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Association between maternal multimorbidity and preterm birth, low birth weight and small for gestational age: a prospective birth cohort study from the Japan Environment and Children's Study

Kentaro Nakanishi ,[1] Yasuaki Saijo ,[2] Eiji Yoshioka ,[2] Yukihiro Sato,[2] Yasuhito Kato,[1,2] Ken Nagaya,[3] Satoru Takahashi,[4] Yoshiya Ito,[5] Sumitaka Kobayashi,[6] Chihiro Miyashita,[6] Atsuko Ikeda-Araki,[6,7,8] Reiko Kishi,[6,9] the Japan Environment and Children's Study (JECS) Group

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For numbered affiliations see end of article.

Correspondence to
Professor Yasuaki Saijo; y-saijo@asahikawa-med.ac.jp

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 categorised 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 ORs (aORs) and 95% CIs.

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

Conclusion Maternal multimorbidity was associated with adverse perinatal outcomes, including PTB, LBW and SGA. The risk of adverse perinatal outcomes tends to increase with a rise in the number of chronic maternal conditions. Multimorbidity becomes more prevalent among pregnant women, making our findings important for preconception counselling.

STRENGTHS AND LIMITATIONS OF THIS STUDY

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

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 healthcare costs compared with 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 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 women of reproductive age, also represent a large proportion of those with multimorbidity, ranging from 8.7% to 18.8%.[3 4 10 11] Regarding pregnant women, the prevalence of multimorbidity has varied from 0.83% to 24.2%.[12–14] Although the prevalence of maternal multimorbidity in Japan has not been thoroughly studied, the prevalence of individual chronic conditions was 0.9% for chronic hypertension, 3.4% for diabetes mellitus, 10.6% for obesity and 18.2% for underweight.[15 16] The number of pregnant women with multimorbidity is expected to increase as with maternal population ages.

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

It has been widely known that maternal physical morbidity such as hypertension, kidney disease and systemic lupus erythematosus increase the risk of preterm births (PTBs) and low birthweight (LBW) infants.[20–23] Moreover, maternal psychological and social morbidity have been also associated with PTB and LBW.[24–29] In their review, McCauley *et al* were trying to assess the impact of each type of morbidity on women's health and well-being during pregnancy and after childbirth; however, a meta-analysis of the associations between multimorbidity and obstetrical complications could not be performed because of the heterogeneity of each study.[17] The evidence of maternal multimorbidity has been insufficient because only a few studies reported the association between maternal multimorbidity and adverse perinatal outcomes.[12 13] Additionally, a previous study in the USA by Admon *et al* underestimated the prevalence of maternal multimorbidity because only eight chronic conditions were included.[13] There is a need to conduct a study covering a broad range of maternal chronic conditions to avoid overlooking pregnant women at risk of potentially adverse perinatal outcomes. Therefore, we hypothesised that the risk of adverse perinatal outcomes, such as PTB, LBW and small for gestational age (SGA), would increase with the number of chronic maternal conditions present in a woman, including physical, psychological and social conditions.

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

METHODS

Study design and participants

This prospective cohort study used the dataset jecsta-20190930 from the Japan Environment and Children's Study (JECS). The JECS is an ongoing nationwide birth cohort study in Japan, the details of which have already been reported.[30 31] The 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 centres selected to cover Japan's geographical areas: Hokkaido, Miyagi, Fukushima, Chiba, Kanagawa, Koshin, Toyama, Aichi, Kyoto, Osaka, Hyogo, Tottori, Kochi, Fukuoka and South Kyusyu/Okinawa, between January 2011 and March 2014. The recruitment strategy in the JECS is shown in online supplemental appendix 1.[30]

During the study period, 104 062 fetal records were included in the baseline survey of the JECS. Miscarriages (n=1254), stillbirths (n=382) and unknown birth outcomes (n=2123) were excluded, leaving 100 303 live births in the present study. When a mother had more than one pregnancy, only the first pregnancy was included in this study. After excluding pregnancies in the same mothers, there were 94 753 participants. Finally, patients with multiple pregnancies (n=1809), 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=2166), missing values of domestic violence from intimate partners (n=880), missing values of maternal infection (n=2418) and missing values of maternal pre-pregnancy body mass index (BMI) (n=33) were excluded, and the final number of study participants was 86 885 singleton pregnant women (figure 1). In the SGA analyses, the number of participants decreased to 86 674 because 211 deliveries at a gestational age of >41 weeks were excluded (figure 1).

