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Title: Association between maternal multimorbidity and neurodevelopment of offspring: a prospective birth cohort study from the Japan Environment and Children's Study

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ABSTRAT

Objectives: To investigate the association between multimorbidity during pregnancy and neurodevelopmental delay in offspring using data from a Japanese nationwide birth cohort study.

Design: This study was a prospective birth cohort study.

Setting: This study population included 104,059 fetal records who participated in The Japan Environment and Children's Study (JECS) from 2011 to 2014.

Participants: Pregnant women whose children had undergone developmental testing were included in this analysis.

Primary and secondary outcome measures: Neurodevelopment of offspring were assessed using the Japanese version of the Ages and Stages Questionnaire, third edition (J-ASQ-3), comprising five developmental domains. The number of comorbidities among the pregnant women was categorized as zero, single disease, or multimorbidity (two or more diseases). Maternal chronic conditions included in multimorbidity were defined as conditions with high prevalence among women of reproductive age. A multivariate logistic regression analysis was conducted to examine the association between multimorbidity in pregnant women and offspring development.

Results: Pregnant women with multimorbidity, single disease, and no disease accounted for 3.6%, 30.6%, and 65.8%, respectively. The adjusted odds ratios (ORs) of multimorbidity for neurodevelopmental delay of offspring evaluated by J-ASQ-3 domains at 4 years of age were higher than those of a single disease at the same age in all domains like communication, gross motor, fine motor, problem solving, and personal-social. The adjusted ORs for multimorbidity at 4 years of age were also higher than those at 6 months in all domains.

Conclusion: An association was observed between the number of comorbidities in pregnant women and developmental delay in offspring. Pregnant women with multimorbidities are at a higher risk of neurodevelopmental delays in their offspring. Further research is required in this regard in many other regions of the world.

Keywords

pregnant, women, multimorbidity, Japan, offspring, neurodevelopment, delay

Word counts

Abstract: 284 words; Main text,1921words

Tables/figures: 3 tables/2 figures

References: 24 references

Strengths and limitations of this study

- The study size was adequate for effective investigation.
- Neurodevelopmental progress was assessed in detail using the results of eight points (6 months, 1 year, 1.5 year, 2 years, 2.5 years, 3 years, 3.5 years, and 4 years).
- Chronic diseases that are diagnosed but not treated were ruled out.
- Infants are unable to communicate well, which renders accurate assessment of their neurodevelopment difficult.

INTRODUCTION

Multimorbidity is defined as the coexistence of two or more chronic diseases, whether physical or mental, in the same individual.(1) Multimorbidity is considered one of the principal challenges in older people as the incidence of chronic diseases such as hypertension, dyslipidemia, diabetes, cardiac disease, and malignant tumors, increases with age. Therefore, many studies have focused on older patients with multimorbidities.(2,3) However, diseases such as asthma, arthritis, mental disorders, and

HIV can also occur in young people. There are few studies on multimorbidity in young people,(4) including pregnant women.(5,6) Maternal physical morbidities, such as hypertension, kidney disease, and systemic lupus erythematosus, are potential risk factors for preterm birth (PTB) and low birth weight infants (LBW).(7) Moreover, maternal mental and social morbidities have also been associated with PTB and LBW.(7) Previous studies also reported the relationship between maternal environment such as maternal asthma, maternal intake of fats, maternal and cord blood Mn levels and child development.(8–10)

Infancy is considered to be the period in which language, cognition, motor skills, and socioemotional domains form the basis for subsequent social participation.(11) It is essential to receive appropriate support, early detection, and intervention during this period.(12) Although maternal nutritional status, certain diseases, and blood substances can affect the neurodevelopment of offspring(8–11), the impacts of multimorbidity in pregnant women on the neurodevelopment of offspring has not been extensively studied.(5,6) A major difference between previous reports and this study was the investigation of the association between multiple diseases of pregnant women and child neurodevelopment; previous reports have mainly focused on the relationship between a single disease or single substance in pregnant women and child neurodevelopment.

The present study aimed to investigate the association between multimorbidity during pregnancy and neurodevelopmental delay in offspring (every 6 months from birth to age 4 years) using data from an ongoing nationwide birth cohort, namely the Japan Environment and Children's Study (JECS)(13); the neurodevelopment of the participants was evaluated using the Japanese version of the Ages and Stages Questionnaires, Third Edition: Infant Developmental Examination (ASQ-3).(14)

METHODS

Study population

The JECS is a nationwide and government-funded birth cohort study that started recruiting expecting mothers in January 2011.(13); the primary objective was to investigate environmental factors such as exposure to chemicals and airborne pollutants that can affect children's health and development during the fetal stage and early childhood, in order to help policymakers to formulate measures to safeguard the environment for future generations.(15) The study population included 104,059 fetal records who participated in JECS from 2011 to 2014. A flowchart of the study participants is presented in the Figure 1 . The exclusion criteria included: miscarriage, stillbirth, or unknown birth outcomes (n = 2,123). Second, participants with multiple births,

pregnancies with chromosomal abnormalities, participated for the second time and more, and missing information about drug history, domestic violence, maternal infection, or maternal BMI were excluded (n = 13,377). Moreover, pregnant women whose children were not tested using the ASQ-3 once from 6 months to 4 years old (n=4,046) were excluded. Finally, a total of 82,877 pregnant women were included in the analysis.

Figure 1. Fetal records selection flow chart

Ethics

The JECS protocol was reviewed and approved by the Ministry of the Environment's Institutional Review Board on Epidemiological Studies and the Ethics Committees of all participating institutions (No. 100910001).(13) The JECS was performed following the Declaration of Helsinki. All the participants provided written informed consent.

Patient and Public Involvement statement

This study did not involve patients or public.

Assessment of pregnant multimorbidity

In this study, multimorbidity was defined as the coexistence of two or more physical,

mental, or social conditions in an individual according to previous reports.(7) Maternal chronic conditions included in multimorbidity were defined as conditions with high prevalence among women of reproductive age.(7) To identify pregnant women with disease more rigorously, the diseases of pregnant women were defined as those that were medically treated at the time of pregnancy. Information was collected through self-reports, medical record transcripts, and medication interviews. The targeted diseases included allergic diseases, such as asthma, anemia, diabetes mellitus, dyslipidemia, epilepsy, gastric or duodenal ulcers, 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), mental disorders, rheumatic or collagen diseases, and thyroid disease. Having an episode of domestic violence, substance abusing, being obese (BMI ≥25), and being thin (BMI <18.5) were each defined as one disease. Pregnant women with two or more of these diseases during pregnancy were defined as having multimorbidities.

Assessment of neurodevelopment of offspring

Score results from the Japanese version of the ASQ-3 (Ages and Stages Questionnaires, Third Edition: Infant Development Test) at 6 months, 1 year, 1.5 years, 2 years, 2.5 years

and, 3 years, 3.5 years, and 4 years were used to evaluate neurodevelopmental measures.(15) These scores were obtained by mailed questionnaire survey filled by caregivers. Neurodevelopmental assessments were performed in the domains of communication, gross motor, fine motor, problem solving, and personal-social. Offspring with scores below the cut-off were defined as having neurodevelopmental delays. The cut-off values were those reported in the Japanese validation version.(14)

Covariates

The covariates were: maternal age at birth, parity, alcohol consumption status, smoking status, educational attainment, household income, and sex of the child; they were selected based on previous studies.(7,10)

Statistical analysis

This study used the dataset jecs-ta-20190930 and jecs-qa-20210401 from JECS. STATA ®(MP17) and R®(version 4.2.2) were used for statistical analysis. Multivariate logistic regression analysis was performed to determine the adjusted odds ratios (ORs). The objective variable was neurodevelopment of the offspring, and the explanatory variable was multimorbidity in pregnant women. The covariates were: maternal age at birth,

alcohol consumption status, smoking status, educational attainment, household income, sex of the child, and number of births. Multiple imputation methods were performed using R to impute the missing values. Other analyses were performed using the STATA software.

RESULTS

The characteristics of the pregnant women analyzed in this study are presented in Table 1. Pregnant women with multimorbidity, single disease, and no disease accounted for 3.6% (n = 3,001), 30.6% (n = 25,341), and 65.8% (n = 54,535), respectively. Household income of 2–7.99 million/year was accounted for 84.7%; n = 70,184. In total, 51.4% (n = 42,563) and 48.6% (n = 40,314) of the offspring were male and female, respectively. After pregnancy, 4.1 % (n = 3, 408) and 2.7 % (n = 2, 253) of pregnant women had smoking and drinking habits, respectively.

Table 1. Characteristics of pregnant women and their offspring (n = 82,877)

Characteristics		n		%
Number of coexist disease				
	0	54,535		65.8
	1	25,341		30.6
	≧2	3,001		3.6
Mother age at birth				
	<24	7,815		9.4

	25-29	22,721		27.4
	30-34	29,555		35.7
	35-39	18,940		22.9
	≧40	3,846		4.6
Parity				
	0	36,302		43.8
	1	30,646		37.0
	≧2	15,929		19.2
Mother education				
	Junior high school	3,630		4.4
	High school	25,917		31.3
	Vocational junior or technical college	35,323		42.6
	≧University	18,007		21.7
Maternal smoking habits				
	Non-smoking or exit-smoking before pregnancy	68,145		82.2
	Exit-smoking after pregnancy	11,324		13.7
	Still-smoking	3,408		4.1
Maternal drinking habits				
	Non-drinker	41,481		50.1
	Exit drinking after pregnancy	39,143		47.2
	drinking	2,253		2.7
Annual household income (10,00 JPY)				
	<200	4,193		5.1
	200-399	28,476		34.4
	400-599	28,663		34.6
	600-799	13,045		15.7
	800-999	5,233		6.3
	1000-1199	1,870		2.3
	1200-1499	735		0.9
	1500-1999	427		0.5
	≧2000	235		0.3
Child sex				

	boys	42,563		51.4
	girls	40,314		48.6

The prevalence of 23 maternal diseases are described in supplemental table 1. Maternal underweight (BMI <18.5) (15.6%) was the most frequently observed chronic conditions, followed by maternal obesity (BMI ≥25) (10.7%). The most frequent diseases on medication were allergic diseases (3.1%), other sexually transmitted diseases (1.3%), anemia (0.7%), mental disorders (0.7%) and thyroid disease (0.7%).

The prevalence of neurodevelopmental delay in offspring are presented in Table 2. The prevalence of communication delays at 6 months and 1 year was significantly lower than that of the others.

Table 2. Prevalence of neurodevelopment delay of offspring

Age	Number of maternal comorbidity	Communication		Gross motor		Fine motor		Problem solving		Personal-social	
		n	%	n	%	n	%	n	%	n	%
6 months	0	318	0.4	5,540	6.7	2,778	3.4	5,675	6.8	1,898	2.3
	1	123	0.1	2,603	3.1	1,237	1.5	2,596	3.1	891	1.1
	2	19	0.02	316	0.4	137	0.2	294	0.4	101	0.1
1 year	0	54	0.1	2,711	3.3	2,743	3.3	2,478	3.0	566	0.7
	1	31	0.04	1,324	1.6	1,383	1.7	1,226	1.5	282	0.3

	2	6	0.01	148	0.2	154	0.2	172	0.2	57	0.1
1 half years	0	1,091	1.3	2,138	2.6	2,000	2.4	1,831	2.2	1,209	1.5
	1	528	0.6	1,100	1.3	984	1.2	949	1.1	564	0.7
	2	76	0.1	148	0.2	156	0.2	128	0.2	78	0.1
2 years	0	1,851	2.2	2,816	3.4	1,060	1.3	2,106	2.5	1,400	1.7
	1	1,048	1.3	1,474	1.8	590	0.7	1,004	1.2	706	0.9
	2	147	0.2	176	0.2	84	0.1	122	0.1	99	0.1
2 half years	0	2,445	3.0	2,042	2.5	2,696	3.3	2,708	3.3	1,634	2.0
	1	1,376	1.7	1,086	1.3	1,389	1.7	1,445	1.7	860	1.0
	2	199	0.2	132	0.2	186	0.2	187	0.2	112	0.1
3 years	0	1,901	2.3	2,037	2.5	3,492	4.2	3,406	4.1	1,603	1.9
	1	1,030	1.2	1,102	1.3	1,843	2.2	1,783	2.2	861	1.0
	2	164	0.2	144	0.2	245	0.3	260	0.3	122	0.1
3 half years	0	2,873	3.5	2,020	2.4	2,522	3.0	2,689	3.2	2,130	2.6
	1	1,467	1.8	1,098	1.3	1,341	1.6	1,508	1.8	1,171	1.4
	2	219	0.3	155	0.2	182	0.2	218	0.3	154	0.2
4 years	0	2,157	2.6	2,597	3.1	3,038	3.7	1,733	2.1	2,629	3.2
	1	1,118	1.3	1,347	1.6	1,651	2.0	977	1.2	1,362	1.6

2	166	0.2	177	0.2	239	0.3	145	0.2	194	0.2	

The results of the multivariate logistic regression analysis conducted on the number of comorbidities in pregnant women and the neurodevelopment of offspring are shown in Table 3 and Figure 2. Except at 6 months, the ORs were more than 1 for any of the following items: communication, gross motor, fine motor, problem solving, and personal and social. The ORs at 6 months were lower than those at other ages for all items, both single disease comorbidity and multimorbidity. ORs tended to be higher with increasing age of the offspring, and the ORs for all items were higher at 4 years than at 6 months for both single-disease coexistence and multimorbidity. The ORs for single disease comorbidities ranged from 0.85 to 1.28. The OR range for multimorbidity was 0.95–2.29, and that at 4 years of age was 1.30–1.40 for all domains.

Table 3. Adjusted odds ratio for developmental delay of offspring for multimorbidity during pregnancy by logistic regression.

Age	Communication		Gross motor		Fine motor		problem solving		Personal-social	
	Adjusted OR(95% CI)		Adjusted OR(95% CI)		Adjusted OR(95% CI)		Adjusted OR(95% CI)		Adjusted OR(95% CI)	
	Single disease	Multimorbidity	Single disease	Multimorbidity	Single disease	Multimorbidity	Single disease	Multimorbidity	Single disease	Multimorbidity
6 months	0.85 (0.69 - 1.05)	1.14 (0.71 - 1.81)	1.03 (0.98 - 1.08)	1.08 (0.96 - 1.22)	0.99 (0.92 - 1.06)	0.95 (0.8 - 1.14)	1.01 (0.96 - 1.06)	0.98 (0.86 - 1.11)	1.02 (0.94 - 1.11)	0.99 (0.8 - 1.21)

1year	1.28 (0.82 - 1.99)	2.29 (0.98 - 5.36)	1.09 (1.02 - 1.16)	1.08 (0.91 - 1.28)	1.10 (1.03 - 1.18)	1.05 (0.89 - 1.24)	1.08 (1.01 - 1.16)	1.32 (1.12 - 1.55)	1.08 (0.94 - 1.25)	1.90 (1.44 - 2.50)
1half years	1.04 (0.94 - 1.16)	1.29 (1.02 - 1.64)	1.13 (1.05 - 1.22)	1.34 (1.13 - 1.59)	1.05 (0.97 - 1.14)	1.42 (1.20 - 1.68)	1.12 (1.04 - 1.22)	1.31 (1.09 - 1.57)	1.02 (0.92 - 1.13)	1.23 (0.97 - 1.56)
2years	1.21 (1.12 - 1.30)	1.42 (1.19 - 1.69)	1.15 (1.08 - 1.23)	1.21 (1.03 - 1.41)	1.19 (1.08 - 1.32)	1.42 (1.13 - 1.78)	1.04 (0.96 - 1.12)	1.09 (0.9 - 1.32)	1.09 (0.99 - 1.19)	1.31 (1.06 - 1.61)
2half years	1.19 (1.11 - 1.27)	1.42 (1.22 - 1.65)	1.17 (1.09 - 1.26)	1.26 (1.05 - 1.51)	1.11 (1.04 - 1.19)	1.28 (1.09 - 1.49)	1.14 (1.07 - 1.22)	1.23 (1.05 - 1.44)	1.14 (1.04 - 1.24)	1.26 (1.04 - 1.54)
3years	1.14 (1.05 - 1.23)	1.48 (1.25 - 1.75)	1.19 (1.10 - 1.28)	1.37 (1.15 - 1.63)	1.13 (1.06 - 1.19)	1.26 (1.10 - 1.45)	1.12 (1.06 - 1.19)	1.39 (1.22 - 1.59)	1.13 (1.04 - 1.24)	1.33 (1.10 - 1.61)
3half years	1.04 (0.98 - 1.11)	1.24 (1.07 - 1.44)	1.18 (1.10 - 1.28)	1.46 (1.23 - 1.73)	1.12 (1.04 - 1.20)	1.26 (1.07 - 1.47)	1.19 (1.11 - 1.27)	1.42 (1.22 - 1.64)	1.18 (1.09 - 1.27)	1.30 (1.09 - 1.54)
4years	1.10 (1.02 - 1.18)	1.35 (1.14 - 1.59)	1.13 (1.06 - 1.21)	1.30 (1.11 - 1.52)	1.15 (1.08 - 1.22)	1.37 (1.19 - 1.58)	1.18 (1.08 - 1.27)	1.42 (1.19 - 1.69)	1.11 (1.03 - 1.18)	1.32 (1.14 - 1.54)

Models were adjusted for maternal age at birth, parity, history of alcohol consumption, history of smoking, maternal educational attainment, sex of child, household income, and sex of child.

Figure 2. Adjusted odds ratio for developmental delay of offspring for multimorbidity during pregnancy by logistic regression.

Models were adjusted for maternal age at birth, parity, history of alcohol consumption, history of smoking, maternal educational attainment, sex of child, household income, and

sex of child. Error bars indicate 95% confidence intervals.

*95% confidence interval: 0.98 – 5.3

DISCUSSION

This investigation showed significant associations between multimorbidities in pregnant women and delayed neurodevelopment in the offspring. The ORs were higher for most of the neurodevelopmental items in pregnant women with multimorbidities than in those with a single disease. This study is the first to highlight the significance of the association between multimorbidity in pregnant women and the neurodevelopment in the offspring, despite the existence of reports on the association between specific diseases, such as asthma, chronic inflammatory arthritis, depression, thyroid conditions, diabetes, and epilepsy, in pregnant women and the neurodevelopment of their children.(8,16–18) As the number of comorbidities in pregnant women increases, the factors contributing to neurodevelopmental delay in the offspring may increase. In the future, health education and treatment in terms of the number of comorbidities during pregnancy should be considered.

The ORs for neurodevelopmental delay increased with the increase in the offspring's age. This may have been caused by the increasing accuracy of the assessment

as the offspring aged. An accurate assessment of neurodevelopment cannot be made until the child has grown to a certain age.(19) Parents' assessments of their children's neurodevelopment may not be established until a certain period of parenting time. Neurodevelopmental delays may have been caused by social factors.(20) It has been reported that depressed mothers tend to form family environments that are socially and economically disadvantageous to their children.(21) Pregnant women with multimorbidities and certain mental diseases may have tended to form socioeconomically undesirable family environments.(22) Further, a great deal of the brain's ultimate structure and capacity is shaped up to 3 years of age.(11) Neurodevelopmental delays in children may have gradually appeared as a result of the undesirable family environment.

This study has few limitations. First, Pregnant women with diagnoses but no medication were not included in the disease sample in this study, with the exception of domestic violence, obese, and skinny women. The criterion for disease was defined as the presence of medication; the number of pregnant women with disease may have been higher if the study had been conducted using different criteria. Some have criticized the definition of multimorbidity as simply having more than one disease, which would include a large population.(23) In the future, a definition of multimorbidity that is suitable for the target community will be required since the significant diseases and conditions

vary depending on the target population.(23) Second, it was difficult in this study to discuss the biological mechanisms of the association between multimorbidity and neurodevelopmental delay. The association between various diseases and neurodevelopmental delays has been reported in previous studies.(8,16–18,24) Further studies on disease characteristics and disease combinations may allow for hypotheses to be made regarding the biological mechanisms underlying the association between multimorbidity and neurodevelopmental delay. Third, as participants in the JECS were only collaborators, selection bias may have occurred.(15) The prevalence of multimorbidity and the results of the association between multimorbidity and neurodevelopmental delay might have been different if the study design included pregnant women who did not participate in the JECS. The number of pregnant women with multimorbidities would increase and the results of the effects on the neurodevelopment of the children might be different if all pregnant women and children registered in the administration were included in the study.

Previous reports on multimorbidities in pregnant women have focused on its prevalence and impact on pregnant women themselves.(5–7) This study is a new report in terms of the effect of multimorbidity in pregnant women on their offspring and provides important recommendations regarding the health of pregnant women.

This study demonstrated an association between multimorbidities in pregnant women and neurodevelopmental delays in their offspring in Japan. To clarify its mechanisms and effects, researches need to done in other regions of the world.

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Contributors

TA and YaS designed this study. JECS collected the data and obtained funding. YaS, EY, KNag, ST, YI, CM, SI, and RK collected the data. TA and YaS conducted the data analysis. TA, YaS, EY, YuS, KNak, YK, KNag, ST, YI, HI, TY, CM, SI, and RK contributed to data interpretation. TA, YaS, EY, YuS, KNak, YK, KNag, ST, YI, HI, TY, CM, SI, RK,and the JECS Group conducted critical reviews. TA drafted the manuscript. YaS made critical revisions. All the authors have reviewed and commented on the manuscript. All the authors approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

Patient and public involvement

The patients and/or the public were not involved in the design, conduct, reporting, or dissemination of this study.

Patient consent for publication

Not applicable.

Ethics approval

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

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

Data are unsuitable for public deposition due to ethical restrictions and legal framework of Japan. It is prohibited by the Act on the Protection of Personal Information (Act No. 57 of 30 May 2003, amendment on 9 September 2015) to publicly deposit the data containing personal information. Ethical Guidelines for Medical and Health Research Involving Human Subjects enforced by the Japan Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare also restricts the open sharing of the epidemiologic data. All inquiries about access to data should be sent to: jecs-en@nies.go.jp. The person responsible for handling enquiries sent to this e-mail address is Dr Shoji F. Nakayama, JECS Programme Office, National Institute for Environmental Studies.

