perinatal outcomes.^{23, 24, 44} The
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53 present study also showed that the risk of PTB and SGA might vary depending on the
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56 presence or absence of psychiatric disorders. In previous studies on depression during
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6 pregnancy, depression was found to be associated with PTB, LBW, and SGA.^{23, 24} In
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9 addition, common antenatal mental disorders also increased the risk of PTB and LBW.⁴⁴
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12 In the present study, domestic violence from intimate partners was the third most
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14 frequent chronic condition at 4.6%. Multimorbidity with and without domestic violence
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16 was significantly associated with PTB, LBW, and SGA, although the point estimate of
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18 the aOR for multimorbidity with domestic violence was slightly smaller than the aOR for
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20 those without domestic violence in this study. Social morbidity, including domestic
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22 violence, has been highlighted as a risk factor associated with adverse perinatal
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24 outcomes.^{15, 26, 27} A cross-sectional study in Iran found a significant association between
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26 intimate partner violence during pregnancy and PTB.²⁶ A prospective cohort study in
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28 Tanzania reported that physical violence during pregnancy significantly increased the risk
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30 of PTB and LBW.²⁷ However, a population-based study in Canada reported no
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32 association between domestic violence before and during pregnancy and adverse perinatal
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34 outcomes, including PTB and SGA.⁴⁵ This previous study had the limitation that the
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36 prevalence of domestic violence was 10.9% and only 3.3% occurred during pregnancy.⁴⁵
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51 The mechanism by which maternal multimorbidity affected perinatal outcomes
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53 was not clear in the present study. Although previous studies reported that each chronic
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55 condition, including physical, psychological, and social conditions, increased the risk of
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6 adverse perinatal outcomes, evidence on maternal multimorbidity is lacking.² Based on
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9 the results of our study, we hypothesized that each chronic condition that composes
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12 multimorbidity, such as underweight, obesity, psychiatric disorder, and domestic violence,
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15 provides a risk for PTB, and the combination of these chronic conditions might further
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18 increase the risk of adverse perinatal outcomes.
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20 21 22 23 24 **CONCLUSIONS**

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27 The present study reported an association between maternal multimorbidity and adverse
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30 perinatal outcomes including PTB, LBW, and SGA. The risk of adverse perinatal
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33 outcomes increases with an increase in the number of chronic maternal conditions. Since
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36 the number of reproductive-aged women with multimorbidity has been increasing as the
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39 maternal population ages, preconception care for maternal multimorbidity is becoming
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42 increasingly important. Our findings provide essential information for preconception
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45 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

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6 dissemination plans of this research.
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12 **Patient consent for publication**
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15 Not applicable.
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21 **Ethics approval**
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24 The study protocol was approved by the Ministry of the Environment'S Institutional
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27 Review Board on Epidemiological Studies and by the Ethics Committees of all
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30 participating institutions (No. 100910001). The JECS was performed in accordance with
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33 the Declaration of Helsinki. All the participants provided written informed consent.
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40 **Provenance and peer review**
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42 Not commissioned; externally peer reviewed.
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49 **Data availability statement**
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51 Data are unsuitable for public deposition because of ethical restrictions and Japan's legal
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54 framework. The Act on the Protection of Personal Information (Act No. 57 of May 30,
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57 2003, amended on September 9, 2015) prohibits making data containing personal
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6 information publicly available. The Ethical Guidelines for Medical and Health Research
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9 Involving Human Subjects enforced by the Japan Ministry of Education, Culture, Sports,
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12 Science and Technology and the Ministry of Health, Labour and Welfare also restrict the
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15 open sharing of epidemiological data. All inquiries about access to data were sent to jecs-
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18 en@nies.go.jp. The person responsible for handling inquiries sent to this e-mail address
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21 is Dr. Shoji F. Nakayama, JECS Program Office, National Institute for Environmental
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6 **Figure legends**
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9 Figure 1. Flow diagram of the study participants.
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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)

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5	1	31,810	20,848	9,825 (36.7)	1,137 (35.1)
6					
7		(36.6)	(36.7)		
8					
9					
10	≥ 2	17,040	10,914	5,368 (20.0)	758 (23.4)
11					
12		(19.6)	(19.2)		
13					
14	Missing	2,062	1,391	615 (2.3)	56 (1.7)
15					
16		(2.4)	(2.5)		
17					
18					
19	Smoking during				
20	pregnancy				
21					
22					
23	No	49,414	33,392	14,613	1,409 (43.5)
24					
25		(56.9)	(58.7)	(54.5)	
26					
27	Quit before pregnancy	20,152	13,268	6,124 (22.9)	760 (23.5)
28					
29		(23.2)	(23.3)		
30					
31	Quit after pregnancy	12,042	7,230	4,139 (15.4)	673 (20.8)
32					
33		(13.9)	(12.7)		
34					
35	Yes	3,859	2,086	1,460 (5.5)	313 (9.7)
36					
37		(4.4)	(3.7)		
38					
39	Missing	1,418	867 (1.5)	469 (1.8)	82 (2.5)
40					
41		(1.6)			
42					
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46	Drinking during				
47	pregnancy				
48					
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50	No	28,652	18,367	9,223 (34.4)	1,062 (32.8)
51					
52		(33.0)	(32.3)		
53					
54	Quit before pregnancy	14,108	9,143	4,388 (16.4)	577 (17.8)
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	(16.2)	(16.1)		
Quit after pregnancy	40,354	26,921	12,021	1,412 (43.6)
	(46.5)	(47.4)	(44.9)	
Yes	2,370	1,546	704 (2.6)	120 (3.7)
	(2.7)	(2.7)		
Missing	1,401	866 (1.5)	469 (1.8)	66 (2.0)
	(1.6)			
Maternal educational background				
Junior high school	4,089	2,127	1,625 (6.1)	337 (10.4)
	(4.7)	(3.7)		
High school	27,106	16,881	8,968 (33.5)	1,257 (38.8)
	(31.2)	(29.7)		
Technical junior college or technical/vocational college	36,123	24,192	10,772	1,159 (35.8)
	(41.6)	(42.6)	(40.2)	
University or above	18,415	12,922	5,073 (18.9)	420 (13.0)
	(21.2)	(22.7)		
Missing	1,152	721 (1.3)	367 (1.4)	64 (2.0)
	(1.3)			