Patient and public involvement

This study did not involve patients or the public.

Maternal and neonatal baseline information

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

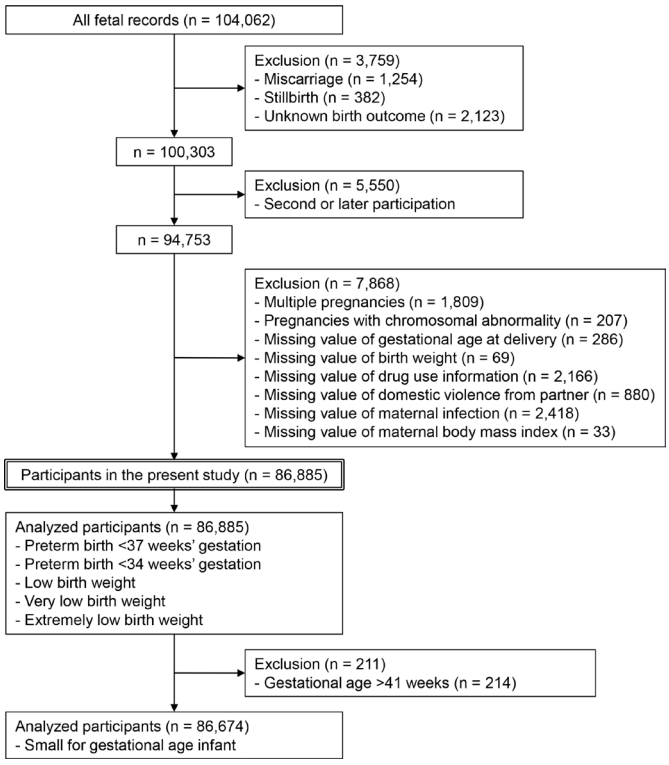

Figure 1 Flow diagram of the study participants.

was obtained from self-administered questionnaires applied to the enrolled pregnant women during the first trimester. The following maternal information was obtained from the medical record transcripts: maternal infection, neonate's date of birth, parity and gestational period. Although maternal pre-pregnancy height and weight were collected from medical record transcripts, in instances where the above information was missing, the values were obtained from mothers' self-reports. Maternal age at delivery was calculated from the birth dates of mothers and neonates. Parity was categorised as 0, 1, 2 or higher. The categories of maternal smoking status were defined as follows: never; previously did, but quit before recognising the current pregnancy; previously did, but quit after identifying the current pregnancy; and current smoker. The categories of maternal alcohol consumption were defined as follows: never consumed; previously consumed, but quit before identifying current pregnancy; previously consumed, but quit after identifying current pregnancy; and current drinker. The highest educational level of the mother was defined as follows: junior high school, high school, technical junior college, technical/vocational college or associate degree, bachelor's degree or graduate degree (master/doctor). Annual household income was categorised as follows: <2 000 000; 2 000 000–3 990 000; 4 000 000–5 990 000; 6 000 000–7 990 000; 8 000 000–9 990 000 and ≥10 000 000 Japanese yen. Maternal and neonatal medical information, such as maternal age at delivery, gestational age at delivery, neonatal birth weight and neonatal sex, were collected from the medical record transcripts at birth.

Exposure: maternal multimorbidity

In our study, multimorbidity was defined as the coexistence of two or more physical, psychological or social conditions in an individual according to previous reports.[13 14 17 18] Maternal chronic conditions included in multimorbidity were defined as the conditions with high prevalence among women of reproductive age or that had the potential to affect perinatal outcomes. The chronic conditions in this study were heterogeneous because the JECS lacked information regarding the disease severity. However, the definition of multimorbidity varies among studies.[18 32] To identify pregnant women with chronic conditions more rigorously, a maternal chronic condition was defined as a condition that was medically treated at the time of pregnancy. This information was collected from self-reports, medical record transcripts and medication interviews. Maternal chronic conditions included allergic diseases such as asthma, anaemia, diabetes mellitus, dyslipidaemia, epilepsy, gastric or duodenal ulcer, heart disease, hepatitis, HIV infection, hypertension, inflammatory bowel disease, kidney disease, malignancy, migraine, neurological disease, other sexually transmitted diseases (*Chlamydia trachomatis* and syphilis), psychiatric disorders, rheumatic or collagen diseases, and thyroid disease.