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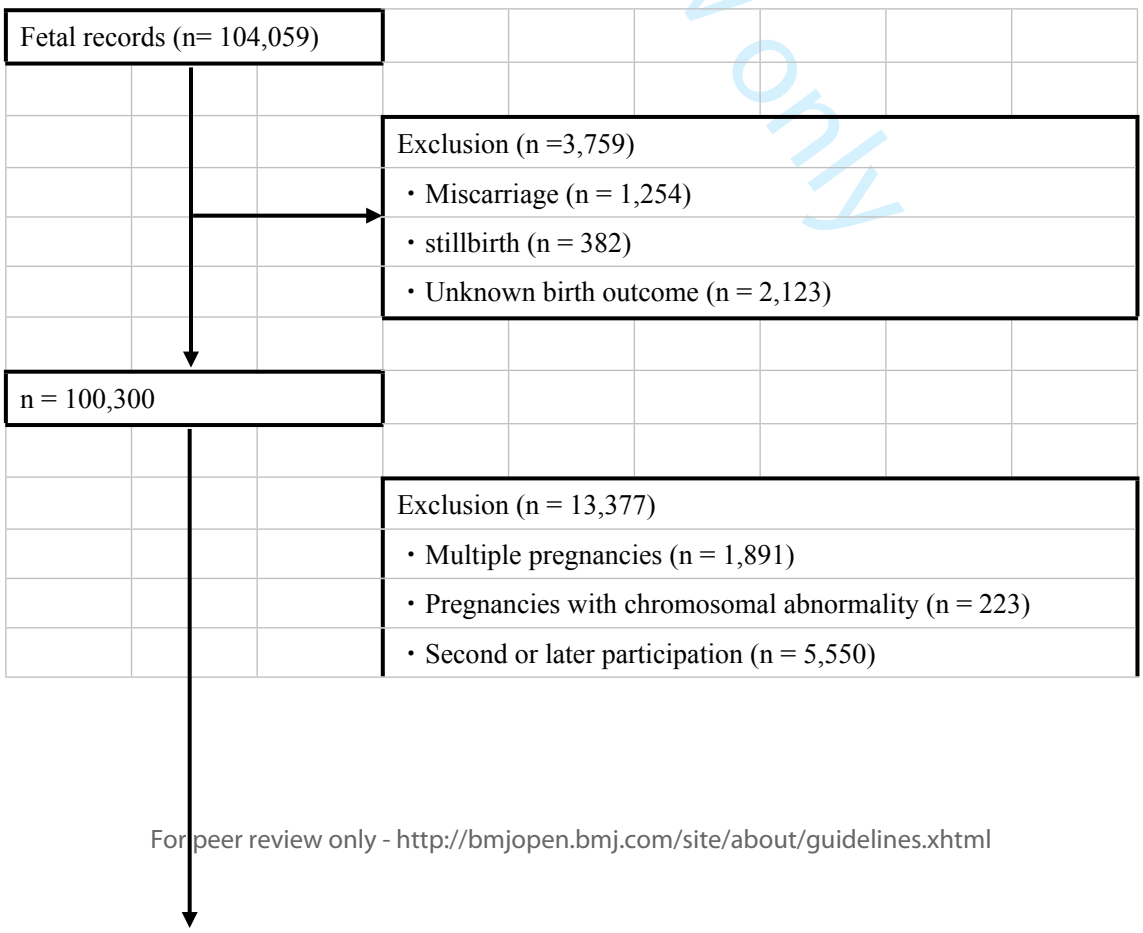
Figure legends



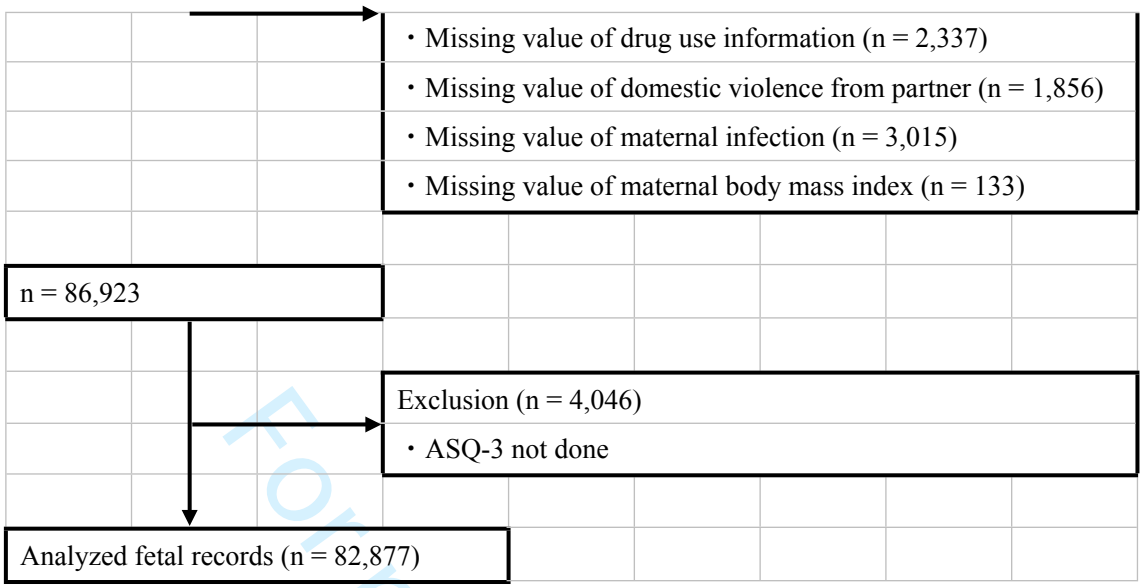


Figure 1. Participants selection flow chart

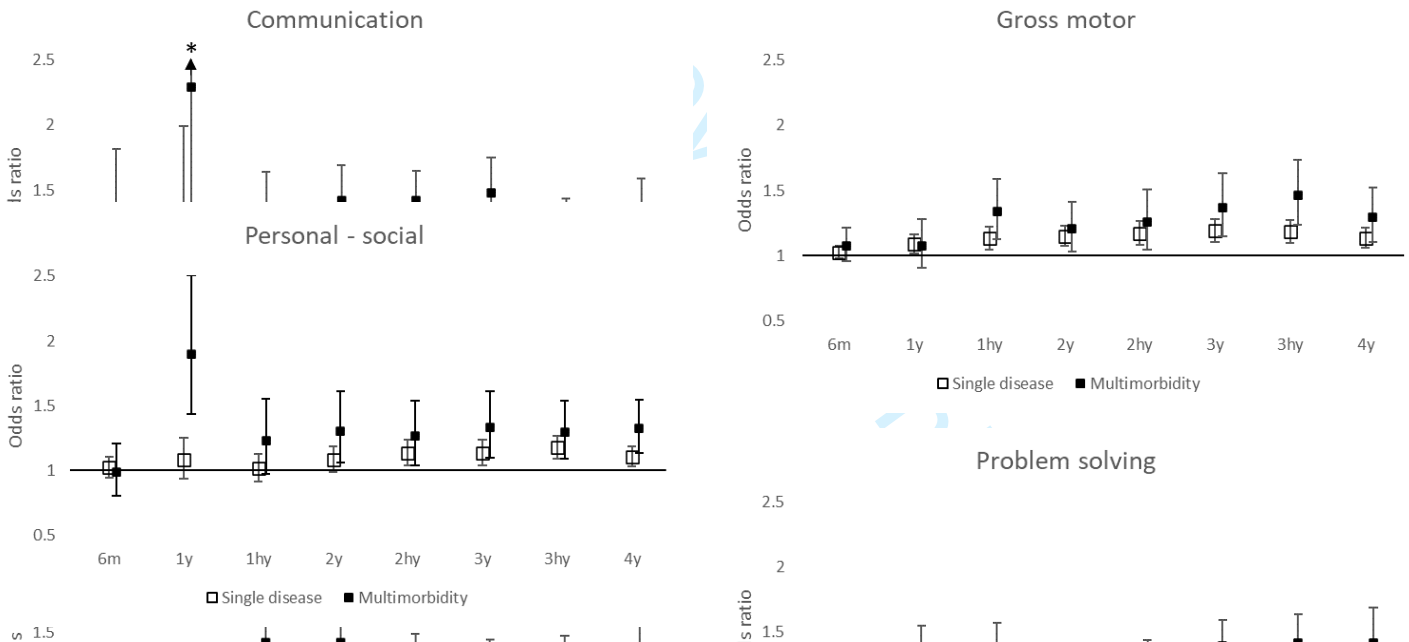


Figure 2. Adjusted odds ratio for developmental delay of offspring for

multimorbidity during pregnancy by logistic regression.

Models were adjusted for maternal age at birth, parity, history of alcohol consumption, history of smoking, maternal educational attainment, sex of child, household income, and sex of child. Error bars indicate 95% confidence intervals.

*95% confidence interval: 0.98 – 5.3

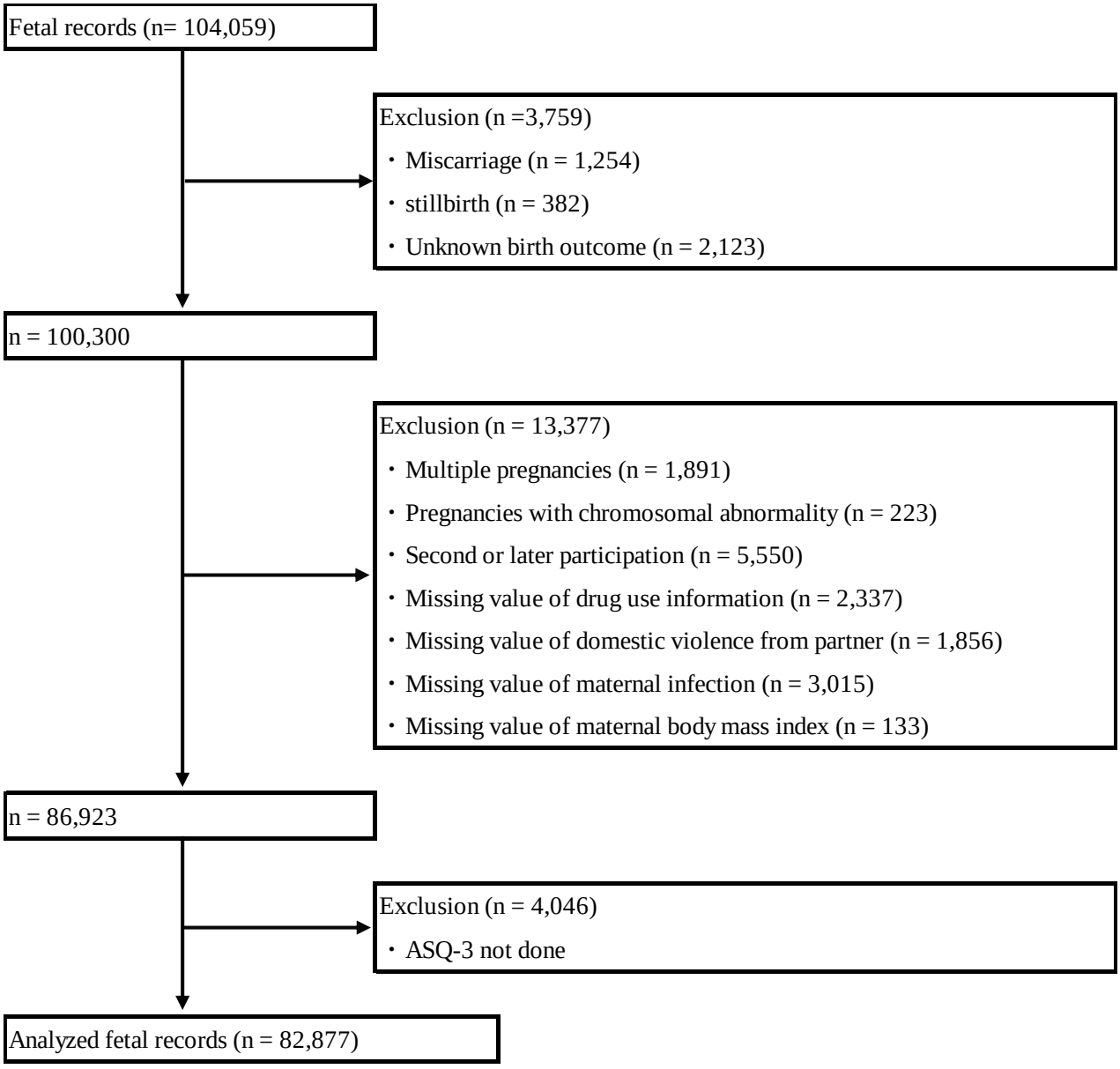


Figure 1. Fetal records selection flow chart

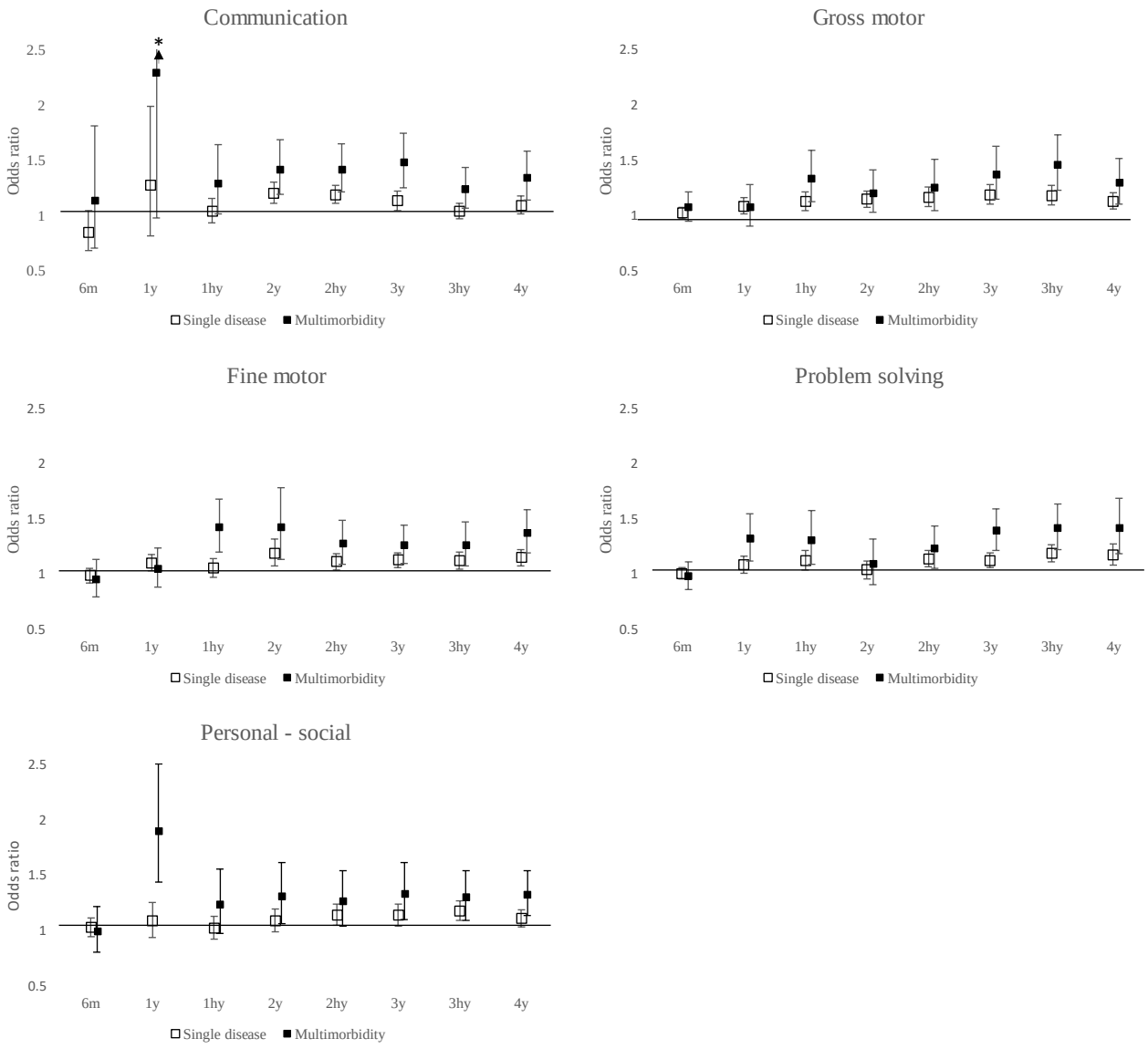


Figure 2. Adjusted odds ratio for developmental delay of offspring for multimorbidity during pregnancy by logistic regression.
Models were adjusted for maternal age at birth, parity, history of alcohol consumption, history of smoking, maternal educational attainment, sex of child, household income, and sex of child. Error bars indicate 95% confidence intervals.
*95% confidence interval: 0.98 – 5.3

Supplemental Table 1. Prevalence of 23 maternal diseases

Condition	n	%
Abnormal pre-pregnancy BMI		
Underweight (BMI <18.5 kg/m2)	12,889	15.6
Obesity (BMI >25.0 kg/m2)	8,848	10.7
Allergic disease	2,557	3.1
Anaemia	592	0.7
Diabetes mellitus	124	0.2
Domestic violence	3,632	4.4
Dyslipidaemia	6	0.01
Epilepsy	122	0.2
Gastric or duodenal ulcer	285	0.3
Heart disease	7	0.01
Hepatitis	5	0.01
HIV infection	7	0.01
Hypertension	83	0.1
Inflammatory bowel disease	16	0.02
Kidney disease	17	0.02
Malignancy	0	0
Migraine	41	0.05
Neurological disease	0	0
Other sexually transmitted diseases	1,089	1.3
Mental disorder	550	0.7
Rheumatic or collagen disease	91	0.1
Substance abuse	1	0.001
Thyroid disease	614	0.7

BMI, body mass index.

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	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3,4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5,6
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3,7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7,8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	7,8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-10
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	7,8
Bias	9	Describe any efforts to address potential sources of bias	19
Study size	10	Explain how the study size was arrived at	5,7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10,11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10
		(*b*) Describe any methods used to examine subgroups and interactions	10
		(*c*) Explain how missing data were addressed	10,11
		(*d*) If applicable, explain how loss to follow-up was addressed	-
		(*e*) Describe any sensitivity analyses	-
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	7,8
		(b) Give reasons for non-participation at each stage	7,8
		(c) Consider use of a flow diagram	7,8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11,12
		(b) Indicate number of participants with missing data for each variable of interest	-
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	13-15

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	15,16 - -
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	17
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	18,19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19,20
Generalisability	21	Discuss the generalisability (external validity) of the study results	20
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21,22

*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 neurodevelopment of offspring: a prospective birth cohort study from the Japan Environment and Children's Study

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Title: Association between maternal multimorbidity and neurodevelopment of offspring: a prospective birth cohort study from the Japan Environment and Children's Study

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ABSTRAT

Objectives: To investigate the association between multimorbidity during pregnancy and neurodevelopmental delay in offspring using data from a Japanese nationwide birth cohort study.

Design: This study was a prospective birth cohort study.

Setting: This study population included 104,059 fetal records who participated in The Japan Environment and Children's Study (JECS) from 2011 to 2014.

Participants: Pregnant women whose children had undergone developmental testing were included in this analysis.

Primary and secondary outcome measures: Neurodevelopment of offspring were assessed using the Japanese version of the Ages and Stages Questionnaire, third edition (J-ASQ-3), comprising five developmental domains. The number of comorbidities among the pregnant women was categorized as zero, single disease, or multimorbidity (two or more diseases). Maternal chronic conditions included in multimorbidity were defined as conditions with high prevalence among women of reproductive age. A multivariate logistic regression analysis was conducted to examine the association between multimorbidity in pregnant women and offspring development.

Results: Pregnant women with multimorbidity, single disease, and no disease accounted for 3.6%, 30.6%, and 65.8%, respectively. The Odds Ratios (ORs) for single disease

comorbidities ranged from 0.85 (95% Confidence Interval [CI] 0.69–1.05) to 1.28 (95% Cl 0.82–1.99), and they had no statistical significance. However, the OR range for multimorbidity was 0.95 (95% CI 0.80–1.14) to 2.29 (95% CI 0.98–5.36), which was statistically significant, and, restricted among 4 years of age, they ranged from 1.30 (95% CI 1.11–1.52) to 1.42 (95% CI 1.19–1.69) with all statistical significances.

Conclusion: An association was observed between the number of comorbidities in pregnant women and developmental delay in offspring. Pregnant women with multimorbidities are at a higher risk of neurodevelopmental delays in their offspring. Further research is required in this regard in many other regions of the world.

Keywords

pregnant, women, multimorbidity, Japan, offspring, neurodevelopment, delay

Word counts

Abstract: 286 words; Main text, 2,492 words

Tables/figures: 3 tables/2 figures

References: 27 references

Strengths and limitations of this study

- The study size was adequate for effective investigation.
- Neurodevelopmental progress was assessed in detail using the results of eight points (6 months, 1 year, 1.5 year, 2 years, 2.5 years, 3 years, 3.5 years, and 4 years).
- Chronic diseases that were diagnosed but not treated were ruled out.
- Infants were unable to communicate well, which renders accurate assessment of their neurodevelopment difficult.

INTRODUCTION

Multimorbidity is defined as the coexistence of two or more chronic diseases, whether physical or mental, in the same individual.(1) Multimorbidity is considered one of the principal challenges in older people as the incidence of chronic diseases such as hypertension, dyslipidemia, diabetes, cardiac disease, and malignant tumors, increases with age. Therefore, many studies have focused on older patients with multimorbidities.(2,3) However, diseases such as asthma, arthritis, mental disorders, and HIV can also occur in young people. There are few studies on multimorbidity in young people,(4) including pregnant women.(5,6) Maternal physical morbidities, such

as hypertension, kidney disease, and systemic lupus erythematosus, are potential risk factors for preterm birth (PTB) and low birth weight infants (LBW).(7) Moreover, maternal mental and social morbidities have also been associated with PTB and LBW.(7) Previous studies also reported the relationship between maternal environment such as maternal asthma, maternal intake of fats, maternal and cord blood Manganese levels and child development.(8–10)

Infancy is considered to be the period in which language, cognition, motor skills, and socioemotional domains form the basis for subsequent social participation.(11) It is essential to receive appropriate support, early detection, and intervention during this period.(12) Although maternal nutritional status, certain diseases, and blood substances can affect the neurodevelopment of offspring(8–11), the impacts of multimorbidity in pregnant women on the neurodevelopment of offspring has not been extensively studied.(5,6) A major difference between previous reports and this study was the investigation of the association between multiple diseases of pregnant women and child neurodevelopment; previous reports have mainly focused on the relationship between a single disease or single substance in pregnant women and child neurodevelopment.

The present study aimed to investigate the association between multimorbidity

during pregnancy and neurodevelopmental delay in offspring (every 6 months from birth to age 4 years) using data from an ongoing nationwide birth cohort, namely the Japan Environment and Children's Study (JECS)(13); the neurodevelopment of the participants was evaluated using the Japanese version of the Ages and Stages Questionnaires, Third Edition: Infant Developmental Examination (ASQ-3).(14)

METHODS

Study population

The JECS is a nationwide and government-funded birth cohort study that started recruiting expecting mothers in January 2011.(13); the primary objective was to investigate environmental factors such as exposure to chemicals and airborne pollutants that can affect children's health and development during the fetal stage and early childhood, in order to help policymakers to formulate measures to safeguard the environment for future generations.(15) The study population included 104,059 fetal records who participated in JECS from 2011 to 2014. A flowchart of the study participants is presented in the Figure 1. The exclusion criteria included: miscarriage, stillbirth, or unknown birth outcomes (n = 2,123). Second, participants with multiple births, pregnancies with chromosomal abnormalities, participated for the second time

and more, and missing information about drug history, domestic violence, maternal infection, or maternal BMI were excluded (n = 13,377). Moreover, pregnant women whose children were not tested using the ASQ-3 once from 6 months to 4 years old (n=4,046) were excluded. Finally, a total of 82,877 pregnant women were included in the analysis.

Ethics

The JECS protocol was reviewed and approved by the Ministry of the Environment's Institutional Review Board on Epidemiological Studies and the Ethics Committees of all participating institutions (No. 100910001).(13) The JECS was performed following the Declaration of Helsinki. All the participants provided written informed consent.

Patient and Public Involvement statement

This study did not involve patients or public.

Assessment of pregnant multimorbidity

In this study, multimorbidity was defined as the coexistence of two or more physical, mental, or social conditions in an individual according to previous reports.(7) Maternal

chronic conditions included in multimorbidity were defined as conditions with high prevalence among women of reproductive age.(7) To identify pregnant women with disease more rigorously, the diseases of pregnant women were defined as those that were medically treated at the time of pregnancy. Information was collected through self-reports, medical record transcripts, and medication interviews. The targeted diseases included allergic diseases, such as asthma, anemia, diabetes mellitus, dyslipidemia, epilepsy, gastric or duodenal ulcers, 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), mental disorders, rheumatic or collagen diseases, and thyroid disease. Having an episode of domestic violence, substance abusing, being obese (BMI ≥25), and being thin (BMI <18.5) were each defined as one disease. We used maternal pre-pregnancy body weight data for analysis. Pregnant women with two or more of these diseases during pregnancy were defined as having multimorbidities.

