

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

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

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

Antibacterial, Antiviral, Antifungal, Carcinostatic drugs

- 0 Antimicrobial
- 1 Antiviral
- 2 Antifungal
- 3 Carcinostatic

Corticosteroids

- 4 Corticosteroids: oral administration, inhalation, infusion
- 5 Corticosteroids: external use, enema

Antipyretic, Analgesic drugs

- 6 Antipyretic, Analgesic, Medicine for common cold: prescription
- 7 Antipyretic, Analgesic, Medicine for common cold: over the counter
- 8 Poultice which the analgesic is included in

Antirheumatic drugs

- 9 Immunosuppressant, Immunoregulation
- 10 Infliximab, Etanercept
- 11 Antirheumatic drug unidentified in detail

Antiallergy drugs

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

Respiratory drugs

- 13 β stimulative (oral administration, inhalation)
- 14 Nontypeable inhalant

15 Antitussive, Expectorant

16 Theophylline

17 Other respiratory drug

Antidiabetic drugs, Antihyperlipidemic drugs

21 Insulin preparation

22 Hypoglycemic tablet

23 Antihyperlipidemic

24 Antigout

Hormone-related drugs

25 Thyroid hormone preparation/levothyroxine sodium

26 Antithyroid/Thiamazole

27 Other hormone drugs

Blood-related drugs

28 Iron preparation

29 Other blood-related

Cardiovascular drugs

31 Antihypertensive (including diuretic)

32 Pressor

33 Antiarrhythmic, Antianginal

34 Heart failure therapeutic

35 Other cardiovascular drugs

Gastrointestinal drugs

36 Antiulcer (Proton pump inhibitor, H2 blocker)

37 General gastrointestinal agents

38 Other gastrointestinal agents

Psychoactive drugs

- 41 Selective serotonin reuptake inhibitors (SSRI)
- 42 Antidepressant drug except the SSRI
- 43 Antianxiety
- 44 Sleeping pill
- 45 Antipsychotic
- 46 Valproic acid
- 47 Antiepileptic except the above
- 48 Lithium carbonate
- 49 Other psychoactive drugs

Perinatal drugs

- 51 Utero relaxants
- 52 Utero-tonic
- 53 Ovulation inducing
- 54 Other perinatal related drugs

Other drugs

- 61 Anesthetic, pain block injection
- 62 Chinese herbal medicines
- 63 External application (non-identified contents)
- 64 Injection, Drip infusion (non-identified contents)
- 65 Bone and Calcium metabolism
- 66 Antimigraine headache
- 67 Muscle relaxant
- 68 Antiemetic drug
- 69 AntiParkinson

70 Hemorrhoids

Supplements, vitamins/minerals

71 Vitamin A

72 Vitamin B

73 Vitamin C

74 Vitamin D

75 Vitamin E

76 Folic acid

77 Minerals

78 Multi vitamins supplement

79 Total supplement

Illegal drugs

80 Marijuana

81 Psychostimulant

82 Ecstasy

83 Thinner

84 Toluene

85 Other illegal drugs

90 Vaccines

98 Drugs not included in the list mentioned above

99 Forgot the drug name

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

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

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

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

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

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

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

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

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

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

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

Outcome	The number of chronic conditions					<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
----------------------	-----------	-------------------------	-------------------------	------------------	------------------	---------

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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