Additionally, abnormal pre-pregnancy BMI, including underweight and obesity, physical or verbal domestic violence from intimate partners, and substance abuse were included in the maternal chronic conditions.[18 33] Maternal pre-pregnancy BMI was calculated from the maternal pre-pregnancy weight divided by the square of maternal height collected from medical record transcripts or self-reports. Pregnant women were categorised according to their pre-pregnancy BMI as follows: underweight (BMI <18.5 kg/m^2), normal weight (18.5 kg/m^2≤BMI<25.0 kg/m^2) and obesity (BMI ≥25.0 kg/m^2).[34 35] Information on domestic violence from intimate partners was obtained from a questionnaire administered during the first trimester: 'Have you been verbally insulted or yelled at by your partner during pregnancy?' and 'Have you been physically abused, such as being slapped or beaten, resulting in injury because of a quarrel between you and your partner during pregnancy?'[36] Each response was selected from one of four predefined categories: never, rarely, sometimes and often. If the response 'rarely' or 'sometimes' or 'often' was chosen, it was considered as presence of domestic violence. Medication information was obtained from interviews (online supplemental appendix 2).[37] Medication was considered relevant from pregnancy diagnosis to 12 weeks of gestation to investigate the impact of maternal pre-pregnancy chronic conditions on perinatal outcomes. The types of medication in early pregnancy included antiallergic drugs, lipid-lowering drugs, antimigraine drugs, anti-parkinsonian drugs, antirheumatic drugs, antithyroid drugs, antiviral drugs, anticancer drugs, cardiovascular drugs, corticosteroids, gastrointestinal drugs, illegal drugs including marijuana, psychostimulant, ecstasy, thinner and toluene, insulin

preparations, iron preparations, psychoactive drugs, respiratory drugs and thyroid hormone preparations.[37]

Outcomes

The primary outcome of this study was the incidence of adverse perinatal outcomes, including PTB, LBW and SGA. The secondary outcomes were the incidences of very preterm birth (VPTB), very low birth weight (VLBW) and extremely low birth weight (ELBW). PTB was defined as a gestational age of less than 37 weeks at delivery. VPTB was defined as a gestational age of less than 34 weeks at delivery. LBW, VLBW and ELBW were defined as neonatal birth weights of less than 2500 g, 1500 g and 1000 g, respectively. SGA was defined as birth weight below the 10th percentile, accounting for parity, gestational age and neonatal sex according to the Japan Pediatric Society guidelines,[38] and percentiles were calculated using Excel-based clinical tools for growth evaluation of children distributed by the Japanese Society for Pediatric Endocrinology.[39]

Statistical analysis

In the main analyses, adjusted ORs (aORs) and 95% CIs for adverse perinatal outcomes were estimated using a multivariable logistic regression model adjusted for maternal age at delivery (<20, 20–24, 25–29, 30–34, 35–39 and ≥40 years), parity, maternal smoking status, maternal alcohol consumption, maternal educational level, household income and neonatal sex. In the SGA analyses, parity and neonatal sex were removed from the covariates. These covariates were selected based on previous studies on multimorbidity.[13 18 33] Statistical analyses were used to compare pregnant women with multimorbidity or with one chronic condition, with those without chronic conditions as a reference group.