Assessment of neurodevelopment of offspring

Score results from the Japanese version of the ASQ-3 (Ages and Stages Questionnaires, Third Edition: Infant Development Test) at 6 months, 1 year, 1.5 years, 2 years, 2.5

years and, 3 years, 3.5 years, and 4 years were used to evaluate neurodevelopmental measures.(15) These scores were obtained by mailed questionnaire survey filled by caregivers. Neurodevelopmental assessments were performed in the domains of communication, gross motor, fine motor, problem solving, and personal-social. Offspring with scores below the cut-off were defined as having neurodevelopmental delays. The cut-off values were those reported in the Japanese validation version.(14)

Covariates

The covariates were: maternal age at birth, parity, alcohol consumption status, smoking status, educational attainment, household income, and sex of the child; they were selected based on previous studies.(7,10)

Statistical analysis

This study used the dataset jecs-ta-20190930 and jecs-qa-20210401 from JECS. STATA ® (MP17) and R ® (version 4.2.2) were used for statistical analysis. Multivariate logistic regression analysis was performed to determine the adjusted odds ratios (ORs). The objective variable was neurodevelopment of the offspring, and the explanatory variable was multimorbidity in pregnant women. The covariates were:

maternal age at birth, alcohol consumption status, smoking status, educational attainment, household income, sex of the child, and number of births. Multiple imputation methods were performed using R to impute the missing values. Other analyses were performed using the STATA software.

RESULTS

The characteristics of the pregnant women analyzed in this study are presented in Table 1. Pregnant women with multimorbidity, single disease, and no disease accounted for 3.6% (n = 3,001), 30.6% (n = 25,341), and 65.8% (n = 54,535), respectively. Household income of 2–7.99 million/year was accounted for 84.7%; n = 70,184. In total, 51.4% (n = 42,563) and 48.6% (n = 40,314) of the offspring were male and female, respectively. After pregnancy, 4.1 % (n = 3, 408) and 2.7 % (n = 2, 253) of pregnant women had smoking and drinking habits, respectively.

Table 1. Characteristics of pregnant women and their offspring (n = 82,877)

Characteristics		n		%
Number of coexist disease				
	0	54,535		65.8
	1	25,341		30.6
	≥2	3,001		3.6
Mother age at birth				
	<24	7,815		9.4
	25-29	22,721		27.4

	30-34	29,555		35.7
	35-39	18,940		22.9
	≥40	3,846		4.6
Parity				
	0	36,302		43.8
	1	30,646		37.0
	≥2	15,929		19.2
Mother education				
	Junior high school	3,630		4.4
	High school	25,917		31.3
	Vocational junior or technical college	35,323		42.6
	≥University	18,007		21.7
Maternal smoking habits				
	Non-smoking or exit-smoking before pregnancy	68,145		82.2
	Exit-smoking after pregnancy	11,324		13.7
	Still-smoking	3,408		4.1
Maternal drinking habits				
	Non-drinker	41,481		50.1
	Exit drinking after pregnancy	39,143		47.2
	drinking	2,253		2.7
Annual household income (10,00 JPY)				
	<200	4,193		5.1
	200-399	28,476		34.4
	400-599	28,663		34.6
	600-799	13,045		15.7
	800-999	5,233		6.3
	1000-1199	1,870		2.3
	1200-1499	735		0.9
	1500-1999	427		0.5
	≥2000	235		0.3
Child sex				
	boys	42,563		51.4
	girls	40,314		48.6

The prevalence of 23 maternal diseases are described in supplemental table 1. Maternal underweight (BMI <18.5) (15.6%) was the most frequently observed chronic conditions, followed by maternal obesity (BMI ≥25) (10.7%). The most frequent diseases on medication were allergic diseases (3.1%), other sexually transmitted diseases (1.3%), anemia (0.7%), mental disorders (0.7%) and thyroid disease (0.7%).

The prevalence of neurodevelopmental delay in offspring are presented in Table 2. The prevalence of communication delays at 6 months and 1 year was significantly lower than that of the others.

Table 2. Prevalence of neurodevelopment delay of offspring

Age	Number of maternal comorbidity	Communication	Gross motor	Fine motor	Problem solving	Personal-social
		n (%)	n (%)	n (%)	n (%)	n (%)
6 months	0	318 (0.4)	5,540 (6.7)	2,788 (3.4)	5,675 (6.8)	1,898 (2.3)
	1	123 (0.1)	2,603 (3.1)	1,237 (1.5)	2,596 (3.1)	891 (1.1)
	≥2	19 (0.02)	316 (0.4)	137 (0.2)	334 (0.4)	101 (0.1)
1 year	0	54 (0.1)	2,711 (3.3)	2,743 (3.3)	2,478 (3.0)	566 (0.7)
	1	31 (0.04)	1,324 (1.6)	1,383 (1.7)	1,256 (1.5)	282 (0.3)
	≥2	6 (0.01	148 (0.2)	154 (0.2)	142 (0.2)	57 (0.1)
1 half years	0	1,091 (1.3)	2,138 (2.6)	2,000 (2.4)	1,871 (2.2)	1,209 (1.5)
	1	528 (0.6)	1,100 (1.3)	984 (1.2)	939 (1.1)	564 (0.7)
	≥2	76 (0.1)	148 (0.2)	156 (0.2)	168 (0.2)	78 (0.1)
2 years	0	1,851 (2.2)	2,816 (3.4)	1,060 (1.3)	2,106 (2.5)	1,400 (1.7)
	1	1,048 (1.3)	1,474 (1.8)	590 (0.7)	1,004 (1.2)	706 (0.9)
	≥2	147 (0.2)	176 (0.2)	84 (0.1)	122 (0.1)	99 (0.1)
2 half years	0	2,445 (3.0)	2,042 (2.5)	2,696 (3.3)	2,708 (3.3)	1,634 (2.0)
	1	1,376 (1.7)	1,086 (1.3)	1,389 (1.7)	1,445 (1.7)	860 (1.0)
	≥2	199 (0.2)	132 (0.2)	186 (0.2)	187 (0.2)	112 (0.1)
3 years	0	1,901 (2.3)	2,037 (2.5)	3,492 (4.2)	3,406 (4.1)	1,603 (1.9)
	1	1,030 (1.2)	1,102 (1.3)	1,843 (2.2)	1,723 (2.2)	861 (1.0)
	≥2	164 (0.2)	144 (0.2)	245 (0.3)	269 (0.3)	122 (0.1)
3 half years	0	2,873 (3.5)	2,020 (2.4)	2,522 (3.0)	2,659 (3.2)	2,130 (2.6)
	1	1,467 (1.8)	1,098 (1.3)	1,341 (1.6)	1,508 (1.8)	1,171 (1.4)
	≥2	219 (0.3)	155 (0.2)	182 (0.2)	218 (0.3)	154 (0.2)
4 years	0	2,157 (2.6)	2,597 (3.1)	3,038 (3.7)	1,733 (2.1)	2,629 (3.2)
	1	1,118 (1.3)	1,347 (1.6)	1,651 (2.0)	977 (1.2)	1,362 (1.6)
	≥2	166 (0.2)	177 (0.2)	239 (0.3)	145 (0.2)	194 (0.2)

The number of the offsprings tested as well as the mean ASQ-3 scores at each time point in the offspring those were analyzed and those who were excluded are shown in supplemental table 2. The number of the offsprings tested at 6 months and 4 years were 74,195 and 65,705, respectively. The number of the offsprings tested at 6 months and 4 years were 9,642 and 9,019, respectively. The examination rates in offsprings who were excluded were lower overall. The number of the offsprings tested tended to decrease with age in both groups. The difference in the mean scores of the offsprings excluded from the mean scores of those included ranged from -2.44 to 0.11. The mean scores in the offspring who were excluded were lower from 6 months to 4 years in most time points. The ASQ-3 scores and the number of the offsprings by categories of the number of tests at each time point are shown in the supplemental table 3. The Offsprings were categorized into three groups: until 4 years, tested in all time points, 1 to 3 times, and 4 to 7 times. The number of the offsprings tested at all time points, 4 to 7 times, and 1 to 3 times was 46,766, 26,578, and 9,530 respectively. The number of the offsprings tended to decrease with age in groups tested less frequently. There was a particularly large decrease in the group tested 1 to 3 times. The difference in ASQ-3 scores of the groups tested less frequently from those of the group tested in all time

points ranged from -1.62 to 3.37. Comparing the group tested in all time points, the groups tested less frequently tended to have higher scores until 2 years and lower scores after 2.5 years. The results of the multivariate logistic regression analysis conducted on the number of comorbidities in pregnant women and the neurodevelopment of offspring are shown in Table 3 and Figure 2. Except at 6 months, the ORs were more than 1 for any of the following items: communication, gross motor, fine motor, problem solving, and personal and social. The ORs at 6 months were lower than those at other ages for all items, both single disease comorbidity and multimorbidity. ORs tended to be higher with increasing age of the offspring, and the ORs for all items were higher at 4 years than at 6 months for both single-disease coexistence and multimorbidity. The ORs for single disease comorbidities ranged from 0.85 (95% CI 0.69–1.05) to 1.28 (95% Cl 0.82–1.99). The OR range for multimorbidity was 0.95 (95% CI 0.80–1.14) to 2.29 (95% CI 0.98–5.36), and that at 4 years of age was 1.30 (95% CI 1.11–1.52) to 1.42 (95% CI 1.19–1.69) for all domains.

Table 3. Adjusted odds ratio for developmental delay of offspring for multimorbidity during pregnancy by logistic regression

Age	Number of maternal comorbidity	Communication	Gross motor	Fine motor	Problem solving	Personal-social
		Adjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)
6 months	1	0.85 (0.69–1.05)	1.03 (0.98–1.08)	0.99 (0.92–1.06)	1.01 (0.96–1.06)	1.02 (0.94–1.11)
	≥2	1.14 (0.71–1.81)	1.08 (0.96–1.22)	0.95 (0.8–1.14)	0.99 (0.86–1.11)	0.99 (0.8–1.21)
1 year	1	1.28 (0.82–1.99)	1.09 (1.02–1.16)	1.10 (1.03–1.18)	1.08 (1.01–1.16)	1.08 (0.94–1.25)
	≥2	2.29 (0.98–5.36)	1.08 (0.91–1.28)	1.05 (0.89–1.24)	1.32 (1.12–1.55)	1.90 (1.44–2.50)
1 half years	1	1.04 (0.94–1.16)	1.13 (1.05–1.22)	1.05 (0.97–1.14)	1.13 (1.04–1.22)	1.02 (0.92–1.13)
	≥2	1.29 (1.02–1.64)	1.34 (1.13–1.59)	1.42 (1.20–1.68)	1.32 (1.09–1.57)	1.23 (0.97–1.56)
2 years	1	1.21 (1.12–1.30)	1.15 (1.08–1.23)	1.19 (1.08–1.32)	1.04 (0.96–1.12)	1.09 (0.99–1.19)
	≥2	1.42 (1.19–1.69)	1.21 (1.03–1.41)	1.42 (1.13–1.78)	1.1 (0.9–1.32)	1.31 (1.06–1.61)
2 half years	1	1.19 (1.11–1.27)	1.17 (1.09–1.26)	1.11 (1.04–1.19)	1.14 (1.07–1.22)	1.14 (1.04–1.24)
	≥2	1.42 (1.22–1.65)	1.26 (1.05–1.51)	1.28 (1.09–1.49)	1.23 (1.05–1.44)	1.26 (1.04–1.54)
3 years	1	1.14 (1.05–1.23)	1.19 (1.10–1.28)	1.13 (1.06–1.19)	1.12 (1.06–1.19)	1.13 (1.04–1.24)
	≥2	1.48 (1.25–1.75)	1.37 (1.15–1.63)	1.26 (1.10–1.45)	1.39 (1.22–1.59)	1.33 (1.10–1.61)
3 half years	1	1.04 (0.98–1.11)	1.18 (1.10–1.28)	1.12 (1.04–1.20)	1.19 (1.11–1.27)	1.18 (1.09–1.27)
	≥2	1.24 (1.07–1.44)	1.46 (1.23–1.73)	1.26 (1.07–1.47)	1.42 (1.22–1.64)	1.30 (1.09–1.54)
4 years	1	1.10 (1.02–1.18)	1.13 (1.06–1.21)	1.15 (1.08–1.22)	1.18 (1.08–1.27)	1.11 (1.03–1.18)
	≥2	1.35 (1.14–1.59)	1.30 (1.11–1.52)	1.37 (1.19–1.58)	1.42 (1.19–1.69)	1.32 (1.14–1.54)

Models were adjusted for maternal age at birth, parity, history of alcohol consumption, history of smoking, maternal educational attainment, sex of child, household income, and sex of child.

DISCUSSION

This investigation showed significant associations between multimorbidities in pregnant women and delayed neurodevelopment in the offspring. The ORs were higher for most of the neurodevelopmental items in pregnant women with multimorbidities than in those with a single disease. This study is the first to highlight the significance of the association between multimorbidity in pregnant women and the neurodevelopment in the offspring, despite the existence of reports on the association between specific diseases, such as asthma, chronic inflammatory arthritis, depression, thyroid conditions, diabetes, and epilepsy, in pregnant women and the neurodevelopment of their children.(8,16–18) As the number of comorbidities in pregnant women increases, the factors contributing to neurodevelopmental delay in the offspring may increase. In the future, health education and treatment in terms of the number of comorbidities during pregnancy should be considered.

The ORs for neurodevelopmental delay increased with the increase in the offspring's age. This may have been caused by the increasing accuracy of the assessment as the offspring aged. An accurate assessment of neurodevelopment cannot be made until the child has grown to a certain age.(19) Parents' assessments of their

children's neurodevelopment may not be established until a certain period of parenting time. Neurodevelopmental delays may have been caused by social factors.(20) It has been reported that depressed mothers tend to form family environments that are socially and economically disadvantageous to their children.(21) Pregnant women with multimorbidities and certain mental diseases may have tended to form socioeconomically undesirable family environments.(22) Further, a great deal of the brain's ultimate structure and capacity is shaped up to 3 years of age.(11) The maternal immune activation may be caused by comorbidities during pregnancy, and components of the maternal immune system such as microglia and cytokines produced by microglia may trigger inappropriate fetal immune responses and may lead to neurodevelopment delay in the future.(23) Neurodevelopmental delays in children may have gradually appeared as a result of multiple factors such as the postnatal brain development process, the undesirable family environment, and the caregiver's assessments of their children. Future research should take into account the prospect that factors such as children's birthweight and/or gestational age at birth, nutritional status, Apgar score, and maternal psychological status can be intermediate variables in the association between multimorbidity and neurodevelopmental delay.

This study has few limitations. First, Pregnant women with diagnoses but no

medication were not included in the disease sample in this study, with the exception of domestic violence, obese, and skinny women. The criterion for disease was defined as the presence of medication; the number of pregnant women with disease may have been higher if the study had been conducted using different criteria. Some have criticized the definition of multimorbidity as simply having more than one disease, which would include a large population.(24) In the future, a definition of multimorbidity that is suitable for the target community will be required since the significant diseases and conditions vary depending on the target population.(24) Second, it was difficult in this study to discuss the biological mechanisms of the association between multimorbidity and neurodevelopmental delay. The association between various diseases and neurodevelopmental delays has been reported in previous studies.(8,16–18,25) Further studies on disease characteristics and disease combinations may allow for hypotheses to be made regarding the biological mechanisms underlying the association between multimorbidity and neurodevelopmental delay. Third, as participants in the JECS were only collaborators, selection bias may have occurred.(15) The prevalence of multimorbidity and the results of the association between multimorbidity and neurodevelopmental delay might have been different if the study design included pregnant women who did not participate in the JECS. The number of pregnant women

with multimorbidities would increase and the results of the effects on the neurodevelopment of the children might be different if all pregnant women and children registered in the administration were included in the study. Fourth, we didn't use the data on maternal situation after delivery. Incomplete questionnaire responses were reported to be influenced by maternal situation after delivery as health status, number of siblings, partner, and primary caregiver.(26,27) The ASQ-3 scores of the offsprings who were excluded were lower than those of the offsprings included in most time points. In the analyzed population, the changes in the ASQ-3 scores of the offspring tested less frequently differed from those of the offspring tested at all time points. Except for the group tested at all time points, the number of the offspring tested tended to decrease with age. It was difficult to examine the association between incomplete responses and the ASQ-3 scores in this study. In the future, we need to consider studies with regard to incomplete participants and neurodevelopmental delay of offsprings.

Previous reports on multimorbidities in pregnant women have focused on its prevalence and impact on pregnant women themselves.(5–7) This study is a new report in terms of the effect of multimorbidity in pregnant women on their offspring and provides important recommendations regarding the health of pregnant women.

This study demonstrated an association between multimorbidities in pregnant

women and neurodevelopmental delays in their offspring in Japan. To clarify its mechanisms and effects, more researches need to be done in many regions of the world with different economic, geographic, and racial conditions.

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Contributors

TA and YaS designed this study. JECS collected the data and obtained funding. YaS, EY, KNag, ST, YI, CM, SI, and RK collected the data. TA and YaS conducted the data analysis. TA, YaS, EY, YuS, KNak, YK, KNag, ST, YI, HI, TY, CM, SI, and RK contributed to data interpretation. TA, YaS, EY, YuS, KNak, YK, KNag, ST, YI, HI, TY, CM, SI, RK,and the JECS Group conducted critical reviews. TA drafted the manuscript. YaS made critical revisions. All the authors have reviewed and commented on the manuscript. All the authors approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

Patient and public involvement

The patients and/or the public were not involved in the design, conduct, reporting, or dissemination of this study.

Patient consent for publication

Not applicable.

Ethics approval

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

Provenance and peer review

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Data availability statement

Data are unsuitable for public deposition due to ethical restrictions and legal framework of Japan. It is prohibited by the Act on the Protection of Personal Information (Act No. 57 of 30 May 2003, amendment on 9 September 2015) to publicly deposit the data containing personal information. Ethical Guidelines for Medical and Health Research Involving Human Subjects enforced by the Japan Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare also restricts the open sharing of the epidemiologic data. All inquiries about access to data should be sent to: jecs-en@nies.go.jp. The person responsible for handling enquiries sent to this e-mail address is Dr Shoji F. Nakayama, JECS Programme Office, National Institute for Environmental Studies.

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Figure legends

Figure 1. Fetal records selection flow chart.

Figure 2. Adjusted odds ratio for developmental delay of offspring for multimorbidity during pregnancy by logistic regression.

Models were adjusted for maternal age at birth, parity, history of alcohol consumption, history of smoking, maternal educational attainment, sex of child, household income, and sex of child. Error bars indicate 95% confidence intervals.

*** 95% confidence interval: 0.98–5.3**

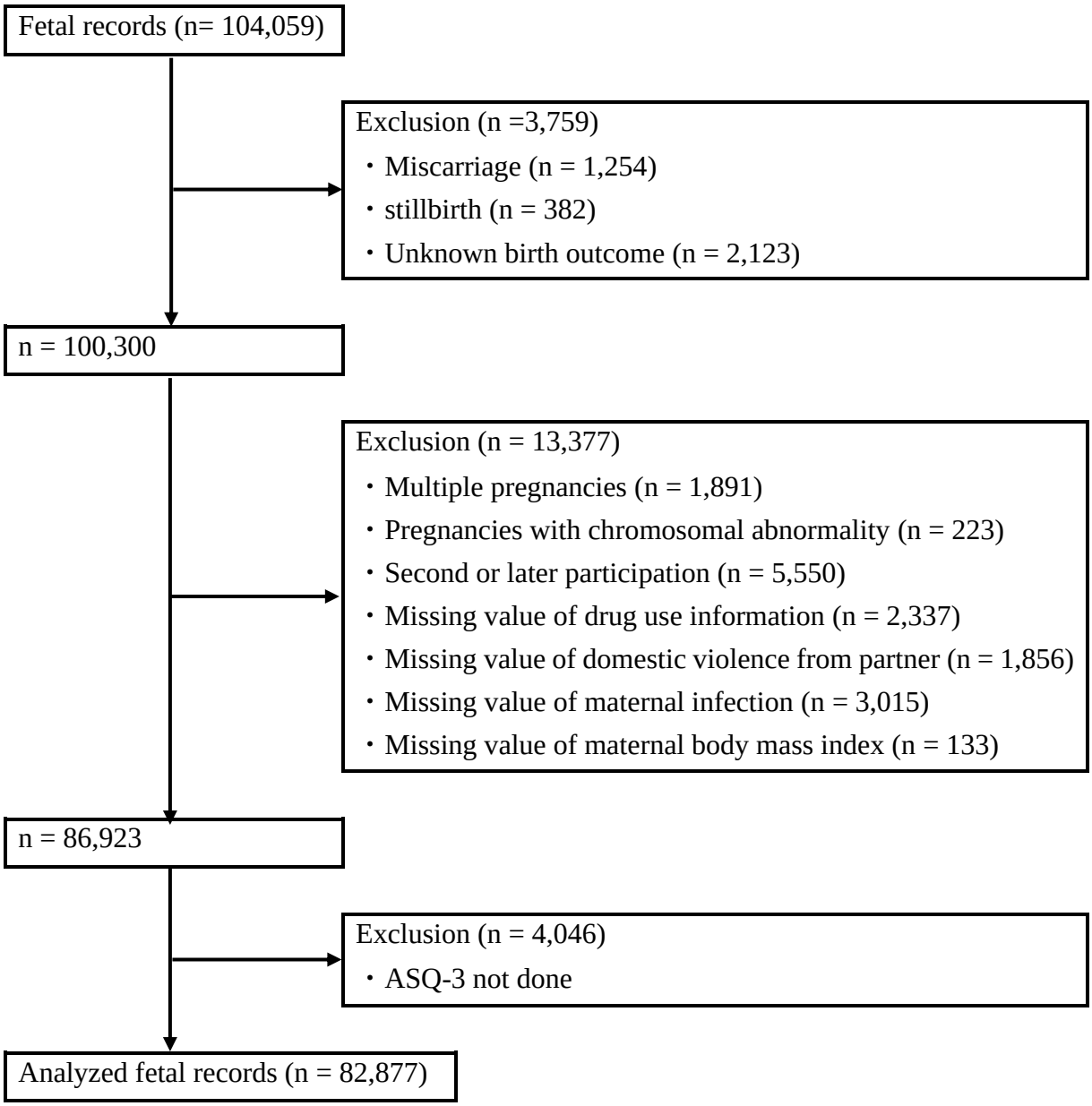

Figure 1. Fetal records selection flow chart.