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

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

Outcomes	The number of chronic conditions			
	Total	0 (n =	1 (n =	≥2 (n =
		56,843)	26,805)	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)

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5	Rheumatic or collagen disease	94 (0.1)
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7	Substance abuse	1 (0.0)
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10	Thyroid disease	638 (0.7)
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13 BMI, body mass index.

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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.

All fetal records (n = 104,062)

Exclusion (n = 3,759)
- Miscarriage (n = 1,254)
- Stillbirth (n = 382)
- Unknown birth outcome (n = 2,123)

n = 100,303

Exclusion (n = 5,550)
- Second or later participation

n = 94,753

Exclusion (n = 7,868)
- Multiple pregnancies (n = 1,809)
- Pregnancies with chromosomal abnormality (n = 207)
- Missing value of gestational age at delivery (n = 286)
- Missing value of birth weight (n = 69)
- Missing value of drug use information (n = 2,166)
- Missing value of domestic violence from partner (n = 880)
- Missing value of maternal infection (n = 2,418)
- Missing value of maternal body mass index (n = 33)

Participants in the present study (n = 86,885)

Analyzed participants (n = 86,885)
- Preterm birth <37 weeks' gestation
- Preterm birth <34 weeks' gestation
- Low birth weight
- Very low birth weight
- Extremely low birth weight

Exclusion (n = 211)
- Gestational age <22 and ≥42 weeks (n = 214)

Analyzed participants (n = 86,674)
- Small for gestational age infant

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

1	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	17-18
2			(b) Report category boundaries when continuous variables were categorized	
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
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9	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	18
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11	Discussion			
12				
13	Key results	18	Summarise key results with reference to study objectives	19
14	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
15				
16	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
17				
18				
19	Generalisability	21	Discuss the generalisability (external validity) of the study results	24
20				
21	Other information			
22	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
23				
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*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>.

BMJ Open

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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7 **Title: Association between maternal multimorbidity and preterm birth, low birth**
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9 **weight, and small for gestational age: a prospective birth cohort study from the**
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11 **Japan Environment Children's Study**
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1 ABSTRACT

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

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

14 **Results:** Of the 104,062 fetal records, 86,885 singleton pregnant women were analyzed.
15 The median maternal age and body mass index were 31 years and 20.5 kg/m², respectively.
16 The prevalence of pregnant women with one or more chronic conditions was 40.2%. The
17 prevalence of maternal multimorbidity was 6.3%, and that of PTB, LBW, and SGA were
18 4.6%, 8.1%, and 7.5%, respectively. Pre-pregnancy underweight women were the most

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7 19 common, observed in 15.6% of multimorbidity cases, followed by domestic violence
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10 20 from intimate partner in 13.0%. Maternal multimorbidity was significantly associated
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13 21 with PTB (aOR, 1.50; 95% CI, 1.33-1.69), LBW (aOR, 1.49; 95% CI, 1.35-1.63), and
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16 22 SGA (aOR, 1.33; 95% CI, 1.20-1.46).

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18 23 **Conclusion:** Maternal multimorbidity was associated with adverse perinatal outcomes,
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21 24 including PTB, LBW, and SGA. The risk of adverse perinatal outcomes tends to increase
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24 25 with a rise in the number of chronic maternal conditions. As multimorbidity becomes
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27 26 more prevalent among pregnant women, making our findings important for preconception
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30 27 counseling.
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36 29 **Keywords:** chronic diseases, Japan, low birth weight, multimorbidity, preterm birth,
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39 30 small for gestational age.
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42 31
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45 32 **Word counts:** 3,934
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7 **33 Strengths and limitations of this study**

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

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

59 Although the prevalence of multimorbidity is highest in those aged 65 years or
60 older, younger persons, including reproductive-age women, also represent a large
61 proportion of those with multimorbidity, ranging from 8.7 to 18.8%.^{3,4,10,11} Regarding
62 pregnant women, the prevalence of multimorbidity has varied from 0.83 to 24.2%.¹²⁻¹⁴
63 Although the prevalence of maternal multimorbidity in Japan has not been thoroughly
64 studied, the prevalence of individual chronic conditions was 0.9% for chronic
65 hypertension, 3.4% for diabetes mellitus, 10.6% for obesity, and 18.2% for