We used the k-nearest neighbour (kNN) imputation method in the R package 'VIM' (V.4.1.2; R Foundation for Statistical Computing, Vienna, Austria),[40] introducing all outcomes and adjusted variables because the dataset had some missing values. The covariates, such as maternal age, parity, smoking status during pregnancy, drinking status during pregnancy, maternal education, household income and neonatal sex, were among the imputed missing data. kNN is a widely accepted single imputation method whose validity has been established.[41] We performed an additional analysis to test the robustness of our findings using a complete dataset, which excluded all missing values. We also analytically evaluated the dose–response relationship between the number of chronic conditions and perinatal adverse outcomes using a detailed classification of the number of chronic conditions (0, 1, 2, 3 and ≥4) and a test for trend. Sensitivity analyses focusing on underweight, obesity, psychiatric disorders and domestic violence were performed. Each of these chronic conditions was categorised separately as included or not included in the multimorbidity category. The results of these analyses are shown in online supplemental tables 2-4. Statistical significance was defined as a two-tailed p<0.05. All analyses, except kNN imputation, were performed using STATA V.16.1, for Windows (Stata Corporation, College Station, Texas, USA). kNN imputation was conducted using R (V.4.1.2; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Of the 104 062 fetal records included in this study, 17 177 (16.5%) were excluded, leaving a final number of 86 885 singleton pregnant women (figure 1). The main and all maternal characteristics are shown in table 1 and online supplemental table 1, respectively. The median maternal age was 31 years (range, 14–48), and the median pre-pregnancy BMI was 20.5 kg/m^2 (range, 13.2–52.8). In the present study, 40.2% of pregnant women had one or more chronic conditions (table 1). The prevalence of maternal multimorbidity was 6.3% (5462 of 86 885). Regarding perinatal outcomes, the prevalence of PTB and VPTB was 4.6% and 1.0%, respectively. The prevalence of LBW, VLBW, ELBW and SGA was 8.1%, 0.6%, 0.2%, and 7.5%, respectively (table 2). The details of the maternal chronic conditions are shown in table 3. Maternal underweight (15.6%) was the most frequently observed in chronic conditions, followed by domestic violence (13.0%). The prevalence of maternal obesity was 10.9%. The other most frequent chronic conditions were allergic diseases (3.1%), other sexually transmitted diseases (1.4%), anaemia (0.7%), psychiatric disorders (0.7%) and thyroid disease (0.7%).

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

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

Online supplemental table 3 shows the additional analysis for PTB, LBW and SGA using exposure as the number of chronic conditions (0, 1, 2, 3 and ≥4). All of the trend p values were statistically significant.

Online supplemental table 4 demonstrates the aOR for adverse perinatal outcomes, focusing on each disease, including underweight, obesity, psychiatric disorders and domestic violence. Regarding PTB and LBW, significant differences were found between maternal multimorbidity and no chronic conditions, regardless of the presence or absence of specific chronic conditions (online supplemental table 4A–D). For SGA, maternal multimorbidity

Table 1 Main maternal characteristics (n=86 885)

Characteristics	Total	The number of chronic conditions		
		0 (n=51 964)	1 (n=29 459)	≥2 (n=5462)
Maternal age (years)				
≤24	8599 (9.9)	4451 (8.6)	3342 (11.3)	806 (14.8)
25–29	23 873 (27.5)	14 205 (27.3)	8232 (27.9)	1436 (26.3)
30–34	30 686 (35.3)	18 776 (36.1)	10 142 (34.4)	1768 (32.4)
35–39	19 703 (22.7)	12 121 (23.3)	6381 (21.7)	1201 (22.0)
≥40	4018 (4.6)	2409 (4.6)	1359 (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)	2049 (37.5)
1	31 810 (36.6)	19 030 (36.6)	10 750 (36.5)	2030 (37.2)
≥2	17 040 (19.6)	9691 (18.7)	6059 (20.6)	1290 (23.6)
Missing	2062 (2.4)	1291 (2.5)	678 (2.3)	93 (1.7)
Smoking during pregnancy				
No	49 414 (56.9)	31 028 (59.7)	15 937 (54.1)	2449 (44.8)
Quit before pregnancy	20 152 (23.2)	12 094 (23.3)	6777 (23.0)	1281 (23.5)
Quit after pregnancy	12 042 (13.9)	6320 (12.2)	4613 (15.7)	1109 (20.3)
Yes	3859 (4.4)	1757 (3.4)	1604 (5.4)	498 (9.1)
Missing	1418 (1.6)	765 (1.5)	528 (1.8)	125 (2.3)
Drinking during pregnancy				
No	28 652 (33.0)	16 928 (32.6)	9957 (33.8)	1767 (32.4)
Quit before pregnancy	14 108 (16.2)	8321 (16.0)	4832 (16.4)	955 (17.5)
Quit after pregnancy	40 354 (46.5)	24 554 (47.3)	13 378 (45.4)	2422 (44.3)
Yes	2370 (2.7)	1386 (2.7)	771 (2.6)	213 (3.9)
Missing	1401 (1.6)	775 (1.5)	521 (1.8)	105 (1.9)

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

with underweight, without obesity, without psychiatric disorder, and with and without domestic violence showed significant differences compared with no chronic conditions (online supplemental table 4A–D).