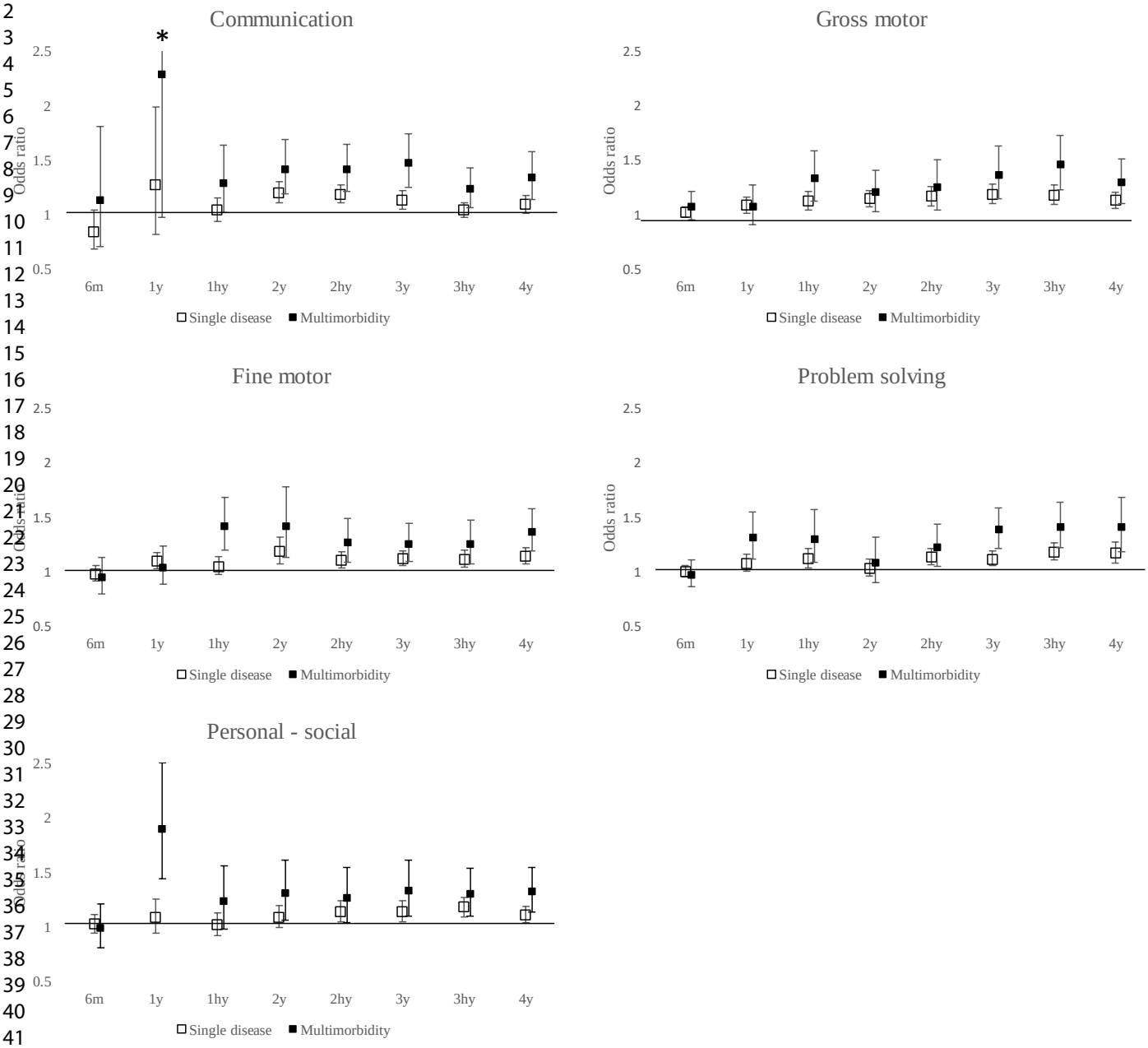

Figure 2. Adjusted odds ratio for developmental delay of offspring for multimorbidity during pregnancy by logistic regression.

Models were adjusted for maternal age at birth, parity, history of alcohol consumption, history of smoking, maternal educational attainment, sex of child, household income, and sex of child. Error bars indicate 95% confidence intervals.* 95% confidence interval: 0.98–5.3

Supplemental Table 1. Prevalence of 23 maternal diseases

Condition	n	%
Abnormal pre-pregnancy BMI		
Underweight (BMI <18.5 kg/m2)	12,889	15.6
Obesity (BMI >25.0 kg/m2)	8,848	10.7
Allergic disease	2,557	3.1
Anaemia	592	0.7
Diabetes mellitus	124	0.2
Domestic violence	3,632	4.4
Dyslipidaemia	6	0.01
Epilepsy	122	0.2
Gastric or duodenal ulcer	285	0.3
Heart disease	7	0.01
Hepatitis	5	0.01
HIV infection	7	0.01
Hypertension	83	0.1
Inflammatory bowel disease	16	0.02
Kidney disease	17	0.02
Malignancy	0	0
Migraine	41	0.05
Neurological disease	0	0
Other sexually transmitted diseases	1,089	1.3
Mental disorder	550	0.7
Rheumatic or collagen disease	91	0.1
Substance abuse	1	0.001
Thyroid disease	614	0.7

BMI, body mass index.

Supplemental Table 2. The mean ASQ-3 scores and the number of offspring analyzed (n = 82,877) and those excluded (n = 11,927)

Age	Group	Communication				Gross motor				Fine motor				problem solving				Personal-social			
		Mean score	δ*	n	%**	Mean score	δ*	n	%**	Mean score	δ*	n	%**	Mean score	δ*	n	%**	Mean score	δ*	n	%**
6 months	Excluded	46.14	-0.55	9,636	80.8	32.54	-1.07	9,637	80.8	39.81	-1.11	9,605	80.5	42.80	-1.44	9,629	80.7	32.03	-2.44	9,611	80.6
	Included	46.69		74,135	89.5	33.61		74,126	89.4	40.92		73,928	89.2	44.24		74,137	89.5	34.47		74,043	89.3
1 year	Excluded	36.57	-1.30	9,236	77.4	42.01	-0.90	9,241	77.5	47.16	-1.19	9,227	77.4	42.47	-1.89	9,223	77.3	35.88	-1.34	9,204	77.2
	Included	37.86		70,443	85.0	42.90		70,445	85.0	48.35		70,416	85.0	42.36		70,347	84.9	37.22		70,229	84.7
1.5 years	Excluded	32.27	-0.79	8,669	72.7	53.98	-0.61	8,669	72.7	49.36	-0.54	8,664	72.6	42.06	-1.44	8,613	72.2	47.86	-0.08	8,659	72.6
	Included	33.06		66,543	80.3	54.60		66,563	80.3	49.90		66,525	80.3	42.48		66,133	79.8	47.94		66,528	80.3
2 years	Excluded	43.91	-1.19	9,632	80.8	52.81	-0.94	9,630	80.7	49.47	-0.35	9,626	80.7	48.58	-1.25	9,603	80.5	46.14	-0.20	9,620	80.7
	Included	45.11		69,541	83.9	53.75		69,542	83.9	49.82		69,478	83.8	48.83		69,346	83.7	46.34		69,435	83.8
2.5 years	Excluded	51.99	-0.94	9,377	78.6	53.86	-0.90	9,389	78.7	46.34	-0.90	9,337	78.3	49.79	-1.74	9,360	78.5	50.07	0.01	9,370	78.6
	Included	52.92		67,899	81.9	54.75		67,915	81.9	47.25		67,597	81.6	50.52		67,749	81.7	50.06		67,809	81.8
3 years	Excluded	52.28	-0.88	9,663	81.0	54.50	-0.96	9,657	81.1	48.07	-1.15	9,645	80.9	51.14	-1.69	9,597	80.5	50.36	0.03	9,661	81.0
	Included	53.16		69,466	83.8	55.47		69,566	83.9	49.21		69,291	83.6	51.83		68,907	83.1	50.33		69,404	83.7
3.5 years	Excluded	53.44	-0.65	9,222	77.3	55.77	-0.67	9,226	77.4	52.36	-0.69	9,211	77.2	53.91	-1.61	9,163	76.8	54.52	-0.18	9,214	77.3
	Included	54.09		67,447	81.4	56.44		67,398	81.3	53.05		67,361	81.3	54.53		67,140	81.0	54.70		67,358	81.3
4 years	Excluded	52.99	-0.81	8,939	74.9	53.76	-0.58	8,982	75.3	50.91	-0.77	8,983	75.3	54.06	-1.45	8,966	75.2	53.25	-0.27	9,002	75.5
	Included	53.80		65,162	78.6	54.34		65,426	78.9	51.68		65,429	78.9	54.51		65,311	78.8	53.52		65,505	79.0

*Difference in the mean scores from those of the offspring included at each point. **Percentage of total group population.

Supplemental Table 3. The ASQ scores and the number of offspring by testing times from 6 months to 4 years

Age	Testing times	Communication				Gross motor				Fine motor				Problem solving				Personal-social			
		Mean score	n	δ*	%**	Mean score	n	δ*	%**	Mean score	n	δ*	%**	Mean score	n	δ*	%**	Mean score	n	δ*	%**
6 months	1-3	47.39	6,285	0.94	65.9	35.57	6,284	2.57	65.9	43.51	6,271	3.37	65.8	46.40	6,290	2.76	66.0	36.69	6,281	2.90	65.9
	4-7	46.98	21,111	0.52	79.4	34.39	21,110	1.39	79.4	41.86	21,043	1.73	79.2	44.93	21,117	1.30	79.5	35.32	21,072	1.53	79.3
	8	46.46	46,739		99.9	33.00	46,732		99.9	40.14	46,614		99.7	43.64	46,730		99.9	33.79	46,690		99.8
1 year	1-3	40.28	4,028	3.01	42.3	44.55	4,025	2.07	42.2	49.27	4,028	1.15	42.3	44.09	4,018	2.22	42.2	39.19	4,004	2.47	42.0
	4-7	38.78	19,665	1.52	74.0	43.58	19,666	1.10	74.0	48.70	19,645	0.58	73.9	43.18	19,614	1.32	73.8	37.99	19,582	1.26	73.7
	8	37.27	46,750		99.9	42.48	46,754		99.9	48.12	46,743		99.9	41.86	46,715		99.9	36.73	46,643		99.7
1.5 years	1-3	35.21	2,367	2.55	24.8	54.84	2,368	0.36	24.8	50.46	2,364	0.70	24.8	43.53	2,342	1.34	24.6	49.52	2,363	1.91	24.8
	4-7	33.86	17,431	1.20	65.6	54.85	17,434	0.37	65.6	50.19	17,427	0.43	65.6	43.10	17,278	0.91	65.0	48.60	17,424	0.99	65.6
	8	32.65	46,745		99.9	54.49	46,761		100.0	49.76	46,734		99.9	42.19	46,513		99.5	47.61	46,741		99.9
2 years	1-3	45.71	1,719	0.72	18.0	54.29	1,717	0.56	18.0	50.42	1,720	0.68	18.0	49.42	1,710	0.60	17.9	47.14	1,714	0.91	18.0
	4-7	45.30	21,067	0.31	79.3	53.75	21,066	0.02	79.3	49.94	21,048	0.20	79.2	48.80	20,982	-0.01	78.9	46.52	21,028	0.29	79.1
	8	44.99	46,755		99.9	53.73	46,759		99.9	49.74	46,710		99.9	48.82	46,654		99.8	46.23	46,693		99.8
2.5 years	1-3	52.41	1,217	-0.62	12.8	54.66	1,217	-0.12	12.8	47.09	1,200	-0.23	12.6	50.68	1,206	0.12	12.7	50.75	1,211	0.77	12.7
	4-7	52.70	19,941	-0.33	75.0	54.69	19,945	-0.09	75.0	47.08	19,809	-0.24	74.5	50.44	19,873	-0.11	74.8	50.21	19,912	0.22	74.9
	8	53.03	46,741		99.9	54.78	46,753		99.9	47.32	46,588		99.6	50.55	46,670		99.8	49.98	46,686		99.8
3 years	1-3	52.96	1,369	-0.29	14.4	55.69	1,374	0.21	14.4	49.17	1,355	-0.12	14.2	52.17	1,336	0.29	14.0	51.13	1,365	0.89	14.3
	4-7	52.98	21,417	-0.26	80.6	55.44	21,462	-0.03	80.8	49.06	21,339	-0.22	80.3	51.70	21,184	-0.18	79.7	50.47	21,406	0.22	80.5
	8	53.25	46,680		99.8	55.48	46,730		99.9	49.29	46,597		99.6	51.88	46,387		99.2	50.24	46,633		99.7
3.5 years	1-3	53.78	1,080	-0.31	11.3	56.25	1,078	-0.20	11.3	52.58	1,077	-0.53	11.3	53.88	1,065	-0.70	11.2	54.51	1,079	-0.15	11.3
	4-7	54.13	19,641	0.04	73.9	56.41	19,618	-0.05	73.8	52.93	19,593	-0.18	73.7	54.44	19,480	-0.13	73.3	54.83	19,613	0.17	73.8
	8	54.09	46,726		99.9	56.46	46,702		99.9	53.11	46,691		99.8	54.58	46,595		99.6	54.66	46,666		99.8
4y ears	1-3	53.77	909	0.01	9.5	54.40	912	0.09	9.6	51.30	913	-0.46	9.6	53.99	899	-0.57	9.4	53.36	913	-0.12	9.6
	4-7	53.93	17,807	0.17	67.0	54.41	17,900	0.09	67.3	51.51	17,895	-0.25	67.3	54.42	17,862	-0.14	67.2	53.63	17,946	0.14	67.5
	8	53.76	46,446		99.3	54.32	46,614		99.7	51.76	46,621		99.7	54.56	46,550		99.5	53.49	46,646		99.7

*Difference in the mean scores from those of the offspring tested all at each point. **Percentage of total group population.

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	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3,4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5,6
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3,7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7,8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	7,8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-10
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	7,8
Bias	9	Describe any efforts to address potential sources of bias	19
Study size	10	Explain how the study size was arrived at	5,7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10,11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10
		(*b*) Describe any methods used to examine subgroups and interactions	10
		(*c*) Explain how missing data were addressed	10,11
		(*d*) If applicable, explain how loss to follow-up was addressed	-
		(*e*) Describe any sensitivity analyses	-
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	7,8
		(b) Give reasons for non-participation at each stage	7,8
		(c) Consider use of a flow diagram	7,8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11,12
		(b) Indicate number of participants with missing data for each variable of interest	-
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	13-15

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	15,16 - -
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	17
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	18,19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19,20
Generalisability	21	Discuss the generalisability (external validity) of the study results	20
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21,22

*Give information separately for exposed and unexposed groups.

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

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Association between maternal multimorbidity and neurodevelopment of offspring: a prospective birth cohort study from the Japan Environment and Children's Study

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Title: Association between maternal multimorbidity and neurodevelopment of offspring: a prospective birth cohort study from the Japan Environment and Children's Study

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ABSTRAT

Objectives: To investigate the association between multimorbidity during pregnancy and neurodevelopmental delay in offspring using data from a Japanese nationwide birth cohort study.

Design: This study was a prospective birth cohort study.

Setting: This study population included 104,059 fetal records who participated in The Japan Environment and Children's Study (JECS) from 2011 to 2014.

Participants: Pregnant women whose children had undergone developmental testing were included in this analysis.

Primary and secondary outcome measures: Neurodevelopment of offspring were assessed using the Japanese version of the Ages and Stages Questionnaire, third edition (J-ASQ-3), comprising five developmental domains. The number of comorbidities among the pregnant women was categorized as zero, single disease, or multimorbidity (two or more diseases). Maternal chronic conditions included in multimorbidity were defined as conditions with high prevalence among women of reproductive age. A multivariate logistic regression analysis was conducted to examine the association between multimorbidity in pregnant women and offspring development.

Results: Pregnant women with multimorbidity, single disease, and no disease accounted for 3.6%, 30.6%, and 65.8%, respectively. The odds ratios (ORs) for

neurodevelopmental impairment during the follow-up period were similar for infants of mothers with no disease comorbidity and those with a single disease comorbidity. However, the ORs for neurodevelopmental impairment were significantly higher for children born to mothers with multimorbidity compared with those born to healthy mothers.

Conclusion: An association was observed between the number of comorbidities in pregnant women and developmental delay in offspring. Pregnant women with multimorbidities are at a higher risk of neurodevelopmental delays in their offspring. Further research is required in this regard in many other regions of the world.

Keywords

pregnant, women, multimorbidity, Japan, offspring, neurodevelopment, delay

Word counts

Abstract: 267 words; Main text, 2,568 words

Tables/figures: 3 tables/2 figures

References: 27 references

Strengths and limitations of this study

- The study size was adequate for effective investigation.
- Neurodevelopmental progress was assessed in detail using the results of eight points (6 months, 1 year, 1.5 year, 2 years, 2.5 years, 3 years, 3.5 years, and 4 years).
- Chronic diseases that were diagnosed but not treated were ruled out.
- Infants were unable to communicate well, which renders accurate assessment of their neurodevelopment difficult.

INTRODUCTION

Multimorbidity is defined as the coexistence of two or more chronic diseases, whether physical or mental, in the same individual.(1) Multimorbidity is considered one of the principal challenges in older people as the incidence of chronic diseases such as hypertension, dyslipidemia, diabetes, cardiac disease, and malignant tumors, increases with age. Therefore, many studies have focused on older patients with multimorbidities.(2,3) However, diseases such as asthma, arthritis, mental disorders, and HIV can also occur in young people. There are few studies on multimorbidity in young people,(4) including pregnant women.(5,6) Maternal physical morbidities, such

as hypertension, kidney disease, and systemic lupus erythematosus, are potential risk factors for preterm birth (PTB) and low birth weight infants (LBW).(7) Moreover, maternal mental and social morbidities have also been associated with PTB and LBW.(7) Previous studies also reported the relationship between maternal environment such as maternal asthma, maternal intake of fats, maternal and cord blood Manganese levels and child development.(8–10)

Infancy is considered to be the period in which language, cognition, motor skills, and socioemotional domains form the basis for subsequent social participation.(11) It is essential to receive appropriate support, early detection, and intervention during this period.(12) Although maternal nutritional status, certain diseases, and blood substances can affect the neurodevelopment of offspring(8–11), the impacts of multimorbidity in pregnant women on the neurodevelopment of offspring has not been extensively studied.(5,6) A major difference between previous reports and this study was the investigation of the association between multiple diseases of pregnant women and child neurodevelopment; previous reports have mainly focused on the relationship between a single disease or single substance in pregnant women and child neurodevelopment.

The present study aimed to investigate the association between multimorbidity

during pregnancy and neurodevelopmental delay in offspring (every 6 months from birth to age 4 years) using data from an ongoing nationwide birth cohort, namely the Japan Environment and Children's Study (JECS)(13); the neurodevelopment of the participants was evaluated using the Japanese version of the Ages and Stages Questionnaires, Third Edition: Infant Developmental Examination (ASQ-3).(14)

METHODS

Study population

The JECS is a nationwide and government-funded birth cohort study that started recruiting expecting mothers in January 2011.(13); the primary objective was to investigate environmental factors such as exposure to chemicals and airborne pollutants that can affect children's health and development during the fetal stage and early childhood, in order to help policymakers to formulate measures to safeguard the environment for future generations.(15) The study population included 104,059 fetal records who participated in JECS from 2011 to 2014. A flowchart of the study participants is presented in the Figure 1. The exclusion criteria included: miscarriage, stillbirth, or unknown birth outcomes (n = 2,123). Second, participants with multiple births, pregnancies with chromosomal abnormalities, participated for the second time

and more, and missing information about drug history, domestic violence, maternal infection, or maternal BMI were excluded (n = 13,377). Moreover, pregnant women whose children were not tested using the ASQ-3 once from 6 months to 4 years old (n=4,046) were excluded. Finally, a total of 82,877 pregnant women were included in the analysis.

Ethics

The JECS protocol was reviewed and approved by the Ministry of the Environment's Institutional Review Board on Epidemiological Studies and the Ethics Committees of all participating institutions (No. 100910001).(13) The JECS was performed following the Declaration of Helsinki. All the participants provided written informed consent.

Patient and Public Involvement statement

This study did not involve patients or public.

Assessment of pregnant multimorbidity

In this study, multimorbidity was defined as the coexistence of two or more physical, mental, or social conditions in an individual according to previous reports.(7) Maternal

chronic conditions included in multimorbidity were defined as conditions with high prevalence among women of reproductive age.(7) To identify pregnant women with disease more rigorously, the diseases of pregnant women were defined as those that were medically treated at the time of pregnancy. Information was collected through self-reports, medical record transcripts, and medication interviews. The targeted diseases included allergic diseases, such as asthma, anemia, diabetes mellitus, dyslipidemia, epilepsy, gastric or duodenal ulcers, 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), mental disorders, rheumatic or collagen diseases, and thyroid disease. Having an episode of domestic violence, substance abusing, being obese (BMI ≥25), and being thin (BMI <18.5) were each defined as one disease. We used maternal pre-pregnancy body weight data for analysis. Pregnant women with two or more of these diseases during pregnancy were defined as having multimorbidities.

Assessment of neurodevelopment of offspring

Score results from the Japanese version of the ASQ-3 (Ages and Stages Questionnaires, Third Edition: Infant Development Test) at 6 months, 1 year, 1.5 years, 2 years, 2.5

years and, 3 years, 3.5 years, and 4 years were used to evaluate neurodevelopmental measures.(15) These scores were obtained by mailed questionnaire survey filled by caregivers. Neurodevelopmental assessments were performed in the domains of communication, gross motor, fine motor, problem solving, and personal-social. Offspring with scores below the cut-off were defined as having neurodevelopmental delays. The cut-off values were those reported in the Japanese validation version.(14)

Covariates

The covariates were: maternal age at birth, parity, alcohol consumption status, smoking status, educational attainment, household income, and sex of the child; they were selected based on previous studies.(7,10)

Statistical analysis

This study used the dataset jecs-ta-20190930 and jecs-qa-20210401 from JECS. STATA® (MP17) and R® (version 4.2.2) were used for statistical analysis. Multivariate logistic regression analysis was performed to determine the adjusted odds ratios (ORs). The objective variable was neurodevelopment of the offspring, and the explanatory variable was multimorbidity in pregnant women. The covariates were: maternal age at

birth, alcohol consumption status, smoking status, educational attainment, household income, sex of the child, and number of births. Multiple imputation methods were performed using R to impute the missing values. Other analyses were performed using the STATA software.

RESULTS

The characteristics of the pregnant women analyzed in this study are presented in Table 1. Pregnant women with multimorbidity, single disease, and no disease accounted for 3.6% (n = 3,001), 30.6% (n = 25,341), and 65.8% (n = 54,535), respectively. Household income of 2–7.99 million/year was accounted for 84.7%; n = 70,184. In total, 51.4% (n = 42,563) and 48.6% (n = 40,314) of the offspring were male and female, respectively. After pregnancy, 4.1 % (n = 3, 408) and 2.7 % (n = 2, 253) of pregnant women had smoking and drinking habits, respectively.

Table 1. Characteristics of pregnant women and their offspring (n = 82,877)

Characteristics		n		%
Number of coexist disease				
	0	54,535		65.8
	1	25,341		30.6
	≥2	3,001		3.6
Mother age at birth				
	<24	7,815		9.4
	25-29	22,721		27.4

	30-34	29,555		35.7
	35-39	18,940		22.9
	≥40	3,846		4.6
Parity				
	0	36,302		43.8
	1	30,646		37.0
	≥2	15,929		19.2
Mother education				
	Junior high school	3,630		4.4
	High school	25,917		31.3
	Vocational junior or technical college	35,323		42.6
	≥University	18,007		21.7
Maternal smoking habits				
	Non-smoking or exit-smoking before pregnancy	68,145		82.2
	Exit-smoking after pregnancy	11,324		13.7
	Still-smoking	3,408		4.1
Maternal drinking habits				
	Non-drinker	41,481		50.1
	Exit drinking after pregnancy	39,143		47.2
	drinking	2,253		2.7
Annual household income (10,00 JPY)				
	<200	4,193		5.1
	200-399	28,476		34.4
	400-599	28,663		34.6
	600-799	13,045		15.7
	800-999	5,233		6.3
	1000-1199	1,870		2.3
	1200-1499	735		0.9
	1500-1999	427		0.5
	≥2000	235		0.3
Child sex				
	boys	42,563		51.4
	girls	40,314		48.6

The prevalence of 23 maternal diseases are described in supplemental table 1. Maternal underweight (BMI <18.5) (15.6%) was the most frequently observed chronic conditions, followed by maternal obesity (BMI ≥25) (10.7%). The most frequent diseases on medication were allergic diseases (3.1%), other sexually transmitted diseases (1.3%), anemia (0.7%), mental disorders (0.7%) and thyroid disease (0.7%).

The prevalence of neurodevelopmental delay in offspring are presented in Table 2. The prevalence of communication delays at 6 months and 1 year was significantly lower than that of the others.