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6 66 underweight.^{15, 16} The number of pregnant women with multimorbidity is expected to
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9 67 increase as with maternal population ages.
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12 68 The association between certain specific single maternal chronic diseases and
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15 69 related perinatal outcomes has been well studied; however, there are only a few studies
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18 70 on maternal multimorbidity and perinatal outcomes.^{12, 13, 17} The 2020 systematic review
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21 71 in low- and middle-income countries by McCauley et al. classified maternal
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24 72 multimorbidity into three categories: physical morbidity (such as medical, infectious, and
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27 73 obstetrical conditions), psychological morbidity (such as depression and suicidal
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30 74 ideation), and social morbidity (such as domestic violence and substance abuse).¹⁷ The
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33 75 World Health Organization Maternal Morbidity Working Group also considered physical,
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36 76 psychological, and social morbidity to measure maternal morbidity.¹⁸ Domestic violence
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39 77 against pregnant women has also been a social issue in Japan,¹⁹ not only in low- and
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42 78 middle-income countries.
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45 79 It has been widely known that maternal physical morbidity such as hypertension,
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48 80 kidney disease, and systemic lupus erythematosus increase the risk of preterm births
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51 81 (PTB) and low birth weight infants (LBW).²⁰⁻²³ Moreover, maternal psychological and
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54 82 social morbidity has been also associated with PTB and LBW.²⁴⁻²⁹ In their review,
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57 83 McCauley et al. were trying to assess the impact of each type of morbidity on women's
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7 84 health and well-being during pregnancy and after childbirth, however, a meta-analysis of
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9 85 the associations between multimorbidity and obstetrical complications could not be
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12 86 performed because of the heterogeneity of each study.¹⁷ The evidence of maternal
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15 87 multimorbidity has been insufficient because only a few studies reported the association
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18 88 between maternal multimorbidity and adverse perinatal outcomes.^{12, 13} Additionally, a
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21 89 previous study in the United States by Admon et al. underestimated the prevalence of
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24 90 maternal multimorbidity because only eight chronic conditions were included.¹³ There is
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27 91 a need to conduct a study covering a broad range of maternal chronic conditions to avoid
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30 92 overlooking pregnant women at risk of potentially adverse perinatal outcomes. Therefore,
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33 93 we hypothesized that the risk of adverse perinatal outcomes, such as PTB, LBW, and
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36 94 small for gestational age (SGA), would increase with the number of chronic maternal
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39 95 conditions present in a woman, including physical, psychological, and social conditions.

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42 96 In Japan, the association between maternal multimorbidity and adverse perinatal
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45 97 outcomes has not yet been investigated. The present study aimed to determine the
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48 98 association between maternal multimorbidity and adverse perinatal outcomes, such as
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51 99 PTB, LBW, and SGA, using a Japanese nationwide prospective cohort study.
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6 100 **METHODS**

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9 101 *Study design and participants*

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12 102 This prospective cohort study used the dataset jecs-ta-20190930 from the Japan
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15 103 Environment and Children's Study (JECS). The JECS is an ongoing nationwide birth
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18 104 cohort study in Japan, the details of which have already been reported.^{30, 31} Its main aim
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21 105 of the JECS was to investigate the association between environmental factors and
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24 106 children's health and development. The JECS recruited pregnant women from 15 regional
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27 107 centers selected to cover the Japanese geographical areas: Hokkaido, Miyagi, Fukushima,
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30 108 Chiba, Kanagawa, Koshin, Toyama, Aichi, Kyoto, Osaka, Hyogo, Tottori, Kochi,
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33 109 Fukuoka, and South Kyusyu/Okinawa, between January 2011 and March 2014. The
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36 110 recruitment strategy in the JECS is shown in Supplementary Appendix 1.³⁰

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39 111 During the study period, 104,062 fetal records were included in the baseline
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42 112 survey of the JECS. Miscarriages (n = 1,254), stillbirths (n = 382), and unknown birth
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45 113 outcomes (n = 2,123) were excluded, leaving 100,303 live births in the present study.
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48 114 When a mother had more than one pregnancy, only the first pregnancy was included in
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51 115 this study. After excluding pregnancies in the same mothers, there were 94,753
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54 116 participants. Finally, patients with multiple pregnancies (n = 1,809), pregnancies with
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57 117 chromosomal abnormalities (n = 207), missing values of gestational age at delivery (n =

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6 118 286), missing values of neonatal birth weight (n = 69), missing values of medication
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9 119 information (n = 2,166), missing values of domestic violence from intimate partners (n =
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12 120 880), missing values of maternal infection (n = 2,418), and missing values of maternal
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15 121 pre-pregnancy body mass index (BMI) (n = 33) were excluded and the final number of
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18 122 study participants was 86,885 singleton pregnant women (Figure 1). In the SGA analyses,
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21 123 the number of participants decreased to 86,674 because 211 deliveries at a gestational age
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24 124 of > 41 weeks were excluded (Figure 1).

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126 *Ethics*

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

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132 *Patient and Public Involvement statement*

133 This study did not involve patients or public.

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135 *Maternal and neonatal baseline information*

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6 136 Baseline information on the mothers, including educational level, smoking status, and
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9 137 alcohol consumption, was collected from self-administered questionnaires applied to the
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12 138 enrolled pregnant women during the second or third trimesters. Maternal medical history
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15 139 was obtained using self-administered questionnaires and medical record transcripts
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18 140 during the first trimester of pregnancy. A history of domestic violence from an intimate
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21 141 partner was obtained from self-administered questionnaires applied to the enrolled
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24 142 pregnant women during the first trimester. The following maternal information was
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27 143 obtained from the medical record transcripts: maternal infection, neonate's date of birth,
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30 144 parity, and gestational period. Although maternal pre-pregnancy height and weight were
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33 145 collected from medical record transcripts, in instances where the above information was
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36 146 missing, the values were obtained from mothers' self-reports. Maternal age at delivery
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39 147 was calculated from the birth dates of mothers and neonates. Parity was categorized as 0,
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42 148 1, 2, or higher. The categories of maternal smoking status were defined as follows: never;
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45 149 previously did, but quit before recognizing the current pregnancy; previously did, but quit
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48 150 after identifying the current pregnancy; and current smoker. The categories of maternal
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51 151 alcohol consumption were defined as follows: never consumed; previously consumed,
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54 152 but quit before identifying current pregnancy; previously consumed, but quit after
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57 153 identifying current pregnancy; and current drinker. The highest educational level of the
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6 154 mother was defined as follows: junior high school, high school, technical junior college,
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9 155 technical/vocational college or associate degree, bachelor's degree, or graduate degree
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12 156 (master/doctor). Annual household income was categorized as follows: <2,000,000;
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15 157 2,000,000–3,990,000; 4,000,000–5,990,000; 6,000,000–7,990,000; 8,000,000–
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18 158 9,990,000; and $\geq 10,000,000$ JPY. Maternal and neonatal medical information, such as
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21 159 maternal age at delivery, gestational age at delivery, neonatal birth weight, and neonatal
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24 160 sex, were collected from the medical record transcripts at birth.
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30 162 ***Exposure: Maternal Multimorbidity***