DISCUSSION

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

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

However, this study has several limitations. First, the prevalence of maternal multimorbidity in this study was 6.3%, which was lower than the prevalence noted in reproductive-aged women in previous studies.[3 4 14] The strict definition of a chronic condition in our study may be responsible for the lower prevalence of maternal multimorbidity than in previous studies. However, there is no consensus on the definition of maternal multimorbidity or classification system for reporting.[2 32] Second, the details of the differences in risk by the combination of chronic conditions were not identified. The risk of adverse perinatal outcomes may vary depending on the combination of the chronic conditions. Although sensitivity analyses focusing on underweight, obesity, psychiatric disorders and domestic violence demonstrated the

Table 2 Perinatal characteristics (n=86 885)

Outcomes	Total	The number of chronic conditions		
		0 (n=51 964)	1 (n=29 459)	≥2 (n=5462)
Gestational age at delivery (weeks)	39 (22–43)	39 (23–42)	39 (22–42)	39 (23–43)
Birth weight (g)	3028 (312–5214)	3038 (312–4700)	3016 (350–5214)	2998 (398–4568)
Neonatal sex				
Male	44 628 (51.4)	26 577 (51.2)	15 225 (51.7)	2826 (51.7)
Female	42 252 (48.6)	25 385 (48.8)	14 233 (48.3)	2634 (48.2)
Missing	5 (0.01)	2 (0.00)	1 (0.00)	2 (0.04)
Preterm birth (<37 weeks' gestation)	3963 (4.6)	2125 (4.1)	1498 (5.1)	340 (6.2)
Very preterm birth (<34 weeks' gestation)	834 (1.0)	441 (098)	328 (1.1)	65 (1.2)
Low birth weight (<2500 g)	7013 (8.1)	3775 (7.3)	2661 (9.0)	577 (10.6)
Very low birth weight (<1500 g)	483 (0.6)	248 (0.5)	193 (0.7)	42 (0.8)
Extremely low birth weight (<1000 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)	4841 (88.6)
Yes	6474 (7.5)	3574 (6.9)	2388 (8.1)	512 (9.4)
Missing	2273 (2.6)	1415 (2.7)	749 (2.5)	109 (2.0)

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

association of adverse perinatal outcomes with the presence or absence of each condition, no further detailed studies were conducted because the main aim of this study was not to examine the impact of each chronic condition. Third, some self-reported biases may exist. Self-reported body weight may be underestimated for underweight and overestimated for obesity.[42 43] The prevalence of self-reported domestic violence may be underestimated due to social desirability bias.[44] Fourth, the numbers of VPTB, VLBW and ELBW cases were small. This study was insufficient to investigate these severe adverse outcomes.

Conducting studies on maternal multimorbidity has been challenging because there is no agreed definition or uniform measurement tool for multimorbidity.[32] A systematic review of multimorbidity in 2012 by Fortin *et al*[3] reported that the prevalence of multimorbidity seemed to be influenced by the operational definition of chronic conditions. Moreover, most studies on multimorbidity conducted in the general population predominantly used questionnaires. As this method was based on self-report, it might present the disadvantage of assigning equal weight to both major and minor chronic conditions.[3] Although the present study also used self-report questionnaires, multimorbidity was defined as chronic conditions treated with medication to reduce the variability in the severity of chronic conditions in multimorbidity. However, our method may have decreased the prevalence of multimorbidities.

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

The present study confirmed that an increase in the number of chronic maternal conditions increases the risk of PTB, LBW and SGA. In a study on chronic diseases in pregnant women in Germany, pregnant women with at least one chronic condition had an increased risk of PTB.[12] A study on maternal multimorbidity in the USA reported that the incidence of PTB less than 37 weeks of gestation, caesarean delivery, severe maternal morbidity and mortality in pregnant women with multimorbidity was higher than those without chronic conditions.[13] These results were consistent with the present study, although the definition of maternal chronic conditions was different from our study.