Table 2. Prevalence of neurodevelopment delay of offspring

Age	Number of maternal comorbidity	Communication	Gross motor	Fine motor	Problem solving	Personal-social
		n (%)	n (%)	n (%)	n (%)	n (%)
6 months	0	318 (0.4)	5,540 (6.7)	2,788 (3.4)	5,675 (6.8)	1,898 (2.3)
	1	123 (0.1)	2,603 (3.1)	1,237 (1.5)	2,596 (3.1)	891 (1.1)
	≥2	19 (0.02)	316 (0.4)	137 (0.2)	334 (0.4)	101 (0.1)
1 year	0	54 (0.1)	2,711 (3.3)	2,743 (3.3)	2,478 (3.0)	566 (0.7)
	1	31 (0.04)	1,324 (1.6)	1,383 (1.7)	1,256 (1.5)	282 (0.3)
	≥2	6 (0.01	148 (0.2)	154 (0.2)	142 (0.2)	57 (0.1)
1 half years	0	1,091 (1.3)	2,138 (2.6)	2,000 (2.4)	1,871 (2.2)	1,209 (1.5)
	1	528 (0.6)	1,100 (1.3)	984 (1.2)	939 (1.1)	564 (0.7)
	≥2	76 (0.1)	148 (0.2)	156 (0.2)	168 (0.2)	78 (0.1)
2 years	0	1,851 (2.2)	2,816 (3.4)	1,060 (1.3)	2,106 (2.5)	1,400 (1.7)
	1	1,048 (1.3)	1,474 (1.8)	590 (0.7)	1,004 (1.2)	706 (0.9)
	≥2	147 (0.2)	176 (0.2)	84 (0.1)	122 (0.1)	99 (0.1)
2 half years	0	2,445 (3.0)	2,042 (2.5)	2,696 (3.3)	2,708 (3.3)	1,634 (2.0)
	1	1,376 (1.7)	1,086 (1.3)	1,389 (1.7)	1,415 (1.7)	860 (1.0)
	≥2	199 (0.2)	132 (0.2)	186 (0.2)	187 (0.2)	112 (0.1)
3 years	0	1,901 (2.3)	2,037 (2.5)	3,492 (4.2)	3,406 (4.1)	1,603 (1.9)
	1	1,030 (1.2)	1,102 (1.3)	1,843 (2.2)	1,723 (2.2)	861 (1.0)
	≥2	164 (0.2)	144 (0.2)	245 (0.3)	269 (0.3)	122 (0.1)
3 half years	0	2,873 (3.5)	2,020 (2.4)	2,522 (3.0)	2,659 (3.2)	2,130 (2.6)
	1	1,467 (1.8)	1,098 (1.3)	1,341 (1.6)	1,508 (1.8)	1,171 (1.4)
	≥2	219 (0.3)	155 (0.2)	182 (0.2)	218 (0.3)	154 (0.2)
4 years	0	2,157 (2.6)	2,597 (3.1)	3,038 (3.7)	1,733 (2.1)	2,629 (3.2)
	1	1,118 (1.3)	1,347 (1.6)	1,651 (2.0)	977 (1.2)	1,362 (1.6)
	≥2	166 (0.2)	177 (0.2)	239 (0.3)	145 (0.2)	194 (0.2)

The number of the offsprings tested as well as the mean ASQ-3 scores at each time point in the offspring those were analyzed and those who were excluded are shown in supplemental table 2. In the included group, the number of the offsprings tested at 6 months and 4 years were 74,195 and 65,705, respectively. In the excluded group, the number of the offsprings tested at 6 months and 4 years were 9,642 and 9,019, respectively. At each time point, the offsprings were defined as tested if they answered at least one domain of the ASQ-3. The examination rates in offsprings who were excluded were lower overall. The number of the offsprings tested tended to decrease with age in both groups. The difference in the mean scores of the offsprings excluded from the mean scores of those included ranged from -2.44 to 0.11. The mean scores in the offspring who were excluded were lower from 6 months to 4 years in most time points. The ASQ-3 scores and the number of the offsprings by categories of the number of tests at each time point are shown in the supplemental table 3. The Offsprings were categorized into three groups: until 4 years, tested in all time points, 1 to 3 times, and 4 to 7 times. The number of the offsprings tested at all time points, 4 to 7 times, and 1 to 3 times was 46,766, 26,578, and 9,530 respectively. The number of the offsprings tended to decrease with age in groups tested less frequently. There was a particularly large

decrease in the group tested 1 to 3 times. The difference in ASQ-3 scores of the groups tested less frequently from those of the group tested in all time points ranged from -1.62 to 3.37. Comparing the group tested in all time points, the groups tested less frequently tended to have higher scores until 2 years and lower scores after 2.5 years. The results of the multivariate logistic regression analysis conducted on the number of comorbidities in pregnant women and the neurodevelopment of offspring are shown in Table 3 and Figure 2. Except at 6 months, the ORs were more than 1 for any of the following items: communication, gross motor, fine motor, problem solving, and personal and social. The ORs at 6 months were lower than those at other ages for all items, both single disease comorbidity and multimorbidity. ORs tended to be higher with increasing age of the offspring, and the ORs for all items were higher at 4 years than at 6 months for both single-disease coexistence and multimorbidity. The ORs for single disease comorbidities ranged from 0.85 (95% CI 0.69–1.05) to 1.28 (95% Cl 0.82–1.99). The OR range for multimorbidity was 0.95 (95% CI 0.80–1.14) to 2.29 (95% CI 0.98–5.36), and that at 4 years of age was 1.30 (95% CI 1.11–1.52) to 1.42 (95% CI 1.19–1.69) for all domains.

Table 3. Adjusted odds ratio for developmental delay of offspring for multimorbidity during pregnancy by logistic regression

Age	Number of maternal comorbidity	Communication	Gross motor	Fine motor	Problem solving	Personal-social
		Adjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)
6 months	1	0.85 (0.69–1.05)	1.03 (0.98–1.08)	0.99 (0.92–1.06)	1.01 (0.96–1.06)	1.02 (0.94–1.11)
	≥2	1.14 (0.71–1.81)	1.08 (0.96–1.22)	0.95 (0.8–1.14)	0.99 (0.86–1.11)	0.99 (0.8–1.21)
1 year	1	1.28 (0.82–1.99)	1.09 (1.02–1.16)	1.10 (1.03–1.18)	1.08 (1.01–1.16)	1.08 (0.94–1.25)
	≥2	2.29 (0.98–5.36)	1.08 (0.91–1.28)	1.05 (0.89–1.24)	1.32 (1.12–1.55)	1.90 (1.44–2.50)
1 half years	1	1.04 (0.94–1.16)	1.13 (1.05–1.22)	1.05 (0.97–1.14)	1.13 (1.04–1.22)	1.02 (0.92–1.13)
	≥2	1.29 (1.02–1.64)	1.34 (1.13–1.59)	1.42 (1.20–1.68)	1.32 (1.09–1.57)	1.23 (0.97–1.56)
2 years	1	1.21 (1.12–1.30)	1.15 (1.08–1.23)	1.19 (1.08–1.32)	1.04 (0.96–1.12)	1.09 (0.99–1.19)
	≥2	1.42 (1.19–1.69)	1.21 (1.03–1.41)	1.42 (1.13–1.78)	1.1 (0.9–1.32)	1.31 (1.06–1.61)
2 half years	1	1.19 (1.11–1.27)	1.17 (1.09–1.26)	1.11 (1.04–1.19)	1.14 (1.07–1.22)	1.14 (1.04–1.24)
	≥2	1.42 (1.22–1.65)	1.26 (1.05–1.51)	1.28 (1.09–1.49)	1.23 (1.05–1.44)	1.26 (1.04–1.54)
3 years	1	1.14 (1.05–1.23)	1.19 (1.10–1.28)	1.13 (1.06–1.19)	1.12 (1.06–1.19)	1.13 (1.04–1.24)
	≥2	1.48 (1.25–1.75)	1.37 (1.15–1.63)	1.26 (1.10–1.45)	1.39 (1.22–1.59)	1.33 (1.10–1.61)
3 half years	1	1.04 (0.98–1.11)	1.18 (1.10–1.28)	1.12 (1.04–1.20)	1.19 (1.11–1.27)	1.18 (1.09–1.27)
	≥2	1.24 (1.07–1.44)	1.46 (1.23–1.73)	1.26 (1.07–1.47)	1.42 (1.22–1.64)	1.30 (1.09–1.54)
4 years	1	1.10 (1.02–1.18)	1.13 (1.06–1.21)	1.15 (1.08–1.22)	1.18 (1.08–1.27)	1.11 (1.03–1.18)
	≥2	1.35 (1.14–1.59)	1.30 (1.11–1.52)	1.37 (1.19–1.58)	1.42 (1.19–1.69)	1.32 (1.14–1.54)

Models were adjusted for maternal age at birth, parity, history of alcohol consumption, history of smoking, maternal educational attainment, sex of child, household income, and sex of child.

DISCUSSION

This investigation showed significant associations between multimorbidities in pregnant women and delayed neurodevelopment in the offspring. The ORs were higher for most of the neurodevelopmental items in pregnant women with multimorbidities than in those with a single disease. This study is the first to highlight the significance of the association between multimorbidity in pregnant women and the neurodevelopment in the offspring, despite the existence of reports on the association between specific diseases, such as asthma, chronic inflammatory arthritis, depression, thyroid conditions, diabetes, and epilepsy, in pregnant women and the neurodevelopment of their children.(8,16–18) As the number of comorbidities in pregnant women increases, the factors contributing to neurodevelopmental delay in the offspring may increase. In the future, health education and treatment in terms of the number of comorbidities during pregnancy should be considered.

The ORs for neurodevelopmental delay increased with the increase in the offspring's age. This may have been caused by the increasing accuracy of the assessment as the offspring aged. An accurate assessment of neurodevelopment cannot be made until the child has grown to a certain age.(19) Parents' assessments of their

children's neurodevelopment may not be established until a certain period of parenting time. Neurodevelopmental delays may have been caused by social factors.(20) It has been reported that depressed mothers tend to form family environments that are socially and economically disadvantageous to their children.(21) Pregnant women with multimorbidities and certain mental diseases may have tended to form socioeconomically undesirable family environments.(22) Further, a great deal of the brain's ultimate structure and capacity is shaped up to 3 years of age.(11) The maternal immune activation may be caused by comorbidities during pregnancy, and components of the maternal immune system such as microglia and cytokines produced by microglia may trigger inappropriate fetal immune responses and may lead to neurodevelopment delay in the future.(23) Neurodevelopmental delays in children may have gradually appeared as a result of multiple factors such as the postnatal brain development process, the undesirable family environment, and the caregiver's assessments of their children. Future research should take into account the prospect that factors such as children's birthweight and/or gestational age at birth, nutritional status, Apgar score, and maternal psychological status can be intermediate variables in the association between multimorbidity and neurodevelopmental delay.

This study has few limitations. First, Pregnant women with diagnoses but no

medication were not included in the disease sample in this study, with the exception of domestic violence, obese, and skinny women. The criterion for disease was defined as the presence of medication; the number of pregnant women with disease may have been higher if the study had been conducted using different criteria. Some have criticized the definition of multimorbidity as simply having more than one disease, which would include a large population.(24) In the future, a definition of multimorbidity that is suitable for the target community will be required since the significant diseases and conditions vary depending on the target population.(24) Second, it was difficult in this study to discuss the biological mechanisms of the association between multimorbidity and neurodevelopmental delay. The association between various diseases and neurodevelopmental delays has been reported in previous studies.(8,16–18,25) Further studies on disease characteristics and disease combinations may allow for hypotheses to be made regarding the biological mechanisms underlying the association between multimorbidity and neurodevelopmental delay. Third, as participants in the JECS were only collaborators, selection bias may have occurred.(15) The prevalence of multimorbidity and the results of the association between multimorbidity and neurodevelopmental delay might have been different if the study design included pregnant women who did not participate in the JECS. The number of pregnant women

with multimorbidities would increase and the results of the effects on the neurodevelopment of the children might be different if all pregnant women and children registered in the administration were included in the study. Fourth, we didn't use the data on maternal situation after delivery. Incomplete questionnaire responses were reported to be influenced by maternal situation after delivery as health status, number of siblings, partner, and primary caregiver.(26,27) The ASQ-3 scores of the offsprings who were excluded were lower than those of the offsprings included in most time points. In the analyzed population, the changes in the ASQ-3 scores of the offspring tested less frequently differed from those of the offspring tested at all time points. Except for the group tested at all time points, the number of the offspring tested tended to decrease with age. It was difficult to examine the association between incomplete responses and the ASQ-3 scores in this study. In the future, we need to consider studies with regard to incomplete participants and neurodevelopmental delay of offsprings. There was no analysis of data from offspring, such as birth weight, gestational age at birth, nutritional status, and Apgar score, but, as we mentioned above, they were not selected as adjusted variables because we considered them as intermediate variables in the association between multimorbidity and neurodevelopmental delay.

Previous reports on multimorbidities in pregnant women have focused on its

prevalence and impact on pregnant women themselves.(5–7) This study is a new report in terms of the effect of multimorbidity in pregnant women on their offspring and provides important recommendations regarding the health of pregnant women.

This study demonstrated an association between multimorbidities in pregnant women and neurodevelopmental delays in their offspring in Japan. To clarify its mechanisms and effects, more researches need to be done in many regions of the world with different economic, geographic, and racial conditions.

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Contributors

TA and YaS designed this study. JECS collected the data and obtained funding. YaS, EY, KNag, ST, YI, CM, SI, and RK collected the data. TA and YaS conducted the data analysis. TA, YaS, EY, YuS, KNak, YK, KNag, ST, YI, HI, TY, CM, SI, and RK contributed to data interpretation. TA, YaS, EY, YuS, KNak, YK, KNag, ST, YI, HI, TY, CM, SI, RK,and the JECS Group conducted critical reviews. TA drafted the manuscript. YaS made critical revisions. All the authors have reviewed and commented on the manuscript. All the authors approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

Patient and public involvement

The patients and/or the public were not involved in the design, conduct, reporting, or dissemination of this study.

Patient consent for publication

Not applicable.

Ethics approval

The JECS protocol was reviewed and approved by the Ministry of the Environment's Institutional Review Board on Epidemiological Studies and the Ethics Committees of all participating institutions (No. 100910001). The JECS protocol was conducted

following the principles of the Declaration of Helsinki. All the participants provided written informed consent.

Provenance and peer review

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Data availability statement

Data are unsuitable for public deposition due to ethical restrictions and legal framework of Japan. It is prohibited by the Act on the Protection of Personal Information (Act No. 57 of 30 May 2003, amendment on 9 September 2015) to publicly deposit the data containing personal information. Ethical Guidelines for Medical and Health Research Involving Human Subjects enforced by the Japan Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare also restricts the open sharing of the epidemiologic data. All inquiries about access to data should be sent to: jecs-en@nies.go.jp. The person responsible for handling enquiries sent to this e-mail address is Dr Shoji F. Nakayama, JECS Programme Office, National Institute for Environmental Studies.

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Figure legends

Figure 1. Fetal records selection flow chart.

Figure 2. Adjusted odds ratio for developmental delay of offspring for multimorbidity during pregnancy by logistic regression. Models were adjusted for maternal age at birth, parity, history of alcohol consumption, history of smoking, maternal educational attainment, household income, and sex of child. Error bars indicate 95% confidence intervals. The 95% confidence interval for communication at 1year with multimorbidity was 0.98-5.3.

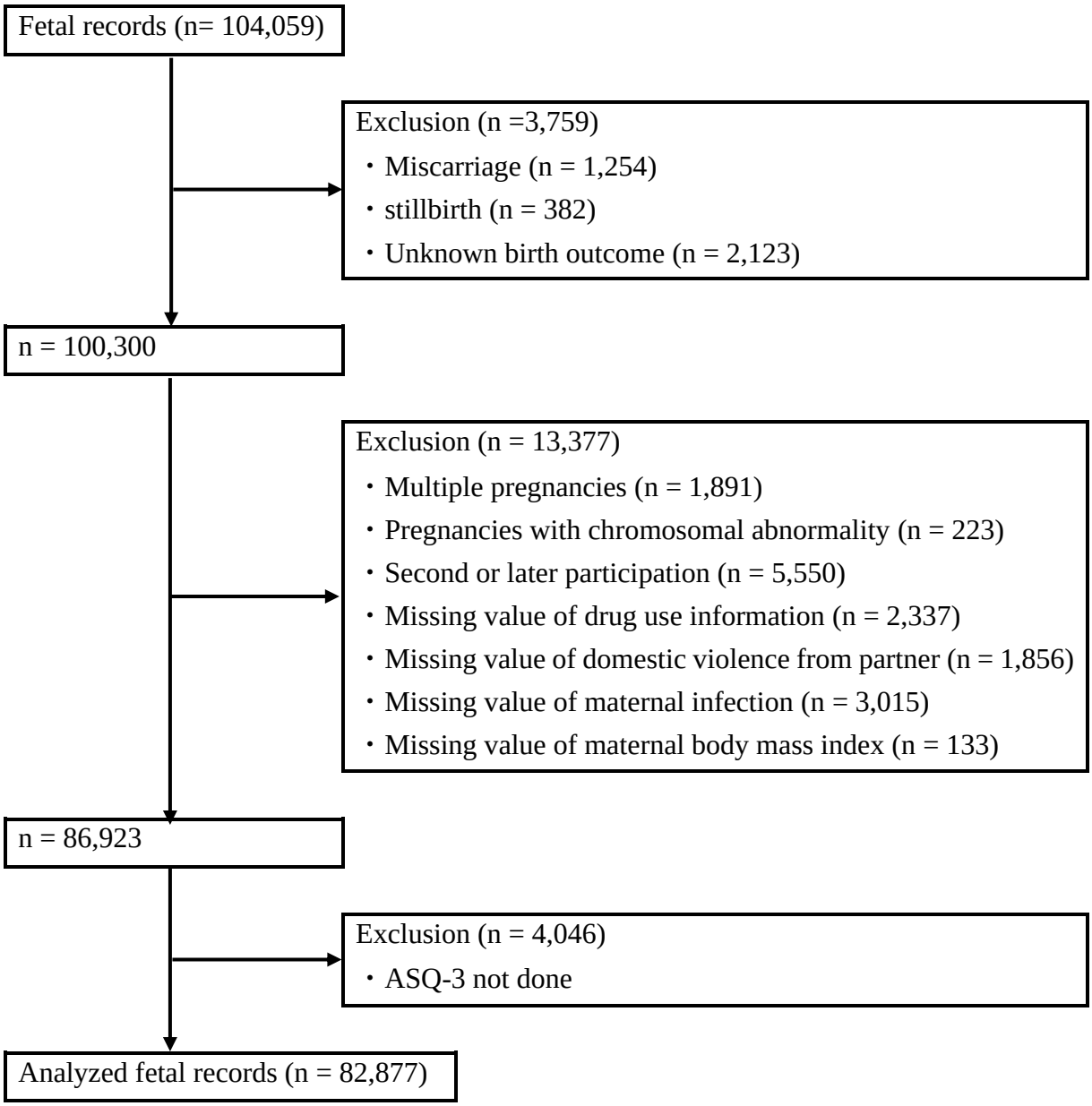

Figure 1. Fetal records selection flow chart.

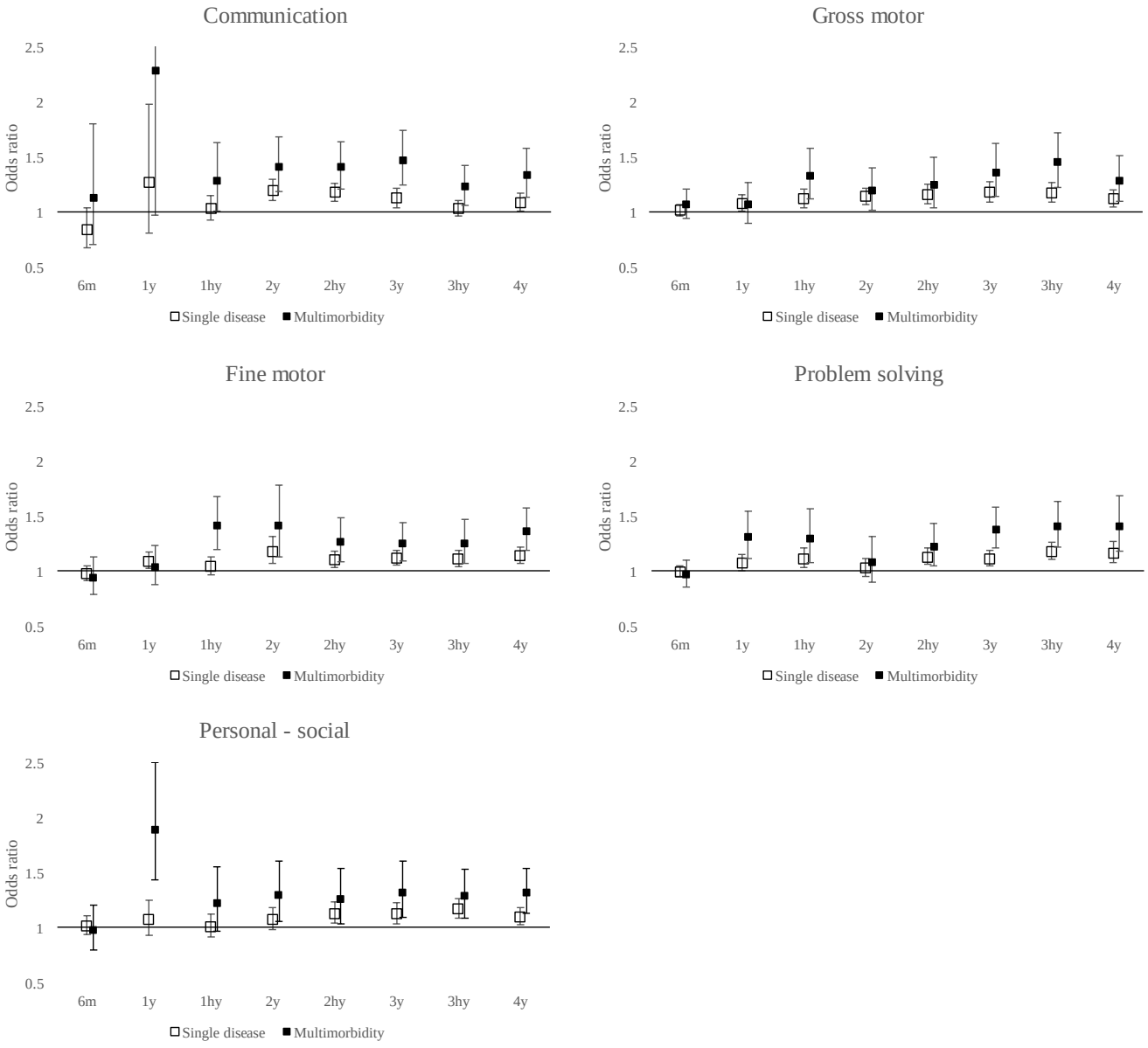

Figure 2. Adjusted odds ratio for developmental delay of offspring for multimorbidity during pregnancy by logistic regression. Models were adjusted for maternal age at birth, parity, history of alcohol consumption, history of smoking, maternal educational attainment, household income, and sex of child. Error bars indicate 95% confidence intervals. The 95% confidence interval for communication at 1year with multimorbidity was 0.98-5.3.