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33 163 In our study, multimorbidity was defined as the coexistence of two or more physical,
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36 164 psychological, or social conditions in an individual according to previous reports.^{13, 14, 17,}
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39 165 ¹⁸ Maternal chronic conditions included in multimorbidity were defined as the conditions
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42 166 with high prevalence among reproductive-age women or that had the potential to affect
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45 167 perinatal outcomes. The chronic conditions in this study were heterogeneous because the
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48 168 JECS lacked information regarding the disease severity. However, the definition of
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51 169 multimorbidity varies among studies.^{18, 32} To identify pregnant women with chronic
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54 170 conditions more rigorously, a maternal chronic condition was defined as a condition that
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57 171 was medically treated at the time of pregnancy. This information was collected from self-
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6 172 reports, medical record transcripts, and medication interviews. Maternal chronic
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9 173 conditions included allergic diseases such as asthma, anemia, diabetes mellitus,
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12 174 dyslipidemia, epilepsy, gastric or duodenal ulcer, heart disease, hepatitis, human
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15 175 immunodeficiency virus (HIV) infection, hypertension, inflammatory bowel disease,
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18 176 kidney disease, malignancy, migraine, neurologic disease, other sexually transmitted
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21 177 diseases (*Chlamydia trachomatis* and syphilis), psychiatric disorders, rheumatic or
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24 178 collagen diseases, and thyroid disease.

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27 179 Additionally, abnormal pre-pregnancy BMI, including underweight and obesity,
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30 180 physical or verbal domestic violence from intimate partners, and substance abuse, were
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33 181 included in the maternal chronic conditions.^{18, 33} Maternal pre-pregnancy BMI was
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36 182 calculated from the maternal pre-pregnancy weight divided by the square of maternal
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39 183 height collected from medical record transcripts or self-reports. Pregnant women were
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42 184 categorized according to their pre-pregnancy BMI as follows: underweight (BMI < 18.5
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45 185 kg/m²), normal weight (18.5 kg/m² ≤ BMI < 25.0 kg/m²), and obesity (BMI ≥ 25.0
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48 186 kg/m²).^{34, 35} Information on domestic violence from intimate partners was obtained from
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51 187 a questionnaire administered during the first trimester: “Have you been verbally insulted
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54 188 or yelled at by your partner during pregnancy?” and “Have you been physically abused,
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57 189 such as being slapped or beaten, resulting in injury because of a quarrel between you and
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6 190 your partner during pregnancy?”³⁶ Each response was selected from one of four
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9 191 predefined categories: never, rarely, sometimes, and often. If the response “rarely” or
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12 192 “sometimes” or “often” was chosen, it was considered as presence of domestic violence.
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15 193 Medication information was obtained from interviews (Supplementary Appendix 2).³⁷
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18 194 Medication was considered relevant from pregnancy diagnosis to 12 weeks of gestation
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21 195 to investigate the impact of maternal pre-pregnancy chronic conditions on perinatal
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24 196 outcomes. The types of medication in early pregnancy included antiallergic drugs, lipid-
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27 197 lowering drugs, antimigraine drugs, anti-parkinsonian drugs, anti-rheumatic drugs,
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30 198 antithyroid drugs, antiviral drugs, anti-cancer drugs, cardiovascular drugs, corticosteroids,
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33 199 gastrointestinal drugs, illegal drugs including marijuana, psychostimulant, ecstasy,
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36 200 thinner, and toluene, insulin preparations, iron preparations, psychoactive drugs,
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39 201 respiratory drugs, and thyroid hormone preparations.³⁷
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44 45 203 **Outcomes**

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48 204 The primary outcome of this study was the incidence of adverse perinatal outcomes,
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51 205 including PTB, LBW, and SGA. The secondary outcomes were the incidences of very
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54 206 preterm birth (VPTB), very low birth weight (VLBW), and extremely low birth weight
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57 207 (ELBW). PTB was defined as a gestational age of less than 37 weeks at delivery. VPTB
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6 208 was defined as a gestational age of less than 34 weeks at delivery. LBW, VLBW, and
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9 209 ELBW were defined as neonatal birth weights of less than 2,500 g, 1,500 g, and 1,000 g,
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12 210 respectively. SGA was defined as birth weight below the 10th percentile, accounting for
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15 211 parity, gestational age, and neonatal sex according to the Japan Pediatric Society
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18 212 guidelines,³⁸ and percentiles were calculated using Excel-based clinical tools for growth
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21 213 evaluation of children distributed by the Japanese Society for Pediatric Endocrinology.³⁹
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27 215 ***Statistical analysis***

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30 216 In the main analyses, adjusted odds ratios (aORs) and 95% confidence intervals (CIs) for
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33 217 adverse perinatal outcomes were estimated using a multivariable logistic regression
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36 218 model adjusted for maternal age at delivery (<20, 20–24, 25–29, 30–34, 35–39, and ≥40
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39 219 years), parity, maternal smoking status, maternal alcohol consumption, maternal
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42 220 educational level, household income, and neonatal sex. In the SGA analyses, parity and
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45 221 neonatal sex were removed from the covariates. These covariates were selected based on
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48 222 previous studies on multimorbidity.^{13, 18, 33} Statistical analyses were used to compare
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51 223 pregnant women with multimorbidity or with one chronic condition, to those without
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54 224 chronic conditions as a reference group.