In maternal multimorbidity, medication during pregnancy may affect perinatal outcomes. The present study defined a physical or psychological condition as one that required medical attention during pregnancy. The study on the exposure to medication for hypertension, diabetes and autoimmune disease during pregnancy reported that the ORs of PTB, LBW and SGA were higher in the antihypertensive and corticosteroid-exposed group compared with those in the unexposed group.[45] However, it was also reported that chronic conditions, with or without

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)	9461 (10.9)
Allergic disease	2680 (3.1)
Anaemia	628 (0.7)
Diabetes mellitus	128 (0.2)
Domestic violence	11 261 (13.0)
Dyslipidaemia	6 (0.01)
Epilepsy	133 (0.2)
Gastric or duodenal ulcer	298 (0.3)
Heart disease	7 (0.01)
Hepatitis	5 (0.01)
HIV 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)
Neurological disease	0 (0)
Other sexually transmitted diseases	1193 (1.4)
Psychiatric disorder	604 (0.7)
Rheumatic or collagen disease	94 (0.1)
Substance abuse	1 (0.0)
Thyroid disease	638 (0.7)

BMI, body mass index.

medication exposure, may have affected perinatal outcomes.

Chronic physical conditions such as hypertension, kidney disease, systemic lupus erythematosus and abnormal pre-pregnancy BMI are associated with adverse perinatal outcomes.[20–23 46 47] Our findings also indicated that multimorbidity might alter the risk of PTB, LBW and SGA depending on whether multimorbidity included or did not include abnormal BMI. Additionally, maternal infections, such as HIV, malaria, syphilis and tuberculosis, have been reported to be associated with adverse perinatal outcomes.[48–51] However, the influence of these infections may be small in the present study because the prevalence of these maternal infections was very low in Japan.

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

In the present study, domestic violence from intimate partners was the second most frequent chronic condition at 13.0%. Multimorbidity with and without domestic violence was significantly associated with PTB, LBW and SGA, although the point estimate of the aOR for multimorbidity with domestic violence was slightly smaller than the aOR for those without domestic violence in this study. Social morbidity, including domestic violence, has been highlighted as a risk factor associated with adverse perinatal outcomes.[17 28 29] A cross-sectional study in Iran found a significant association between intimate partner violence during pregnancy and PTB.[28] A prospective cohort study in Tanzania reported that physical violence during pregnancy significantly increased the risk of PTB and LBW.[29] However, a population-based study in Canada reported no association between domestic violence before and during pregnancy and adverse perinatal outcomes, including PTB and SGA.[54] This previous study had the limitation that the prevalence of domestic violence was 10.9% and only 3.3% occurred during pregnancy.[54]

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

CONCLUSIONS

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

Table 4 Crude and adjusted ORs of maternal chronic conditions for adverse perinatal outcomes (n=86 885)

	The number of chronic conditions		
Outcome	**0**	**1**	**≥2**
PTB			
N (%)	2125 (4.1)	1498 (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 (%)	3775 (7.3)	2661 (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 (%)	3685 (7.1)	2443 (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)**

OR, odds ratio compared with 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).
Adjusted ORs with statistical significance are indicated in bold font.
*The total number of participants was 86 674.
ELBW, extremely low birth weight (<1000 g); LBW, low birth weight (<2500 g); PTB, preterm birth before 37 weeks of gestation; SGA, small for gestational age; VLBW, very low birth weight (<1500 g); VPTB, preterm birth before 34 weeks of gestation.

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

Author affiliations
[1]Department of Obstetrics and Gynecology, Asahikawa Medical University, Asahikawa, Hokkaido, Japan
[2]Division of Public Health and Epidemiology, Department of Social Medicine, Asahikawa Medical University, Asahikawa, Hokkaido, Japan
[3]Division of Neonatology, Perinatal Medical Center, Asahikawa Medical University Hospital, Asahikawa, Hokkaido, Japan
[4]Department of Pediatrics, Asahikawa Medical University, Asahikawa, Hokkaido, Japan
[5]Faculty of Nursing, Japanese Red Cross Hokkaido College of Nursing, Kitami, Hokkaido, Japan
[6]Center for Environmental and Health Sciences, Hokkaido University, Sapporo, Hokkaido, Japan
[7]Faculty of Health Sciences, Hokkaido University, Sapporo, Hokkaido, Japan
[8]Hokkaido Daigaku, Sapporo, Hokkaido, Japan
[9]Hokkaido Daigaku, Sapporo, Japan

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ORCID iDs
Kentaro Nakanishi http://orcid.org/0000-0002-0409-584X
Yasuaki Saijo http://orcid.org/0000-0002-6211-8202
Eiji Yoshioka http://orcid.org/0000-0003-3316-1057

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