Supplemental Table 1. Prevalence of 23 maternal diseases

Condition	n	%
Abnormal pre-pregnancy BMI		
Underweight (BMI <18.5 kg/m2)	12,889	15.6
Obesity (BMI >25.0 kg/m2)	8,848	10.7
Allergic disease	2,557	3.1
Anaemia	592	0.7
Diabetes mellitus	124	0.2
Domestic violence	3,632	4.4
Dyslipidaemia	6	0.01
Epilepsy	122	0.2
Gastric or duodenal ulcer	285	0.3
Heart disease	7	0.01
Hepatitis	5	0.01
HIV infection	7	0.01
Hypertension	83	0.1
Inflammatory bowel disease	16	0.02
Kidney disease	17	0.02
Malignancy	0	0
Migraine	41	0.05
Neurological disease	0	0
Other sexually transmitted diseases	1,089	1.3
Mental disorder	550	0.7
Rheumatic or collagen disease	91	0.1
Substance abuse	1	0.001
Thyroid disease	614	0.7

BMI, body mass index.

Supplemental Table 2. The mean ASQ-3 scores and the number of offspring analyzed (n = 82,877) and those excluded (n = 11,927)

Age	Group	Communication				Gross motor				Fine motor				problem solving				Personal-social			
		Mean score	δ*	n	%**	Mean score	δ*	n	%**	Mean score	δ*	n	%**	Mean score	δ*	n	%**	Mean score	δ*	n	%**
6 months	Excluded	46.14	-0.55	9,636	80.8	32.54	-1.07	9,637	80.8	39.81	-1.11	9,605	80.5	42.80	-1.44	9,629	80.7	32.03	-2.44	9,611	80.6
	Included	46.69		74,135	89.5	33.61		74,126	89.4	40.92		73,928	89.2	44.24		74,137	89.5	34.47		74,043	89.3
1 year	Excluded	36.57	-1.30	9,236	77.4	42.01	-0.90	9,241	77.5	47.16	-1.19	9,227	77.4	42.47	-1.89	9,223	77.3	35.88	-1.34	9,204	77.2
	Included	37.86		70,443	85.0	42.90		70,445	85.0	48.35		70,416	85.0	42.36		70,347	84.9	37.22		70,229	84.7
1.5 years	Excluded	32.27	-0.79	8,669	72.7	53.98	-0.61	8,669	72.7	49.36	-0.54	8,664	72.6	42.06	-1.44	8,613	72.2	47.86	-0.08	8,659	72.6
	Included	33.06		66,543	80.3	54.60		66,563	80.3	49.90		66,525	80.3	42.48		66,133	79.8	47.94		66,528	80.3
2 years	Excluded	43.91	-1.19	9,632	80.8	52.81	-0.94	9,630	80.7	49.47	-0.35	9,626	80.7	48.58	-1.25	9,603	80.5	46.14	-0.20	9,620	80.7
	Included	45.11		69,541	83.9	53.75		69,542	83.9	49.82		69,478	83.8	48.83		69,346	83.7	46.34		69,435	83.8
2.5 years	Excluded	51.99	-0.94	9,377	78.6	53.86	-0.90	9,389	78.7	46.34	-0.90	9,337	78.3	49.79	-1.74	9,360	78.5	50.07	0.01	9,370	78.6
	Included	52.92		67,899	81.9	54.75		67,915	81.9	47.25		67,597	81.6	50.52		67,749	81.7	50.06		67,809	81.8
3 years	Excluded	52.28	-0.88	9,663	81.0	54.50	-0.96	9,657	81.1	48.07	-1.15	9,645	80.9	51.14	-1.69	9,597	80.5	50.36	0.03	9,661	81.0
	Included	53.16		69,466	83.8	55.47		69,566	83.9	49.21		69,291	83.6	51.83		68,907	83.1	50.33		69,404	83.7
3.5 years	Excluded	53.44	-0.65	9,222	77.3	55.77	-0.67	9,226	77.4	52.36	-0.69	9,211	77.2	53.91	-1.61	9,163	76.8	54.52	-0.18	9,214	77.3
	Included	54.09		67,447	81.4	56.44		67,398	81.3	53.05		67,361	81.3	54.53		67,140	81.0	54.70		67,358	81.3
4 years	Excluded	52.99	-0.81	8,939	74.9	53.76	-0.58	8,982	75.3	50.91	-0.77	8,983	75.3	54.06	-1.45	8,966	75.2	53.25	-0.27	9,002	75.5
	Included	53.80		65,162	78.6	54.34		65,426	78.9	51.68		65,429	78.9	54.51		65,311	78.8	53.52		65,505	79.0

*Difference in the mean scores from those of the offspring included at each point. **Percentage of total group population.

Supplemental Table 3. The ASQ scores and the number of offspring by testing times from 6 months to 4 years

Age	Testing times	Communication				Gross motor				Fine motor				Problem solving				Personal-social			
		Mean score	n	δ*	%**	Mean score	n	δ*	%**	Mean score	n	δ*	%**	Mean score	n	δ*	%**	Mean score	n	δ*	%**
6 months	1-3	47.39	6,285	0.94	65.9	35.57	6,284	2.57	65.9	43.51	6,271	3.37	65.8	46.40	6,290	2.76	66.0	36.69	6,281	2.90	65.9
	4-7	46.98	21,111	0.52	79.4	34.39	21,110	1.39	79.4	41.86	21,043	1.73	79.2	44.93	21,117	1.30	79.5	35.32	21,072	1.53	79.3
	8	46.46	46,739		99.9	33.00	46,732		99.9	40.14	46,614		99.7	43.64	46,730		99.9	33.79	46,690		99.8
1 year	1-3	40.28	4,028	3.01	42.3	44.55	4,025	2.07	42.2	49.27	4,028	1.15	42.3	44.09	4,018	2.22	42.2	39.19	4,004	2.47	42.0
	4-7	38.78	19,665	1.52	74.0	43.58	19,666	1.10	74.0	48.70	19,645	0.58	73.9	43.18	19,614	1.32	73.8	37.99	19,582	1.26	73.7
	8	37.27	46,750		99.9	42.48	46,754		99.9	48.12	46,743		99.9	41.86	46,715		99.9	36.73	46,643		99.7
1.5 years	1-3	35.21	2,367	2.55	24.8	54.84	2,368	0.36	24.8	50.46	2,364	0.70	24.8	43.53	2,342	1.34	24.6	49.52	2,363	1.91	24.8
	4-7	33.86	17,431	1.20	65.6	54.85	17,434	0.37	65.6	50.19	17,427	0.43	65.6	43.10	17,278	0.91	65.0	48.60	17,424	0.99	65.6
	8	32.65	46,745		99.9	54.49	46,761		100.0	49.76	46,734		99.9	42.19	46,513		99.5	47.61	46,741		99.9
2 years	1-3	45.71	1,719	0.72	18.0	54.29	1,717	0.56	18.0	50.42	1,720	0.68	18.0	49.42	1,710	0.60	17.9	47.14	1,714	0.91	18.0
	4-7	45.30	21,067	0.31	79.3	53.75	21,066	0.02	79.3	49.94	21,048	0.20	79.2	48.80	20,982	-0.01	78.9	46.52	21,028	0.29	79.1
	8	44.99	46,755		99.9	53.73	46,759		99.9	49.74	46,710		99.9	48.82	46,654		99.8	46.23	46,693		99.8
2.5 years	1-3	52.41	1,217	-0.62	12.8	54.66	1,217	-0.12	12.8	47.09	1,200	-0.23	12.6	50.68	1,206	0.12	12.7	50.75	1,211	0.77	12.7
	4-7	52.70	19,941	-0.33	75.0	54.69	19,945	-0.09	75.0	47.08	19,809	-0.24	74.5	50.44	19,873	-0.11	74.8	50.21	19,912	0.22	74.9
	8	53.03	46,741		99.9	54.78	46,753		99.9	47.32	46,588		99.6	50.55	46,670		99.8	49.98	46,686		99.8
3 years	1-3	52.96	1,369	-0.29	14.4	55.69	1,374	0.21	14.4	49.17	1,355	-0.12	14.2	52.17	1,336	0.29	14.0	51.13	1,365	0.89	14.3
	4-7	52.98	21,417	-0.26	80.6	55.44	21,462	-0.03	80.8	49.06	21,339	-0.22	80.3	51.70	21,184	-0.18	79.7	50.47	21,406	0.22	80.5
	8	53.25	46,680		99.8	55.48	46,730		99.9	49.29	46,597		99.6	51.88	46,387		99.2	50.24	46,633		99.7
3.5 years	1-3	53.78	1,080	-0.31	11.3	56.25	1,078	-0.20	11.3	52.58	1,077	-0.53	11.3	53.88	1,065	-0.70	11.2	54.51	1,079	-0.15	11.3
	4-7	54.13	19,641	0.04	73.9	56.41	19,618	-0.05	73.8	52.93	19,593	-0.18	73.7	54.44	19,480	-0.13	73.3	54.83	19,613	0.17	73.8
	8	54.09	46,726		99.9	56.46	46,702		99.9	53.11	46,691		99.8	54.58	46,595		99.6	54.66	46,666		99.8
4y ears	1-3	53.77	909	0.01	9.5	54.40	912	0.09	9.6	51.30	913	-0.46	9.6	53.99	899	-0.57	9.4	53.36	913	-0.12	9.6
	4-7	53.93	17,807	0.17	67.0	54.41	17,900	0.09	67.3	51.51	17,895	-0.25	67.3	54.42	17,862	-0.14	67.2	53.63	17,946	0.14	67.5
	8	53.76	46,446		99.3	54.32	46,614		99.7	51.76	46,621		99.7	54.56	46,550		99.5	53.49	46,646		99.7

*Difference in the mean scores from those of the offspring tested all at each point. **Percentage of total group population.

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	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3,4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5,6
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3,7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7,8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	7,8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-10
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	7,8
Bias	9	Describe any efforts to address potential sources of bias	19
Study size	10	Explain how the study size was arrived at	5,7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10,11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10
		(*b*) Describe any methods used to examine subgroups and interactions	10
		(*c*) Explain how missing data were addressed	10,11
		(*d*) If applicable, explain how loss to follow-up was addressed	-
		(*e*) Describe any sensitivity analyses	-
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	7,8
		(b) Give reasons for non-participation at each stage	7,8
		(c) Consider use of a flow diagram	7,8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11,12
		(b) Indicate number of participants with missing data for each variable of interest	-
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	13-15

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	15,16 - -
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	17
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	18,19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19,20
Generalisability	21	Discuss the generalisability (external validity) of the study results	20
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21,22

*Give information separately for exposed and unexposed groups.

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

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Association between maternal multimorbidity and neurodevelopment of offspring: a prospective birth cohort study from the Japan Environment and Children's Study

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Primary Subject Heading:	Public health
Secondary Subject Heading:	Obstetrics and gynaecology, Paediatrics
Keywords:	PUBLIC HEALTH, Maternal medicine < OBSTETRICS, Paediatric neurology < PAEDIATRICS, Multimorbidity, Pregnant Women

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Title: Association between maternal multimorbidity and neurodevelopment of offspring: a prospective birth cohort study from the Japan Environment and Children's Study

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ABSTRACT

Objectives: To investigate the association between multimorbidity during pregnancy and neurodevelopmental delay in offspring using data from a Japanese nationwide birth cohort study.

Design: This study was a prospective birth cohort study.

Setting: This study population included 104,059 fetal records who participated in The Japan Environment and Children's Study (JECS) from 2011 to 2014.

Participants: Pregnant women whose children had undergone developmental testing were included in this analysis.

Primary and secondary outcome measures: Neurodevelopment of offspring was assessed using the Japanese version of the Ages and Stages Questionnaire, third edition (J-ASQ-3), comprising five developmental domains. The number of comorbidities among the pregnant women was categorized as zero, single disease, or multimorbidity (two or more diseases). Maternal chronic conditions included in multimorbidity were defined as conditions with high prevalence among women of reproductive age. A multivariate logistic regression analysis was conducted to examine the association between multimorbidity in pregnant women and offspring development.

Results: Pregnant women with multimorbidity, single disease, and no disease accounted for 3.6%, 30.6%, and 65.8%, respectively. The odds ratios (ORs) for

neurodevelopmental impairment during the follow-up period were similar for infants of mothers with no disease comorbidity and those with a single disease comorbidity. However, the ORs for neurodevelopmental impairment were significantly higher for children born to mothers with multimorbidity compared with those born to healthy mothers.

Conclusion: An association was observed between the number of comorbidities in pregnant women and developmental delay in offspring. Pregnant women with multimorbidities are at a higher risk of neurodevelopmental delays in their offspring. Further research is required in this regard in many other regions of the world.

Keywords

pregnant, women, multimorbidity, Japan, offspring, neurodevelopment, delay

Word counts

Abstract: 267 words; Main text, 2,572 words

Tables/figures: 3 tables/2 figures

References: 27 references

Strengths and limitations of this study

- The study size was adequate for effective investigation.
- Neurodevelopmental progress was assessed in detail using the results of eight points (6 months, 1 year, 1.5 years, 2 years, 2.5 years, 3 years, 3.5 years, and 4 years).
- Chronic diseases that were diagnosed but not treated were ruled out.
- Infants were unable to communicate well, which renders accurate assessment of their neurodevelopment difficult.

INTRODUCTION

Multimorbidity is defined as the coexistence of two or more chronic diseases, whether physical or mental, in the same individual.(1) Multimorbidity is considered one of the principal challenges in older people as the incidence of chronic diseases such as hypertension, dyslipidemia, diabetes, cardiac disease, and malignant tumors, increases with age. Therefore, many studies have focused on older patients with multimorbidities.(2,3) However, diseases such as asthma, arthritis, mental disorders, and HIV can also occur in young people. There are few studies on multimorbidity in young people,(4) including pregnant women.(5,6) Maternal physical morbidities, such

as hypertension, kidney disease, and systemic lupus erythematosus, are potential risk factors for preterm birth (PTB) and low birth weight infants (LBW).(7) Moreover, maternal mental and social morbidities have also been associated with PTB and LBW.(7) Previous studies also reported the relationship between maternal environments such as maternal asthma, maternal intake of fats, maternal and cord blood Manganese levels and child development.(8–10)

Infancy is considered to be the period in which language, cognition, motor skills, and socioemotional domains form the basis for subsequent social participation.(11) It is essential to receive appropriate support, early detection, and intervention during this period.(12) Although maternal nutritional status, certain diseases, and blood substances can affect the neurodevelopment of offspring(8–11), the impacts of multimorbidity in pregnant women on the neurodevelopment of offspring have not been extensively studied.(5,6) A major difference between previous reports and this study was the investigation of the association between multiple diseases of pregnant women and child neurodevelopment; previous reports have mainly focused on the relationship between a single disease or single substance in pregnant women and child neurodevelopment.

The present study aimed to investigate the association between multimorbidity

during pregnancy and neurodevelopmental delay in offspring (every 6 months from birth to age 4 years) using data from an ongoing nationwide birth cohort, namely the Japan Environment and Children's Study (JECS)(13); the neurodevelopment of the participants was evaluated using the Japanese version of the Ages and Stages Questionnaires, Third Edition: Infant Developmental Examination (ASQ-3).(14)

METHODS

Study population

The JECS is a nationwide and government-funded birth cohort study that started recruiting expecting mothers in January 2011.(13); the primary objective was to investigate environmental factors such as exposure to chemicals and airborne pollutants that can affect children's health and development during the fetal stage and early childhood, in order to help policymakers to formulate measures to safeguard the environment for future generations.(15) The study population included 104,059 fetal records who participated in JECS from 2011 to 2014. A flowchart of the study participants is presented in Figure 1. The exclusion criteria included: miscarriage, stillbirth, or unknown birth outcomes (n = 2,123). Second, participants with multiple births, pregnancies with chromosomal abnormalities, participated for the second time

and more, and missing information about drug history, domestic violence, maternal infection, or maternal BMI were excluded (n = 13,377). Moreover, pregnant women whose children were not tested using the ASQ-3 once from 6 months to 4 years old (n=4,046) were excluded. Finally, a total of 82,877 pregnant women were included in the analysis.

Ethics

The JECS protocol was reviewed and approved by the Ministry of the Environment's Institutional Review Board on Epidemiological Studies and the Ethics Committees of all participating institutions (No. 100910001).(13) The JECS was performed following the Declaration of Helsinki. All the participants provided written informed consent.

Patient and Public Involvement statement

This study did not involve patients or public.

Assessment of pregnant multimorbidity

In this study, multimorbidity was defined as the coexistence of two or more physical, mental, or social conditions in an individual according to previous reports.(7) Maternal

chronic conditions included in multimorbidity were defined as conditions with high prevalence among women of reproductive age.(7) To identify pregnant women with the disease more rigorously, the diseases of pregnant women were defined as those that were medically treated at the time of pregnancy. Information was collected through self-reports, medical record transcripts, and medication interviews. The targeted diseases included allergic diseases, such as asthma, anemia, diabetes mellitus, dyslipidemia, epilepsy, gastric or duodenal ulcers, 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), mental disorders, rheumatic or collagen diseases, and thyroid disease. Having an episode of domestic violence, substance abuse, being obese (BMI ≥25), and being thin (BMI <18.5) were each defined as one disease. We used maternal pre-pregnancy body weight data for analysis. Pregnant women with two or more of these diseases during pregnancy were defined as having multimorbidities.

Assessment of neurodevelopment of offspring

Score results from the Japanese version of the ASQ-3 (Ages and Stages Questionnaires, Third Edition: Infant Development Test) at 6 months, 1 year, 1.5 years, 2 years, 2.5

years and, 3 years, 3.5 years, and 4 years were used to evaluate neurodevelopmental measures.(15) These scores were obtained by mailed questionnaire survey filled by caregivers. Neurodevelopmental assessments were performed in the domains of communication, gross motor, fine motor, problem solving, and personal-social. Offspring with scores below the cut-off were defined as having neurodevelopmental delays. The cut-off values were those reported in the Japanese validation version.(14)

Covariates

The covariates were: maternal age at birth, parity, alcohol consumption status, smoking status, educational attainment, household income, and sex of the child; they were selected based on previous studies.(7,10)

Statistical analysis

This study used the datasets jecs-ta-20190930 and jecs-qa-20210401 from JECS. STATA® (MP17) and R® (version 4.2.2) were used for statistical analysis. Multivariate logistic regression analysis was performed to determine the adjusted odds ratios (ORs). The objective variable was the neurodevelopment of the offspring, and the explanatory variable was the multimorbidity in pregnant women. The covariates were: maternal age

at birth, alcohol consumption status, smoking status, educational attainment, household income, sex of the child, and number of births. Multiple imputation methods were performed using R to impute the missing values. Other analyses were performed using the STATA software.

RESULTS

The characteristics of the pregnant women analyzed in this study are presented in Table 1. Pregnant women with multimorbidity, single disease, and no disease accounted for 3.6% (n = 3,001), 30.6% (n = 25,341), and 65.8% (n = 54,535), respectively. Household income of 2–7.99 million/year was accounted for 84.7%; n = 70,184. In total, 51.4% (n = 42,563) and 48.6% (n = 40,314) of the offspring were male and female, respectively. After pregnancy, 4.1 % (n = 3, 408) and 2.7 % (n = 2, 253) of pregnant women had smoking and drinking habits, respectively.

Table 1. Characteristics of pregnant women and their offspring (n = 82,877)

Characteristics		n		%
Number of coexist disease				
	0	54,535		65.8
	1	25,341		30.6
	≥2	3,001		3.6
Mother age at birth				
	<24	7,815		9.4
	25-29	22,721		27.4

	30-34	29,555		35.7
	35-39	18,940		22.9
	≥40	3,846		4.6
Parity				
	0	36,302		43.8
	1	30,646		37.0
	≥2	15,929		19.2
Mother education				
	Junior high school	3,630		4.4
	High school	25,917		31.3
	Vocational junior or technical college	35,323		42.6
	≥University	18,007		21.7
Maternal smoking habits				
	Non-smoking or exit-smoking before pregnancy	68,145		82.2
	Exit-smoking after pregnancy	11,324		13.7
	Still-smoking	3,408		4.1
Maternal drinking habits				
	Non-drinker	41,481		50.1
	Exit drinking after pregnancy	39,143		47.2
	drinking	2,253		2.7
Annual household income (10,00 JPY)				
	<200	4,193		5.1
	200-399	28,476		34.4
	400-599	28,663		34.6
	600-799	13,045		15.7
	800-999	5,233		6.3
	1000-1199	1,870		2.3
	1200-1499	735		0.9
	1500-1999	427		0.5
	≥2000	235		0.3
Child sex				
	boys	42,563		51.4
	girls	40,314		48.6

The prevalence of 23 maternal diseases is described in supplemental table 1. Maternal underweight (BMI <18.5) (15.6%) was the most frequently observed chronic condition, followed by maternal obesity (BMI ≥25) (10.7%). The most frequent diseases on medication were allergic diseases (3.1%), other sexually transmitted diseases (1.3%), anemia (0.7%), mental disorders (0.7%) and thyroid disease (0.7%).

The prevalence of neurodevelopmental delay in offspring is presented in Table 2. The prevalence of communication delays at 6 months and 1 year was significantly lower than that of the others.

Table 2. Prevalence of neurodevelopment delay of offspring

Age	Number of maternal comorbidity	Communication	Gross motor	Fine motor	Problem solving	Personal-social
		n (%)	n (%)	n (%)	n (%)	n (%)
6 months	0	318 (0.4)	5,540 (6.7)	2,788 (3.4)	5,625 (6.8)	1,898 (2.3)
	1	123 (0.1)	2,603 (3.1)	1,237 (1.5)	2,596 (3.1)	891 (1.1)
	≥2	19 (0.02)	316 (0.4)	137 (0.2)	334 (0.4)	101 (0.1)
1 year	0	54 (0.1)	2,711 (3.3)	2,743 (3.3)	2,478 (3.0)	566 (0.7)
	1	31 (0.04)	1,324 (1.6)	1,383 (1.7)	1,256 (1.5)	282 (0.3)
	≥2	6 (0.01	148 (0.2)	154 (0.2)	142 (0.2)	57 (0.1)
1 half years	0	1,091 (1.3)	2,138 (2.6)	2,000 (2.4)	1,831 (2.2)	1,209 (1.5)
	1	528 (0.6)	1,100 (1.3)	984 (1.2)	939 (1.1)	564 (0.7)
	≥2	76 (0.1)	148 (0.2)	156 (0.2)	168 (0.2)	78 (0.1)
2 years	0	1,851 (2.2)	2,816 (3.4)	1,060 (1.3)	2,106 (2.5)	1,400 (1.7)
	1	1,048 (1.3)	1,474 (1.8)	590 (0.7)	1,004 (1.2)	706 (0.9)
	≥2	147 (0.2)	176 (0.2)	84 (0.1)	122 (0.1)	99 (0.1)
2 half years	0	2,445 (3.0)	2,042 (2.5)	2,696 (3.3)	2,708 (3.3)	1,634 (2.0)
	1	1,376 (1.7)	1,086 (1.3)	1,389 (1.7)	1,445 (1.7)	860 (1.0)
	≥2	199 (0.2)	132 (0.2)	186 (0.2)	187 (0.2)	112 (0.1)
3 years	0	1,901 (2.3)	2,037 (2.5)	3,492 (4.2)	3,406 (4.1)	1,603 (1.9)
	1	1,030 (1.2)	1,102 (1.3)	1,843 (2.2)	1,723 (2.2)	861 (1.0)
	≥2	164 (0.2)	144 (0.2)	245 (0.3)	269 (0.3)	122 (0.1)
3 half years	0	2,873 (3.5)	2,020 (2.4)	2,522 (3.0)	2,659 (3.2)	2,130 (2.6)
	1	1,467 (1.8)	1,098 (1.3)	1,341 (1.6)	1,508 (1.8)	1,171 (1.4)
	≥2	219 (0.3)	155 (0.2)	182 (0.2)	218 (0.3)	154 (0.2)
4 years	0	2,157 (2.6)	2,597 (3.1)	3,038 (3.7)	1,733 (2.1)	2,629 (3.2)
	1	1,118 (1.3)	1,347 (1.6)	1,651 (2.0)	977 (1.2)	1,362 (1.6)
	≥2	166 (0.2)	177 (0.2)	239 (0.3)	145 (0.2)	194 (0.2)

The number of the offspring tested as well as the mean ASQ-3 scores at each time point in the offspring those were analyzed and those who were excluded are shown in supplemental table 2. In the included group, the number of the offspring tested at 6 months and 4 years were 74,195 and 65,705, respectively. In the excluded group, the number of the offspring tested at 6 months and 4 years were 9,642 and 9,019, respectively. At each time point, the offspring were defined as tested if they answered at least one domain of the ASQ-3. The examination rates in offspring who were excluded were lower overall. The number of the offspring tested tended to decrease with age in both groups. The difference in the mean scores of the offspring excluded from the mean scores of those included ranged from -2.44 to 0.11. The mean scores in the offspring who were excluded were lower from 6 months to 4 years in most time points. The ASQ-3 scores and the number of the offspring by categories of the number of tests at each time point are shown in the supplemental table 3. The offspring were categorized into three groups: until 4 years, tested in all time points, 1 to 3 times, and 4 to 7 times. The number of the offspring tested at all time points, 4 to 7 times, and 1 to 3 times were 46,766, 26,578, and 9,530 respectively. The number of the offspring tended to decrease with age in groups tested less frequently. There was a particularly large decrease in the

group tested 1 to 3 times. The difference in ASQ-3 scores of the groups tested less frequently from those of the group tested in all time points ranged from -1.62 to 3.37. Comparing the group tested in all time points, the groups tested less frequently tended to have higher scores until 2 years and lower scores after 2.5 years. The results of the multivariate logistic regression analysis conducted on the number of comorbidities in pregnant women and the neurodevelopment of offspring are shown in Table 3 and Figure 2. Except at 6 months, the ORs were more than 1 for any of the following items: communication, gross motor, fine motor, problem solving, and personal and social. The ORs at 6 months were lower than those at other ages for all items, both single disease comorbidity and multimorbidity. ORs tended to be higher with increasing age of the offspring, and the ORs for all items were higher at 4 years than at 6 months for both single-disease coexistence and multimorbidity. The ORs for single disease comorbidities ranged from 0.85 (95% CI 0.69–1.05) to 1.28 (95% Cl 0.82–1.99). The OR range for multimorbidity was 0.95 (95% CI 0.80–1.14) to 2.29 (95% CI 0.98–5.36), and that at 4 years of age was 1.30 (95% CI 1.11–1.52) to 1.42 (95% CI 1.19–1.69) for all domains.