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57 225 We used the k-nearest neighbor (kNN) imputation method in the R package
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6 226 “VIM” (version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria),⁴⁰
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9 227 introducing all outcomes and adjusted variables because the dataset had some missing
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12 228 values. The covariates such as maternal age, parity, smoking status during pregnancy,
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15 229 drinking status during pregnancy, maternal education, and household income, and
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18 230 neonatal sex, were among the imputed missing data. kNN is a widely accepted single
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21 231 imputation method whose validity has been established.⁴¹ We performed an additional
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24 232 analysis to test the robustness of our findings using a complete dataset, which excluded
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27 233 all missing values. We also analytically evaluated the dose-response relationship between
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30 234 the number of chronic conditions and perinatal adverse outcomes using a detailed
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33 235 classification of the number of chronic conditions (0, 1, 2, 3, and ≥ 4) and a test for trend.
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36 236 Sensitivity analyses focusing on underweight, obesity, psychiatric disorders, and
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39 237 domestic violence were performed. Each of these chronic conditions was categorized
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42 238 separately as included or not included in the multimorbidity category. The results of these
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45 239 analyses are shown in Supplementary Tables 1, 2 and 3. Statistical significance was
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48 240 defined as a two-tailed *P*-value < 0.05. All analyses, except kNN imputation, were
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51 241 performed using STATA version 16.1, for Windows (Stata Corporation, College Station,
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54 242 TX, USA). kNN imputation was conducted using R (version 4.1.2; R Foundation for
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57 243 Statistical Computing, Vienna, Austria).

244 RESULTS

245 Of the 104,062 fetal records included in this study, 17,177 (16.5%) were excluded,
246 leaving a final number of 86,885 singleton pregnant women (Figure 1). The main and all
247 maternal characteristics are shown in Table 1 and Supplementary Table 1, respectively.
248 The median maternal age was 31 years (range, 14-48), and the median pre-pregnancy
249 BMI was 20.5 kg/m² (range, 13.2-52.8). In the present study, 40.2% of pregnant women
250 had one or more chronic conditions (Table 1). The prevalence of maternal multimorbidity
251 was 6.3% (5,462/86,885). Regarding perinatal outcomes, the prevalences of PTB and
252 VPTB were 4.6% and 1.0%, respectively. The prevalences of LBW, VLBW, ELBW, and
253 SGA were 8.1 %, 0.6%, 0.2%, and 7.5 %, respectively (Table 2). The details of the
254 maternal chronic conditions are shown in Table 3. Maternal underweight (15.6%) was the
255 most frequently observed in chronic conditions, followed by domestic violence (13.0%).
256 The prevalence of maternal obesity was 10.9%. The other most frequent chronic
257 conditions were allergic diseases (3.1%), other sexually transmitted diseases (1.4%),
258 anemia (0.7%), psychiatric disorders (0.7%), and thyroid disease (0.7%).

259 Maternal multimorbidity was significantly associated with PTB (aOR, 1.50; 95%
260 CI, 1.33-1.69), VPTB (aOR, 1.34; 95% CI, 1.03-1.74), LBW (aOR, 1.49; 95% CI, 1.35-
261 1.63), VLBW (aOR, 1.62; 95% CI, 1.16-2.25), ELBW (aOR, 1.81; 95% CI, 1.12-2.90),

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6 262 and SGA (aOR, 1.33; 95% CI, 1.20-1.46) (Table 4). Adjusted odds ratios of PTB, LBW,
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9 263 and SGA tended to increase with multimorbidity rather than with one chronic condition.
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12 264 The association between maternal multimorbidity and adverse perinatal
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15 265 outcomes, using the complete dataset, is shown in Supplementary Table 2. Maternal
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18 266 multimorbidity was also significantly associated with PTB, LBW, and SGA, however, it
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21 267 was not associated with VPTB, VLBW and ELBW. Additionally, the aORs of PTB, LBW,
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24 268 and SGA also tended to increase with multimorbidity rather than with one chronic
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27 269 condition.
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30 270 Supplementary Table 3 shows the additional analysis for PTB, LBW, and SGA
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33 271 using exposure as the number of chronic conditions (0, 1, 2, 3, and ≥ 4). All of the trend
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36 272 *P* values were statistically significant.
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39 273 Supplementary Table 4 demonstrates the aOR for adverse perinatal outcomes,
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42 274 focusing on each disease, including underweight, obesity, psychiatric disorders, and
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45 275 domestic violence. Regarding PTB and LBW, significant differences were found between
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48 276 maternal multimorbidity and no chronic conditions, regardless of the presence or absence
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51 277 of specific chronic conditions (Supplementary Table 4A-D). For SGA, maternal
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54 278 multimorbidity with underweight, without obesity, without psychiatric disorder, and with
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57 279 and without domestic violence showed significant differences compared to no chronic
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280 conditions (Supplementary Table 4A-D).

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6 281 **DISCUSSION**
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9 282 In this study, one-third of pregnant women had one or more chronic conditions, and the
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12 283 prevalence of maternal multimorbidity was lower than that in previous studies.^{3,4} Among
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15 284 maternal chronic conditions, pre-pregnancy underweight was the most common, followed
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18 285 by domestic violence and pre-pregnancy obesity. This study showed that maternal
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21 286 multimorbidity was significantly associated with PTB, LBW, and SGA. The number of
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24 287 chronic conditions in the mother tends to increase the risk of adverse perinatal outcomes.
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27 288 To our knowledge, the present study is the first to investigate the association
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30 289 between maternal multimorbidity, including physical, psychological, and social
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33 290 morbidities, with perinatal outcomes. In the present study, the use of data from the JECS,
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36 291 including 100,000 Japanese mothers and neonates, made it possible to study
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39 292 multimorbidities. The incidence of adverse perinatal outcomes was sufficient to
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42 293 investigate the influence of maternal multimorbidity on PTB, LBW, and SGA.
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45 294 However, this study has several limitations. First, the prevalence of maternal
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48 295 multimorbidity in this study was 6.3%, which was lower than the prevalence noted in
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51 296 reproductive-aged women in previous studies.^{3, 4, 14} The strict definition of a chronic
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54 297 condition in our study may be responsible for the lower prevalence of maternal
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57 298 multimorbidity than in previous studies. However, there is no consensus on the definition
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6 299 of maternal multimorbidity or classification system for reporting.^{2, 32} Second, the details
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9 300 of the differences in risk by the combination of chronic conditions were not identified.
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12 301 The risk of adverse perinatal outcomes may vary depending on the combination of the
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15 302 chronic conditions. Although sensitivity analyses focusing on underweight, obesity,
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18 303 psychiatric disorders, and domestic violence demonstrated the association of adverse
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21 304 perinatal outcomes with the presence or absence of each condition, no further detailed
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24 305 studies were conducted because the main aim of this study was not to examine the impact
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27 306 of each chronic condition. Third, some self-reported biases may exist. Self-reported body
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30 307 weight may be underestimated for underweight and overestimated for obesity.^{42, 43} The
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33 308 prevalence of self-reported domestic violence may be underestimated due to social
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36 309 desirability bias.⁴⁴ Forth, the numbers of VPTB, VLBW, and ELBW cases were small.
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39 310 This study was insufficient to investigate these severe adverse outcomes.

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42 311 Conducting studies on maternal multimorbidity has been challenging because
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45 312 there is no agreed definition or uniform measurement tool for multimorbidity.³² A
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48 313 systematic review of multimorbidity in 2012 by Fortin et al.³ reported that the prevalence
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51 314 of multimorbidity seemed to be influenced by the operational definition of chronic
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54 315 conditions. Moreover, most studies on multimorbidity conducted in the general
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57 316 population predominantly used questionnaires. As this method was based on self-report,
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6 317 it might present the disadvantage of assigning equal weight to both major and minor
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9 318 chronic conditions.³ Although the present study also used self-report questionnaires,
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12 319 multimorbidity was defined as chronic conditions treated with medication to reduce the
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15 320 variability in the severity of chronic conditions in multimorbidity. However, our method
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18 321 may have decreased the prevalence of multimorbidities.
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21 322 This study comprised 23 chronic conditions, which included not only physical
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24 323 morbidity, but also psychological and social morbidity. A systematic review of
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27 324 multimorbidity by Fortin et al.³ suggested using a list of at least the 12 most prevalent
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30 325 chronic conditions to conduct studies on multimorbidity. In a previous study by Admon
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33 326 et al.¹³ on maternal multimorbidity, only seven physical and one social morbidity were
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36 327 defined as chronic conditions, and the prevalence of one chronic condition and
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39 328 multimorbidity were 8.4% and 0.83%, respectively. These values are much lower than
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42 329 those of our results. Although it has been controversial which chronic conditions should
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45 330 be included in maternal multimorbidity, our study may have reduced the chance of
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48 331 missing pregnant women at a potential risk of adverse perinatal outcomes.
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51 332 The present study confirmed that an increase in the number of chronic maternal
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54 333 conditions increases the risk of PTB, LBW, and SGA. In a study on chronic diseases in
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57 334 pregnant women in Germany, pregnant women with at least one chronic condition had an
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6 335 increased risk of PTB.¹² A study on maternal multimorbidity in the United States reported
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9 336 that the incidence of PTB less than 37 weeks of gestation, cesarean delivery, severe
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12 337 maternal morbidity, and mortality in pregnant women with multimorbidity was higher
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15 338 than those without chronic conditions.¹³ These results were consistent with the present
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18 339 study, although the definition of maternal chronic conditions was different from our study.
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21 340 In maternal multimorbidity, medication during pregnancy may affect perinatal
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24 341 outcomes. The present study defined a physical or psychological condition as one that
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27 342 required medical attention during pregnancy. The study on the exposure to medication
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30 343 for hypertension, diabetes, and autoimmune disease during pregnancy reported that the
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33 344 ORs of PTB, LBW, and SGA were higher in the antihypertensives and corticosteroids
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36 345 exposed group compared with those in the unexposed group.⁴⁵ However, it was also
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39 346 reported that chronic conditions, with or without medication exposure, may have affected
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42 347 perinatal outcomes.
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45 348 Chronic physical conditions such as hypertension, kidney disease, systemic
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48 349 lupus erythematosus, and abnormal pre-pregnancy BMI are associated with adverse
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51 350 perinatal outcomes.^{20-23, 46, 47} Our findings also indicated that multimorbidity might alter
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54 351 the risk of PTB, LBW, and SGA depending on whether multimorbidity included or did
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57 352 not include abnormal BMI. Additionally, maternal infections, such as HIV, malaria,
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7 353 syphilis, and tuberculosis, have been reported to be associated with adverse perinatal
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9 354 outcomes.⁴⁸⁻⁵¹ However, the influence of these infections may be small in the present
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12 355 study because the prevalence of these maternal infections was very low in Japan.