Table 3. Adjusted odds ratio for developmental delay of offspring for multimorbidity during pregnancy by logistic regression

Age	Number of maternal comorbidity	Communication	Gross motor	Fine motor	Problem solving	Personal-social
		Adjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)
6 months	1	0.85 (0.69–1.05)	1.03 (0.98–1.08)	0.99 (0.92–1.06)	1.01 (0.96–1.06)	1.02 (0.94–1.11)
	≥2	1.14 (0.71–1.81)	1.08 (0.96–1.22)	0.95 (0.8–1.14)	0.99 (0.86–1.11)	0.99 (0.8–1.21)
1 year	1	1.28 (0.82–1.99)	1.09 (1.02–1.16)	1.10 (1.03–1.18)	1.08 (1.01–1.16)	1.08 (0.94–1.25)
	≥2	2.29 (0.98–5.36)	1.08 (0.91–1.28)	1.05 (0.89–1.24)	1.32 (1.12–1.55)	1.90 (1.44–2.50)
1 half years	1	1.04 (0.94–1.16)	1.13 (1.05–1.22)	1.05 (0.97–1.14)	1.13 (1.04–1.22)	1.02 (0.92–1.13)
	≥2	1.29 (1.02–1.64)	1.34 (1.13–1.59)	1.42 (1.20–1.68)	1.32 (1.09–1.57)	1.23 (0.97–1.56)
2 years	1	1.21 (1.12–1.30)	1.15 (1.08–1.23)	1.19 (1.08–1.32)	1.04 (0.96–1.12)	1.09 (0.99–1.19)
	≥2	1.42 (1.19–1.69)	1.21 (1.03–1.41)	1.42 (1.13–1.78)	1.09 (0.9–1.32)	1.31 (1.06–1.61)
2 half years	1	1.19 (1.11–1.27)	1.17 (1.09–1.26)	1.11 (1.04–1.19)	1.14 (1.07–1.22)	1.14 (1.04–1.24)
	≥2	1.42 (1.22–1.65)	1.26 (1.05–1.51)	1.28 (1.09–1.49)	1.23 (1.05–1.44)	1.26 (1.04–1.54)
3 years	1	1.14 (1.05–1.23)	1.19 (1.10–1.28)	1.13 (1.06–1.19)	1.12 (1.06–1.19)	1.13 (1.04–1.24)
	≥2	1.48 (1.25–1.75)	1.37 (1.15–1.63)	1.26 (1.10–1.45)	1.39 (1.22–1.59)	1.33 (1.10–1.61)
3 half years	1	1.04 (0.98–1.11)	1.18 (1.10–1.28)	1.12 (1.04–1.20)	1.19 (1.11–1.27)	1.18 (1.09–1.27)
	≥2	1.24 (1.07–1.44)	1.46 (1.23–1.73)	1.26 (1.07–1.47)	1.42 (1.22–1.64)	1.30 (1.09–1.54)
4 years	1	1.10 (1.02–1.18)	1.13 (1.06–1.21)	1.15 (1.08–1.22)	1.18 (1.08–1.27)	1.11 (1.03–1.18)
	≥2	1.35 (1.14–1.59)	1.30 (1.11–1.52)	1.37 (1.19–1.58)	1.42 (1.19–1.69)	1.32 (1.14–1.54)

Models were adjusted for maternal age at birth, parity, history of alcohol consumption, history of smoking, maternal educational attainment, sex of child, household income, and sex of child.

DISCUSSION

This investigation showed significant associations between multimorbidities in pregnant women and delayed neurodevelopment in the offspring. The ORs were higher for most of the neurodevelopmental items in pregnant women with multimorbidities than in those with a single disease. This study is the first to highlight the significance of the association between multimorbidity in pregnant women and the neurodevelopment in the offspring, despite the existence of reports on the association between specific diseases, such as asthma, chronic inflammatory arthritis, depression, thyroid conditions, diabetes, and epilepsy, in pregnant women and the neurodevelopment of their children.(8,16–18) As the number of comorbidities in pregnant women increases, the factors contributing to neurodevelopmental delay in the offspring may increase. In the future, health education and treatment in terms of the number of comorbidities during pregnancy should be considered.

The ORs for neurodevelopmental delay increased with the increase in the offspring's age. This may have been caused by the increasing accuracy of the assessment as the offspring aged. An accurate assessment of neurodevelopment cannot be made until the child has grown to a certain age.(19) Parents' assessments of their

children's neurodevelopment may not be established until a certain period of parenting time. Neurodevelopmental delays may have been caused by social factors.(20) It has been reported that depressed mothers tend to form family environments that are socially and economically disadvantageous to their children.(21) Pregnant women with multimorbidities and certain mental diseases may have tended to form socioeconomically undesirable family environments.(22) Further, a great deal of the brain's ultimate structure and capacity is shaped up to 3 years of age.(11) The maternal immune activation may be caused by comorbidities during pregnancy, and components of the maternal immune system such as microglia and cytokines produced by microglia may trigger inappropriate fetal immune responses and may lead to neurodevelopment delay in the future.(23) Neurodevelopmental delays in children may have gradually appeared as a result of multiple factors such as the postnatal brain development process, the undesirable family environment, and the caregiver's assessments of their children. Future research should take into account the prospect that factors such as children's birthweight and/or gestational age at birth, nutritional status, Apgar score, and maternal psychological status can be intermediate variables in the association between multimorbidity and neurodevelopmental delay.

This study has several limitations. First, Pregnant women with diagnoses but

no medication were not included in the disease sample in this study, with the exception of domestic violence, obese, and skinny women. The criterion for the disease was defined as the presence of medication; the number of pregnant women with the disease may have been higher if the study had been conducted using different criteria. Some have criticized the definition of multimorbidity as simply having more than one disease, which would include a large population.(24) In the future, a definition of multimorbidity that is suitable for the target community will be required since the significant diseases and conditions vary depending on the target population.(24) Second, it was difficult in this study to discuss the biological mechanisms of the association between multimorbidity and neurodevelopmental delay. The association between various diseases and neurodevelopmental delays has been reported in previous studies.(8,16–18,25) Further studies on disease characteristics and disease combinations may allow for hypotheses to be made regarding the biological mechanisms underlying the association between multimorbidity and neurodevelopmental delay. Third, as participants in the JECS were only collaborators, selection bias may have occurred.(15) The prevalence of multimorbidity and the results of the association between multimorbidity and neurodevelopmental delay might have been different if the study design included pregnant women who did not participate in the JECS. The number of

pregnant women with multimorbidities would increase and the results of the effects on the neurodevelopment of the children might be different if all pregnant women and children registered in the administration were included in the study. Fourth, we didn't use the data on maternal situation after delivery. Incomplete questionnaire responses were reported to be influenced by the maternal situation after delivery as health status, number of siblings, partner, and primary caregiver.(26,27) The ASQ-3 scores of the offspring who were excluded were lower than those of the offspring included in most time points. In the analyzed population, the changes in the ASQ-3 scores of the offspring tested less frequently differed from those of the offspring tested at all time points. Except for the group tested at all time points, the number of the offspring tested tended to decrease with age. It was difficult to examine the association between incomplete responses and the ASQ-3 scores in this study. In the future, we need to consider studies with regard to incomplete participants and neurodevelopmental delay of offspring. There was no analysis of data from offspring, such as birth weight, gestational age at birth, nutritional status, and Apgar score, but, as we mentioned above, they were not selected as adjusted variables because we considered them as intermediate variables in the association between multimorbidity and neurodevelopmental delay.

Previous reports on multimorbidities in pregnant women have focused on its

prevalence and impact on pregnant women themselves.(5–7) This study is a new report in terms of the effect of multimorbidity in pregnant women on their offspring and provides important recommendations regarding the health of pregnant women.

CONCLUSION

This study demonstrated an association between multimorbidities in pregnant women and neurodevelopmental delays in their offspring in Japan. To clarify its mechanisms and effects, more research needs to be done in many regions of the world with different economic, geographic, and racial conditions.

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Contributors

TA and YaS designed this study. JECS collected the data and obtained funding. YaS, EY, KNag, ST, YI, CM, SI, and RK collected the data. TA and YaS conducted the data analysis. TA, YaS, EY, YuS, KNak, YK, KNag, ST, YI, HI, TY, CM, SI, and RK contributed to data interpretation. TA, YaS, EY, YuS, KNak, YK, KNag, ST, YI, HI, TY, CM, SI, RK, and the JECS Group conducted critical reviews. TA drafted the manuscript. YaS made critical revisions. YaS is responsible for the overall content as guarantor. All the authors have reviewed and commented on the manuscript. All the

authors approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

Patient and public involvement

The patients and/or the public were not involved in the design, conduct, reporting, or dissemination of this study.

Patient consent for publication

Not applicable.

Ethics approval

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

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

Data are unsuitable for public deposition due to ethical restrictions and legal framework of Japan. It is prohibited by the Act on the Protection of Personal Information (Act No. 57 of 30 May 2003, amendment on 9 September 2015) to publicly deposit the data containing personal information. Ethical Guidelines for Medical and Health Research Involving Human Subjects enforced by the Japan Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare also restricts the open sharing of the epidemiologic data. All inquiries about access to data should be sent to: jecs-en@nies.go.jp. The person responsible for handling enquiries

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Figure legends

Figure 1. Fetal records selection flow chart.

Figure 2. Adjusted odds ratio for developmental delay of offspring for multimorbidity during pregnancy by logistic regression. Models were adjusted for maternal age at birth, parity, history of alcohol consumption, history of smoking, maternal educational

attainment, household income, and sex of child. Error bars indicate 95% confidence intervals. The 95% confidence interval for communication at 1 year with multimorbidity was 0.98-5.3.

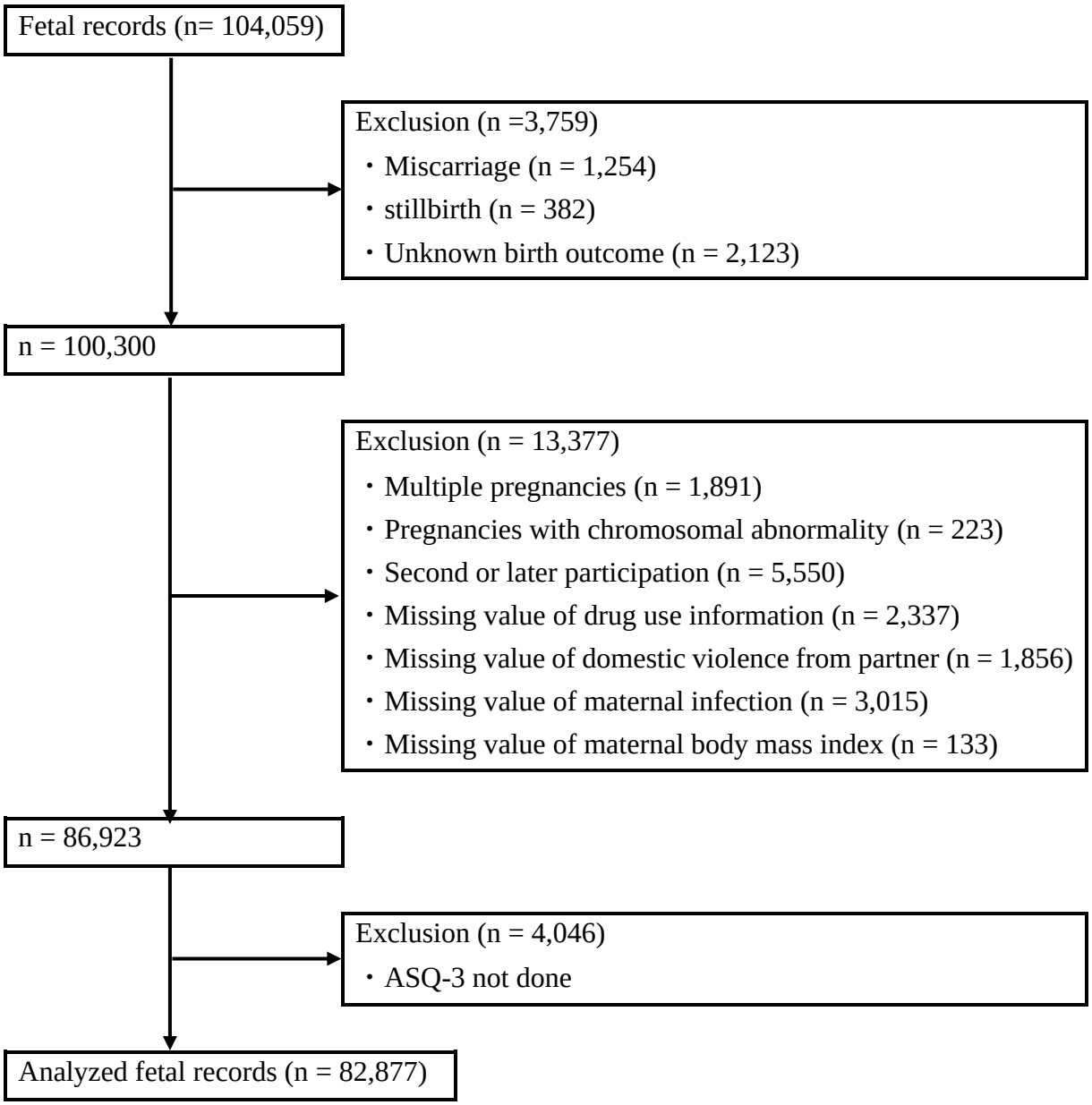

Figure 1. Fetal records selection flow chart.

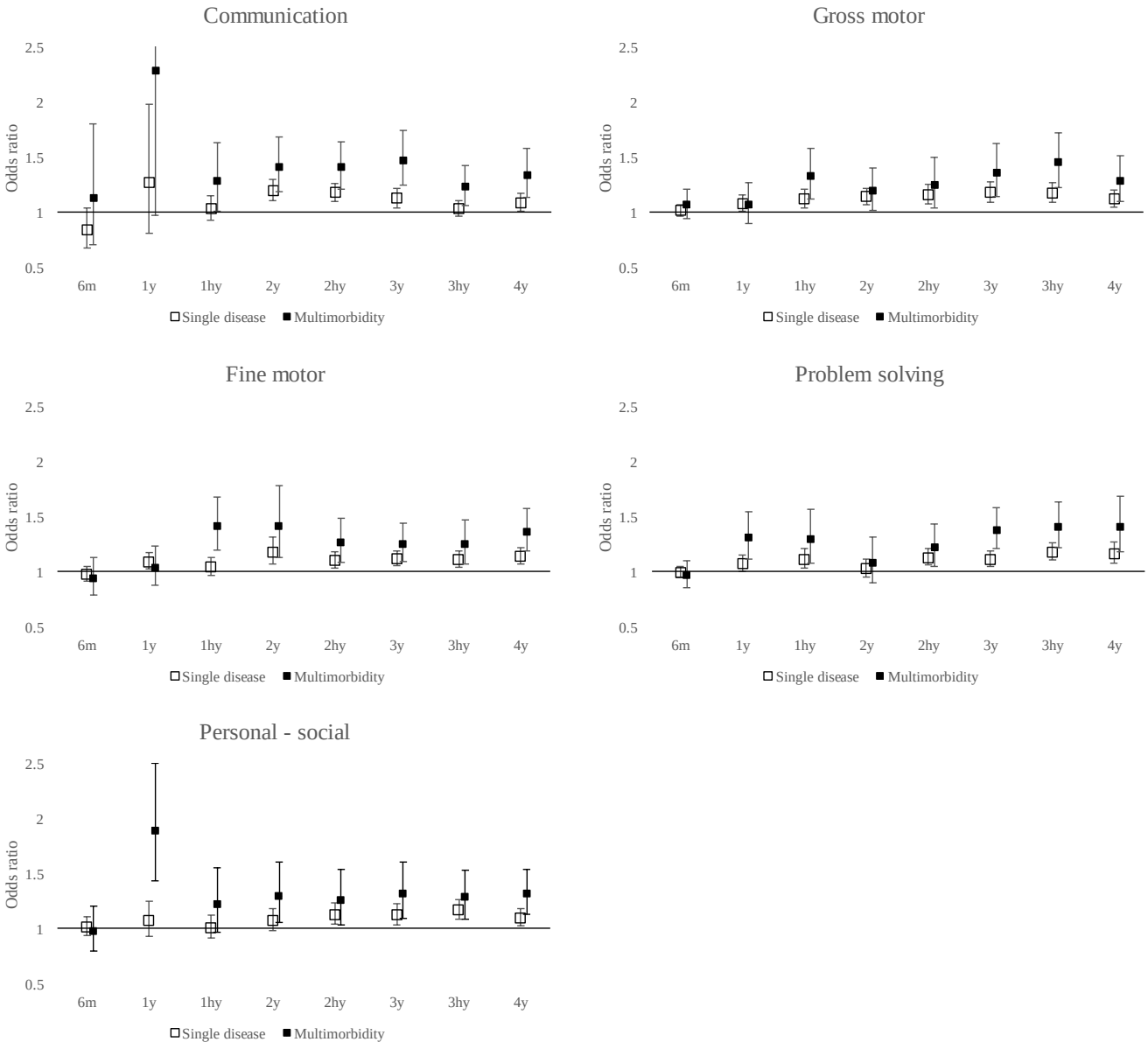

Figure 2. Adjusted odds ratio for developmental delay of offspring for multimorbidity during pregnancy by logistic regression. Models were adjusted for maternal age at birth, parity, history of alcohol consumption, history of smoking, maternal educational attainment, household income, and sex of child. Error bars indicate 95% confidence intervals. The 95% confidence interval for communication at 1 year with multimorbidity was 0.98-5.3.

Supplemental Table 1. Prevalence of 23 maternal diseases

Condition	n	%
Abnormal pre-pregnancy BMI		
Underweight (BMI <18.5 kg/m2)	12,889	15.6
Obesity (BMI >25.0 kg/m2)	8,848	10.7
Allergic disease	2,557	3.1
Anaemia	592	0.7
Diabetes mellitus	124	0.2
Domestic violence	3,632	4.4
Dyslipidaemia	6	0.01
Epilepsy	122	0.2
Gastric or duodenal ulcer	285	0.3
Heart disease	7	0.01
Hepatitis	5	0.01
HIV infection	7	0.01
Hypertension	83	0.1
Inflammatory bowel disease	16	0.02
Kidney disease	17	0.02
Malignancy	0	0
Migraine	41	0.05
Neurological disease	0	0
Other sexually transmitted diseases	1,089	1.3
Mental disorder	550	0.7
Rheumatic or collagen disease	91	0.1
Substance abuse	1	0.001
Thyroid disease	614	0.7

BMI, body mass index.

Supplemental Table 2. The mean ASQ-3 scores and the number of offspring analyzed (n = 82,877) and those excluded (n = 11,927)

Age	Group	Communication				Gross motor				Fine motor				problem solving				Personal-social			
		Mean score	δ*	n	%**	Mean score	δ*	n	%**	Mean score	δ*	n	%**	Mean score	δ*	n	%**	Mean score	δ*	n	%**
6 months	Excluded	46.14	-0.55	9,636	80.8	32.54	-1.07	9,637	80.8	39.81	-1.11	9,605	80.5	42.80	-1.44	9,629	80.7	32.03	-2.44	9,611	80.6
	Included	46.69		74,135	89.5	33.61		74,126	89.4	40.92		73,928	89.2	44.24		74,137	89.5	34.47		74,043	89.3
1 year	Excluded	36.57	-1.30	9,236	77.4	42.01	-0.90	9,241	77.5	47.16	-1.19	9,227	77.4	42.47	-1.89	9,223	77.3	35.88	-1.34	9,204	77.2
	Included	37.86		70,443	85.0	42.90		70,445	85.0	48.35		70,416	85.0	42.36		70,347	84.9	37.22		70,229	84.7
1.5 years	Excluded	32.27	-0.79	8,669	72.7	53.98	-0.61	8,669	72.7	49.36	-0.54	8,664	72.6	42.06	-1.44	8,613	72.2	47.86	-0.08	8,659	72.6
	Included	33.06		66,543	80.3	54.60		66,563	80.3	49.90		66,525	80.3	42.48		66,133	79.8	47.94		66,528	80.3
2 years	Excluded	43.91	-1.19	9,632	80.8	52.81	-0.94	9,630	80.7	49.47	-0.35	9,626	80.7	48.58	-1.25	9,603	80.5	46.14	-0.20	9,620	80.7
	Included	45.11		69,541	83.9	53.75		69,542	83.9	49.82		69,478	83.8	48.83		69,346	83.7	46.34		69,435	83.8
2.5 years	Excluded	51.99	-0.94	9,377	78.6	53.86	-0.90	9,389	78.7	46.34	-0.90	9,337	78.3	49.79	-1.74	9,360	78.5	50.07	0.01	9,370	78.6
	Included	52.92		67,899	81.9	54.75		67,915	81.9	47.25		67,597	81.6	50.52		67,749	81.7	50.06		67,809	81.8
3 years	Excluded	52.28	-0.88	9,663	81.0	54.50	-0.96	9,657	81.1	48.07	-1.15	9,645	80.9	51.14	-1.69	9,597	80.5	50.36	0.03	9,661	81.0
	Included	53.16		69,466	83.8	55.47		69,566	83.9	49.21		69,291	83.6	51.83		68,907	83.1	50.33		69,404	83.7
3.5 years	Excluded	53.44	-0.65	9,222	77.3	55.77	-0.67	9,226	77.4	52.36	-0.69	9,211	77.2	53.91	-1.61	9,163	76.8	54.52	-0.18	9,214	77.3
	Included	54.09		67,447	81.4	56.44		67,398	81.3	53.05		67,361	81.3	54.53		67,140	81.0	54.70		67,358	81.3
4 years	Excluded	52.99	-0.81	8,939	74.9	53.76	-0.58	8,982	75.3	50.91	-0.77	8,983	75.3	54.06	-1.45	8,966	75.2	53.25	-0.27	9,002	75.5
	Included	53.80		65,162	78.6	54.34		65,426	78.9	51.68		65,429	78.9	54.51		65,311	78.8	53.52		65,505	79.0

*Difference in the mean scores from those of the offspring included at each point. **Percentage of total group population.