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15 356 Although the prevalence of psychiatric disorders was 0.7% in the present study,
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18 357 which was very low compared to a previous systematic review of adult women,⁵² maternal
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21 358 psychological morbidity was also associated with adverse perinatal outcomes.^{25, 26, 52} The
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24 359 present study also showed that the risk of PTB and SGA might vary depending on the
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27 360 presence or absence of psychiatric disorders. In previous studies on depression during
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30 361 pregnancy, depression was found to be associated with PTB, LBW, and SGA.^{25, 26} In
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33 362 addition, common antenatal mental disorders also increased the risk of PTB and LBW.⁵³

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36 363 In the present study, domestic violence from intimate partners was the second
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39 364 most frequent chronic condition at 13.0%. Multimorbidity with and without domestic
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42 365 violence was significantly associated with PTB, LBW, and SGA, although the point
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45 366 estimate of the aOR for multimorbidity with domestic violence was slightly smaller than
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48 367 the aOR for those without domestic violence in this study. Social morbidity, including
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51 368 domestic violence, has been highlighted as a risk factor associated with adverse perinatal
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54 369 outcomes.^{17, 28, 29} A cross-sectional study in Iran found a significant association between
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57 370 intimate partner violence during pregnancy and PTB.²⁸ A prospective cohort study in

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6 371 Tanzania reported that physical violence during pregnancy significantly increased the risk
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9 372 of PTB and LBW.²⁹ However, a population-based study in Canada reported no
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12 373 association between domestic violence before and during pregnancy and adverse perinatal
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15 374 outcomes, including PTB and SGA.⁵⁴ This previous study had the limitation that the
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18 375 prevalence of domestic violence was 10.9% and only 3.3% occurred during pregnancy.⁵⁴
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21 376 The mechanism by which maternal multimorbidity affected perinatal outcomes
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24 377 was not clear in the present study. However, maternal multimorbidity appears to affect
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27 378 perinatal outcomes as both an intermediate and direct factor. For example, abnormal
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30 379 maternal BMI, such as underweight and obesity, is known to be an independent risk factor
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33 380 for PTB.⁵⁵ Maternal obesity is also a risk factor for preeclampsia.⁵⁶ Furthermore,
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36 381 preeclampsia promotes the development of PTB. After all, both maternal obesity and
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39 382 preeclampsia are regarded as risk factors for PTB. PTB is considered a syndrome initiated
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42 383 by multiple mechanism, including infection or inflammation, uteroplacental ischemia or
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45 384 hemorrhage, uterine overdistension, stress, and other immunologically mediated
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48 385 processes.⁵⁷ In addition, the associations between other chronic diseases such as
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51 386 hypertension, kidney disease, and autoimmune disease and PTB are similar to the
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54 387 association between obesity and PTB.²⁰⁻²³ Therefore, we hypothesized that each chronic
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57 388 condition that composes multimorbidity, such as underweight, obesity, psychiatric
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6 389 disorder, and domestic violence, played an intermediate or direct role in perinatal
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9 390 outcomes, and that the combination of these chronic conditions might further increase the
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12 391 risk of adverse perinatal outcomes.²
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18 393 **CONCLUSIONS**

21 394 The present study reported an association between maternal multimorbidity and adverse
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24 395 perinatal outcomes including PTB, LBW, and SGA. The risk of adverse perinatal
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27 396 outcomes tends to increase as the number of chronic maternal conditions increases. Since
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30 397 the number of reproductive-aged women with multimorbidity has been increasing as the
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33 398 maternal population ages, preconception care for maternal multimorbidity is becoming
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36 399 increasingly important. Our findings provide essential information for preconception
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39 400 counseling in women with multimorbidities.
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419 **Contributors**

420 KN and YaS designed the study. YaS, EY, KN, ST, YI, SK, CM, AA, RK, and the JECS

421 Group collected data. KN and YaS conducted the data analysis. KN, YaS, EY, YuS, YK,

422 KN, ST, YI, SK, CM, AA, and RK contributed to the data interpretation. YaS, EY, YuS,

423 YK, KN, ST, YI, SK, CM, AA, RK, and the JECS Group conducted the critical reviews.

424 KN drafted the manuscript. YaS made critical revisions. All authors reviewed and

425 commented on the manuscript. All authors approved the final manuscript.

426

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431

432 **Competing interests**

433 The authors declare that they have no competing interests.

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435 **Patient consent for publication**

436 Not applicable.

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9 438 **Ethics approval**

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12 439 The study protocol was approved by the Ministry of the Environment's Institutional
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15 440 Review Board on Epidemiological Studies and by the Ethics Committees of all
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18 441 participating institutions (No. 100910001). The JECS was performed in accordance with
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21 442 the Declaration of Helsinki. All the participants provided written informed consent.
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27 444 **Provenance and peer review**

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30 445 Not commissioned; externally peer reviewed.
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36 447 **Data availability statement**

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39 448 Data are unsuitable for public deposition because of ethical restrictions and Japan's legal
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42 449 framework. The Act on the Protection of Personal Information (Act No. 57 of May 30,
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45 450 2003, amended on September 9, 2015) prohibits making data containing personal
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48 451 information publicly available. The Ethical Guidelines for Medical and Health Research
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51 452 Involving Human Subjects enforced by the Japan Ministry of Education, Culture, Sports,
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54 453 Science and Technology and the Ministry of Health, Labour and Welfare also restrict the
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57 454 open sharing of epidemiological data. All inquiries about access to data were sent to jecs-
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9 456 is Dr. Shoji F. Nakayama, JECS Program Office, National Institute for Environmental
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12 457 Studies.
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6 652 **Figure legends**
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9 653 Figure 1. Flow diagram of the study participants.
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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	Total	The number of chronic conditions		
		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 (0.98)	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).

658 **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.

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660 **Table 4. Crude and adjusted odds ratios of maternal chronic conditions for**
 661 **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)

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

664 CI, confidence interval; ELBW, extremely low birth weight (< 1,000 g); LBW, low birth
 665 weight (< 2,500 g); OR, odds ratio compared to that of infants of mothers without chronic
 666 conditions, adjusted for maternal age at delivery, parity (except for SGA analysis),
 667 maternal smoking status, maternal alcohol consumption, maternal educational
 668 background, and neonatal sex (except for SGA analysis); PTB, preterm birth before 37
 669 weeks of gestation; SGA, small for gestational age; VLBW, very low birth weight (<
 670 1,500 g); VPTB, preterm birth before 34 weeks of gestation.

All fetal records (n = 104,062)

Exclusion (n = 3,759)
- Miscarriage (n = 1,254)
- Stillbirth (n = 382)
- Unknown birth outcome (n = 2,123)

n = 100,303

Exclusion (n = 5,550)
- Second or later participation

n = 94,753

Exclusion (n = 7,868)
- Multiple pregnancies (n = 1,809)
- Pregnancies with chromosomal abnormality (n = 207)
- Missing value of gestational age at delivery (n = 286)
- Missing value of birth weight (n = 69)
- Missing value of drug use information (n = 2,166)
- Missing value of domestic violence from partner (n = 880)
- Missing value of maternal infection (n = 2,418)
- Missing value of maternal body mass index (n = 33)

Participants in the present study (n = 86,885)

Analyzed participants (n = 86,885)
- Preterm birth <37 weeks' gestation
- Preterm birth <34 weeks' gestation
- Low birth weight
- Very low birth weight
- Extremely low birth weight

Exclusion (n = 211)
- Gestational age >41 weeks (n = 214)

Analyzed participants (n = 86,674)
- Small for gestational age infant

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.)

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3 **Supplementary Appendix 2. Medication list in the Japan Environment and Children's**
4 **Study (Nishigori H, et al. Drug use before and during pregnancy in Japan: the Japan**
5 **environment and children's study. Pharmacy (Basel). 2017;5.)**
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12 **Antibacterial, Antiviral, Antifungal, Carcinostatic drugs**
13

14
15 0 Antimicrobial

16
17 1 Antiviral

18
19 2 Antifungal

20
21 3 Carcinostatic
22
23

24 **Corticosteroids**
25

26 4 Corticosteroids: oral administration, inhalation, infusion
27

28 5 Corticosteroids: external use, enema
29
30

31 **Antipyretic, Analgesic drugs**
32

33 6 Antipyretic, Analgesic, Medicine for common cold: prescription
34

35 7 Antipyretic, Analgesic, Medicine for common cold: over the counter
36

37 8 Poultice which the analgesic is included in
38
39

40 **Antirheumatic drugs**
41

42 9 Immunosuppressant, Immunoregulation
43

44 10 Infliximab, Etanercept
45

46 11 Antirheumatic drug unidentified in detail
47
48

49 **Antiallergy drugs**
50

51 12 Antiallergic drug (oral administration, inhalation, nasal drip, tape, Antihistaminic)
52
53

54 **Respiratory drugs**
55

56 13 β stimulative (oral administration, inhalation)
57

58 14 Nontypeable inhalant
59
60

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3 15 Antitussive, Expectorant
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5 16 Theophylline
6

7
8 17 Other respiratory drug
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10 **Antidiabetic drugs, Antihyperlipidemic drugs**
11

12 21 Insulin preparation
13

14 22 Hypoglycemic tablet
15

16 23 Antihyperlipidemic
17

18 24 Antigout
19
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21 **Hormone-related drugs**
22

23 25 Thyroid hormone preparation/levothyroxine sodium
24

25 26 Antithyroid/Thiamazole
26

27 27 Other hormone drugs
28
29

30 **Blood-related drugs**
31

32 28 Iron preparation
33

34 29 Other blood-related
35
36

37 **Cardiovascular drugs**
38

39 31 Antihypertensive (including diuretic)
40

41 32 Pressor
42

43 33 Antiarrhythmic, Antianginal
44

45 34 Heart failure therapeutic
46

47 35 Other cardiovascular drugs
48
49
50

51 **Gastrointestinal drugs**
52

53 36 Antiulcer (Proton pump inhibitor, H2 blocker)
54

55 37 General gastrointestinal agents
56

57 38 Other gastrointestinal agents
58
59
60

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

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3 70 Hemorrhoids
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5 **Supplements, vitamins/minerals**
6

7
8 71 Vitamin A
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10 72 Vitamin B
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12 73 Vitamin C
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14 74 Vitamin D
15

16 75 Vitamin E
17

18 76 Folic acid
19

20 77 Minerals
21

22 78 Multi vitamins supplement
23

24 79 Total supplement
25

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27
28 **Illegal drugs**
29

30 80 Marijuana
31

32 81 Psychostimulant
33

34 82 Ecstasy
35

36 83 Thinner
37

38 84 Toluene
39

40 85 Other illegal drugs
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43
44 **90 Vaccines**
45

46 **98 Drugs not included in the list mentioned above**
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49 **99 Forgot the drug name**
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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					<i>P</i> value for trend
	0 (n = 51,964)	1 (n = 29,459)	2 (n = 5,039)	3 (n = 385)	≥4 (n = 38)	
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
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†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.

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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

1	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	17-18
2			(b) Report category boundaries when continuous variables were categorized	
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
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9	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	18
10				
11	Discussion			
12				
13	Key results	18	Summarise key results with reference to study objectives	20
14	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
15				
16	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
17				
18				
19	Generalisability	21	Discuss the generalisability (external validity) of the study results	26
20				
21	Other information			
22	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
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26 *Give information separately for exposed and unexposed groups.

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