Supplemental Table 3. The ASQ scores and the number of offspring by testing times from 6 months to 4 years

Age	Testing times	Communication				Gross motor				Fine motor				Problem solving				Personal-social			
		Mean score	n	δ*	%**	Mean score	n	δ*	%**	Mean score	n	δ*	%**	Mean score	n	δ*	%**	Mean score	n	δ*	%**
6 months	1-3	47.39	6,285	0.94	65.9	35.57	6,284	2.57	65.9	43.51	6,271	3.37	65.8	46.40	6,290	2.76	66.0	36.69	6,281	2.90	65.9
	4-7	46.98	21,111	0.52	79.4	34.39	21,110	1.39	79.4	41.86	21,043	1.73	79.2	44.93	21,117	1.30	79.5	35.32	21,072	1.53	79.3
	8	46.46	46,739		99.9	33.00	46,732		99.9	40.14	46,614		99.7	43.64	46,730		99.9	33.79	46,690		99.8
1 year	1-3	40.28	4,028	3.01	42.3	44.55	4,025	2.07	42.2	49.27	4,028	1.15	42.3	44.09	4,018	2.22	42.2	39.19	4,004	2.47	42.0
	4-7	38.78	19,665	1.52	74.0	43.58	19,666	1.10	74.0	48.70	19,645	0.58	73.9	43.18	19,614	1.32	73.8	37.99	19,582	1.26	73.7
	8	37.27	46,750		99.9	42.48	46,754		99.9	48.12	46,743		99.9	41.86	46,715		99.9	36.73	46,643		99.7
1.5 years	1-3	35.21	2,367	2.55	24.8	54.84	2,368	0.36	24.8	50.46	2,364	0.70	24.8	43.53	2,342	1.34	24.6	49.52	2,363	1.91	24.8
	4-7	33.86	17,431	1.20	65.6	54.85	17,434	0.37	65.6	50.19	17,427	0.43	65.6	43.10	17,278	0.91	65.0	48.60	17,424	0.99	65.6
	8	32.65	46,745		99.9	54.49	46,761		100.0	49.76	46,734		99.9	42.19	46,513		99.5	47.61	46,741		99.9
2 years	1-3	45.71	1,719	0.72	18.0	54.29	1,717	0.56	18.0	50.42	1,720	0.68	18.0	49.42	1,710	0.60	17.9	47.14	1,714	0.91	18.0
	4-7	45.30	21,067	0.31	79.3	53.75	21,066	0.02	79.3	49.94	21,048	0.20	79.2	48.80	20,982	-0.01	78.9	46.52	21,028	0.29	79.1
	8	44.99	46,755		99.9	53.73	46,759		99.9	49.74	46,710		99.9	48.82	46,654		99.8	46.23	46,693		99.8
2.5 years	1-3	52.41	1,217	-0.62	12.8	54.66	1,217	-0.12	12.8	47.09	1,200	-0.23	12.6	50.68	1,206	0.12	12.7	50.75	1,211	0.77	12.7
	4-7	52.70	19,941	-0.33	75.0	54.69	19,945	-0.09	75.0	47.08	19,809	-0.24	74.5	50.44	19,873	-0.11	74.8	50.21	19,912	0.22	74.9
	8	53.03	46,741		99.9	54.78	46,753		99.9	47.32	46,588		99.6	50.55	46,670		99.8	49.98	46,686		99.8
3 years	1-3	52.96	1,369	-0.29	14.4	55.69	1,374	0.21	14.4	49.17	1,355	-0.12	14.2	52.17	1,336	0.29	14.0	51.13	1,365	0.89	14.3
	4-7	52.98	21,417	-0.26	80.6	55.44	21,462	-0.03	80.8	49.06	21,339	-0.22	80.3	51.70	21,184	-0.18	79.7	50.47	21,406	0.22	80.5
	8	53.25	46,680		99.8	55.48	46,730		99.9	49.29	46,597		99.6	51.88	46,387		99.2	50.24	46,633		99.7
3.5 years	1-3	53.78	1,080	-0.31	11.3	56.25	1,078	-0.20	11.3	52.58	1,077	-0.53	11.3	53.88	1,065	-0.70	11.2	54.51	1,079	-0.15	11.3
	4-7	54.13	19,641	0.04	73.9	56.41	19,618	-0.05	73.8	52.93	19,593	-0.18	73.7	54.44	19,480	-0.13	73.3	54.83	19,613	0.17	73.8
	8	54.09	46,726		99.9	56.46	46,702		99.9	53.11	46,691		99.8	54.58	46,595		99.6	54.66	46,666		99.8
4y ears	1-3	53.77	909	0.01	9.5	54.40	912	0.09	9.6	51.30	913	-0.46	9.6	53.99	899	-0.57	9.4	53.36	913	-0.12	9.6
	4-7	53.93	17,807	0.17	67.0	54.41	17,900	0.09	67.3	51.51	17,895	-0.25	67.3	54.42	17,862	-0.14	67.2	53.63	17,946	0.14	67.5
	8	53.76	46,446		99.3	54.32	46,614		99.7	51.76	46,621		99.7	54.56	46,550		99.5	53.49	46,646		99.7

*Difference in the mean scores from those of the offspring tested all at each point. **Percentage of total group population.

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	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3,4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5,6
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3,7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7,8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	7,8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-10
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	7,8
Bias	9	Describe any efforts to address potential sources of bias	19
Study size	10	Explain how the study size was arrived at	5,7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10,11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10
		(*b*) Describe any methods used to examine subgroups and interactions	10
		(*c*) Explain how missing data were addressed	10,11
		(*d*) If applicable, explain how loss to follow-up was addressed	-
		(*e*) Describe any sensitivity analyses	-
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	7,8
		(b) Give reasons for non-participation at each stage	7,8
		(c) Consider use of a flow diagram	7,8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11,12
		(b) Indicate number of participants with missing data for each variable of interest	-
		(c) Summarise follow-up time (eg, average and total amount)	8
Outcome data	15*	Report numbers of outcome events or summary measures over time	13-15

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	15,16 - -
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			
Key results	18	Summarise key results with reference to study objectives	17
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	18,19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19,20
Generalisability	21	Discuss the generalisability (external validity) of the study results	20
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21,22

*Give information separately for exposed and unexposed groups.

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

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Association between maternal multimorbidity and neurodevelopment of offspring: a prospective birth cohort study from the Japan Environment and Children's Study

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Keywords:	PUBLIC HEALTH, Maternal medicine < OBSTETRICS, Paediatric neurology < PAEDIATRICS, Multimorbidity, Pregnant Women

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Title: Association between maternal multimorbidity and neurodevelopment of offspring: a prospective birth cohort study from the Japan Environment and Children's Study

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ABSTRACT

Objectives: To investigate the association between multimorbidity during pregnancy and neurodevelopmental delay in offspring using data from a Japanese nationwide birth cohort study.

Design: This study was a prospective birth cohort study.

Setting: This study population included 104,059 fetal records who participated in The Japan Environment and Children's Study (JECS) from 2011 to 2014.

Participants: Pregnant women whose children had undergone developmental testing were included in this analysis.

Primary and secondary outcome measures: Neurodevelopment of offspring was assessed using the Japanese version of the Ages and Stages Questionnaire, third edition (J-ASQ-3), comprising five developmental domains. The number of comorbidities among the pregnant women was categorized as zero, single disease, or multimorbidity (two or more diseases). Maternal chronic conditions included in multimorbidity were defined as conditions with high prevalence among women of reproductive age. A multivariate logistic regression analysis was conducted to examine the association between multimorbidity in pregnant women and offspring development.

Results: Pregnant women with multimorbidity, single disease, and no disease accounted for 3.6%, 30.6%, and 65.8%, respectively. The odds ratios (ORs) for

neurodevelopmental impairment during the follow-up period were similar for infants of mothers with no disease comorbidity and those with a single disease comorbidity. However, the ORs for neurodevelopmental impairment were significantly higher for children born to mothers with multimorbidity compared with those born to healthy mothers.

Conclusion: An association was observed between the number of comorbidities in pregnant women and developmental delay in offspring. Multimorbidity in pregnant women may be associated with neurodevelopmental delay in their offspring. Further research is required in this regard in many other regions of the world.

Keywords

pregnant, women, multimorbidity, Japan, offspring, neurodevelopment, delay

Word counts

Abstract: 265 words; Main text, 2,572 words

Tables/figures: 3 tables/2 figures

References: 27 references

Strengths and limitations of this study

- The study size was adequate for effective investigation.
- Neurodevelopmental progress was assessed in detail using the results of eight points (6 months, 1 year, 1.5 years, 2 years, 2.5 years, 3 years, 3.5 years, and 4 years).
- Chronic diseases that were diagnosed but not treated were ruled out.
- Infants were unable to communicate well, which renders accurate assessment of their neurodevelopment difficult.

INTRODUCTION

Multimorbidity is defined as the coexistence of two or more chronic diseases, whether physical or mental, in the same individual.(1) Multimorbidity is considered one of the principal challenges in older people as the incidence of chronic diseases such as hypertension, dyslipidemia, diabetes, cardiac disease, and malignant tumors, increases with age. Therefore, many studies have focused on older patients with multimorbidities.(2,3) However, diseases such as asthma, arthritis, mental disorders, and HIV can also occur in young people. There are few studies on multimorbidity in young people,(4) including pregnant women.(5,6) Maternal physical morbidities, such

as hypertension, kidney disease, and systemic lupus erythematosus, are potential risk factors for preterm birth (PTB) and low birth weight infants (LBW).(7) Moreover, maternal mental and social morbidities have also been associated with PTB and LBW.(7) Previous studies also reported the relationship between maternal environments such as maternal asthma, maternal intake of fats, maternal and cord blood Manganese levels and child development.(8–10)

Infancy is considered to be the period in which language, cognition, motor skills, and socioemotional domains form the basis for subsequent social participation.(11) It is essential to receive appropriate support, early detection, and intervention during this period.(12) Although maternal nutritional status, certain diseases, and blood substances can affect the neurodevelopment of offspring(8–11), the impacts of multimorbidity in pregnant women on the neurodevelopment of offspring have not been extensively studied.(5,6) A major difference between previous reports and this study was the investigation of the association between multiple diseases of pregnant women and child neurodevelopment; previous reports have mainly focused on the relationship between a single disease or single substance in pregnant women and child neurodevelopment.

The present study aimed to investigate the association between multimorbidity

during pregnancy and neurodevelopmental delay in offspring (every 6 months from birth to age 4 years) using data from an ongoing nationwide birth cohort, namely the Japan Environment and Children's Study (JECS)(13); the neurodevelopment of the participants was evaluated using the Japanese version of the Ages and Stages Questionnaires, Third Edition: Infant Developmental Examination (ASQ-3).(14)

METHODS

Study population

The JECS is a nationwide and government-funded birth cohort study that started recruiting expecting mothers in January 2011.(13); the primary objective was to investigate environmental factors such as exposure to chemicals and airborne pollutants that can affect children's health and development during the fetal stage and early childhood, in order to help policymakers to formulate measures to safeguard the environment for future generations.(15) The study population included 104,059 fetal records who participated in JECS from 2011 to 2014. A flowchart of the study participants is presented in Figure 1. The exclusion criteria included: miscarriage, stillbirth, or unknown birth outcomes (n = 2,123). Second, participants with multiple births, pregnancies with chromosomal abnormalities, participated for the second time

and more, and missing information about drug history, domestic violence, maternal infection, or maternal BMI were excluded (n = 13,377). Moreover, pregnant women whose children were not tested using the ASQ-3 once from 6 months to 4 years old (n=4,046) were excluded. Finally, a total of 82,877 pregnant women were included in the analysis.

Ethics

The JECS protocol was reviewed and approved by the Ministry of the Environment's Institutional Review Board on Epidemiological Studies and the Ethics Committees of all participating institutions (No. 100910001).(13) The JECS was performed following the Declaration of Helsinki. All the participants provided written informed consent.

Patient and Public Involvement statement

This study did not involve patients or public.

Assessment of pregnant multimorbidity

In this study, multimorbidity was defined as the coexistence of two or more physical, mental, or social conditions in an individual according to previous reports.(7) Maternal

chronic conditions included in multimorbidity were defined as conditions with high prevalence among women of reproductive age.(7) To identify pregnant women with the disease more rigorously, the diseases of pregnant women were defined as those that were medically treated at the time of pregnancy. Information was collected through self-reports, medical record transcripts, and medication interviews. The targeted diseases included allergic diseases, such as asthma, anemia, diabetes mellitus, dyslipidemia, epilepsy, gastric or duodenal ulcers, 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), mental disorders, rheumatic or collagen diseases, and thyroid disease. Having an episode of domestic violence, substance abuse, being obese (BMI ≥25), and being thin (BMI <18.5) were each defined as one disease. We used maternal pre-pregnancy body weight data for analysis. Pregnant women with two or more of these diseases during pregnancy were defined as having multimorbidities.

Assessment of neurodevelopment of offspring

Score results from the Japanese version of the ASQ-3 (Ages and Stages Questionnaires, Third Edition: Infant Development Test) at 6 months, 1 year, 1.5 years, 2 years, 2.5

years and, 3 years, 3.5 years, and 4 years were used to evaluate neurodevelopmental measures.(15) These scores were obtained by mailed questionnaire survey filled by caregivers. Neurodevelopmental assessments were performed in the domains of communication, gross motor, fine motor, problem solving, and personal-social. Offspring with scores below the cut-off were defined as having neurodevelopmental delays. The cut-off values were those reported in the Japanese validation version.(14)

Covariates

The covariates were: maternal age at birth, parity, alcohol consumption status, smoking status, educational attainment, household income, and sex of the child; they were selected based on previous studies.(7,10)

Statistical analysis

This study used the datasets jecs-ta-20190930 and jecs-qa-20210401 from JECS. STATA® (MP17) and R® (version 4.2.2) were used for statistical analysis. Multivariate logistic regression analysis was performed to determine the adjusted odds ratios (ORs). The objective variable was the neurodevelopment of the offspring, and the explanatory variable was the multimorbidity in pregnant women. The covariates were: maternal age

at birth, alcohol consumption status, smoking status, educational attainment, household income, sex of the child, and number of births. Multiple imputation methods were performed using R to impute the missing values. Other analyses were performed using the STATA software.

RESULTS

The characteristics of the pregnant women analyzed in this study are presented in Table 1. Pregnant women with multimorbidity, single disease, and no disease accounted for 3.6% (n = 3,001), 30.6% (n = 25,341), and 65.8% (n = 54,535), respectively. Household income of 2–7.99 million/year was accounted for 84.7%; n = 70,184. In total, 51.4% (n = 42,563) and 48.6% (n = 40,314) of the offspring were male and female, respectively. After pregnancy, 4.1 % (n = 3, 408) and 2.7 % (n = 2, 253) of pregnant women had smoking and drinking habits, respectively.

Table 1. Characteristics of pregnant women and their offspring (n = 82,877)

Characteristics		n		%
Number of coexist disease				
	0	54,535		65.8
	1	25,341		30.6
	≥2	3,001		3.6
Mother age at birth				
	<24	7,815		9.4
	25-29	22,721		27.4

	30-34	29,555		35.7
	35-39	18,940		22.9
	≥40	3,846		4.6
Parity				
	0	36,302		43.8
	1	30,646		37.0
	≥2	15,929		19.2
Mother education				
	Junior high school	3,630		4.4
	High school	25,917		31.3
	Vocational junior or technical college	35,323		42.6
	≥University	18,007		21.7
Maternal smoking habits				
	Non-smoking or exit-smoking before pregnancy	68,145		82.2
	Exit-smoking after pregnancy	11,324		13.7
	Still-smoking	3,408		4.1
Maternal drinking habits				
	Non-drinker	41,481		50.1
	Exit drinking after pregnancy	39,143		47.2
	drinking	2,253		2.7
Annual household income (10,00 JPY)				
	<200	4,193		5.1
	200-399	28,476		34.4
	400-599	28,663		34.6
	600-799	13,045		15.7
	800-999	5,233		6.3
	1000-1199	1,870		2.3
	1200-1499	735		0.9
	1500-1999	427		0.5
	≥2000	235		0.3
Child sex				
	boys	42,563		51.4
	girls	40,314		48.6

The prevalence of 23 maternal diseases is described in supplemental table 1. Maternal underweight (BMI <18.5) (15.6%) was the most frequently observed chronic condition, followed by maternal obesity (BMI ≥25) (10.7%). The most frequent diseases on medication were allergic diseases (3.1%), other sexually transmitted diseases (1.3%), anemia (0.7%), mental disorders (0.7%) and thyroid disease (0.7%).

The prevalence of neurodevelopmental delay in offspring is presented in Table 2. The prevalence of communication delays at 6 months and 1 year was significantly lower than that of the others.

Table 2. Prevalence of neurodevelopment delay of offspring

Age	Number of maternal comorbidity	Communication	Gross motor	Fine motor	Problem solving	Personal-social
		n (%)	n (%)	n (%)	n (%)	n (%)
6 months	0	318 (0.4)	5,540 (6.7)	2,788 (3.4)	5,625 (6.8)	1,898 (2.3)
	1	123 (0.1)	2,603 (3.1)	1,237 (1.5)	2,596 (3.1)	891 (1.1)
	≥2	19 (0.02)	316 (0.4)	137 (0.2)	334 (0.4)	101 (0.1)
1 year	0	54 (0.1)	2,711 (3.3)	2,743 (3.3)	2,478 (3.0)	566 (0.7)
	1	31 (0.04)	1,324 (1.6)	1,383 (1.7)	1,256 (1.5)	282 (0.3)
	≥2	6 (0.01	148 (0.2)	154 (0.2)	142 (0.2)	57 (0.1)
1 half years	0	1,091 (1.3)	2,138 (2.6)	2,000 (2.4)	1,831 (2.2)	1,209 (1.5)
	1	528 (0.6)	1,100 (1.3)	984 (1.2)	939 (1.1)	564 (0.7)
	≥2	76 (0.1)	148 (0.2)	156 (0.2)	168 (0.2)	78 (0.1)
2 years	0	1,851 (2.2)	2,816 (3.4)	1,060 (1.3)	2,106 (2.5)	1,400 (1.7)
	1	1,048 (1.3)	1,474 (1.8)	590 (0.7)	1,004 (1.2)	706 (0.9)
	≥2	147 (0.2)	176 (0.2)	84 (0.1)	122 (0.1)	99 (0.1)
2 half years	0	2,445 (3.0)	2,042 (2.5)	2,696 (3.3)	2,708 (3.3)	1,634 (2.0)
	1	1,376 (1.7)	1,086 (1.3)	1,389 (1.7)	1,445 (1.7)	860 (1.0)
	≥2	199 (0.2)	132 (0.2)	186 (0.2)	187 (0.2)	112 (0.1)
3 years	0	1,901 (2.3)	2,037 (2.5)	3,492 (4.2)	3,406 (4.1)	1,603 (1.9)
	1	1,030 (1.2)	1,102 (1.3)	1,843 (2.2)	1,723 (2.2)	861 (1.0)
	≥2	164 (0.2)	144 (0.2)	245 (0.3)	269 (0.3)	122 (0.1)
3 half years	0	2,873 (3.5)	2,020 (2.4)	2,522 (3.0)	2,659 (3.2)	2,130 (2.6)
	1	1,467 (1.8)	1,098 (1.3)	1,341 (1.6)	1,508 (1.8)	1,171 (1.4)
	≥2	219 (0.3)	155 (0.2)	182 (0.2)	218 (0.3)	154 (0.2)
4 years	0	2,157 (2.6)	2,597 (3.1)	3,038 (3.7)	1,733 (2.1)	2,629 (3.2)
	1	1,118 (1.3)	1,347 (1.6)	1,651 (2.0)	977 (1.2)	1,362 (1.6)
	≥2	166 (0.2)	177 (0.2)	239 (0.3)	145 (0.2)	194 (0.2)

The number of the offspring tested as well as the mean ASQ-3 scores at each time point in the offspring those were analyzed and those who were excluded are shown in supplemental table 2. In the included group, the number of the offspring tested at 6 months and 4 years were 74,195 and 65,705, respectively. In the excluded group, the number of the offspring tested at 6 months and 4 years were 9,642 and 9,019, respectively. At each time point, the offspring were defined as tested if they answered at least one domain of the ASQ-3. The examination rates in offspring who were excluded were lower overall. The number of the offspring tested tended to decrease with age in both groups. The difference in the mean scores of the offspring excluded from the mean scores of those included ranged from -2.44 to 0.11. The mean scores in the offspring who were excluded were lower from 6 months to 4 years in most time points. The ASQ-3 scores and the number of the offspring by categories of the number of tests at each time point are shown in the supplemental table 3. The offspring were categorized into three groups: until 4 years, tested in all time points, 1 to 3 times, and 4 to 7 times. The number of the offspring tested at all time points, 4 to 7 times, and 1 to 3 times were 46,766, 26,578, and 9,530 respectively. The number of the offspring tended to decrease with age in groups tested less frequently. There was a particularly large decrease in the

group tested 1 to 3 times. The difference in ASQ-3 scores of the groups tested less frequently from those of the group tested in all time points ranged from -1.62 to 3.37. Comparing the group tested in all time points, the groups tested less frequently tended to have higher scores until 2 years and lower scores after 2.5 years. The results of the multivariate logistic regression analysis conducted on the number of comorbidities in pregnant women and the neurodevelopment of offspring are shown in Table 3 and Figure 2. Except at 6 months, the ORs were more than 1 for any of the following items: communication, gross motor, fine motor, problem solving, and personal and social. The ORs at 6 months were lower than those at other ages for all items, both single disease comorbidity and multimorbidity. ORs tended to be higher with increasing age of the offspring, and the ORs for all items were higher at 4 years than at 6 months for both single-disease coexistence and multimorbidity. The ORs for single disease comorbidities ranged from 0.85 (95% CI 0.69–1.05) to 1.28 (95% Cl 0.82–1.99). The OR range for multimorbidity was 0.95 (95% CI 0.80–1.14) to 2.29 (95% CI 0.98–5.36), and that at 4 years of age was 1.30 (95% CI 1.11–1.52) to 1.42 (95% CI 1.19–1.69) for all domains.

Table 3. Adjusted odds ratio for developmental delay of offspring for multimorbidity during pregnancy by logistic regression

Age	Number of maternal comorbidity	Communication	Gross motor	Fine motor	Problem solving	Personal-social
		Adjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)	Adjusted OR (95% CI)
6 months	1	0.85 (0.69–1.05)	1.03 (0.98–1.08)	0.99 (0.92–1.06)	1.01 (0.96–1.06)	1.02 (0.94–1.11)
	≥2	1.14 (0.71–1.81)	1.08 (0.96–1.22)	0.95 (0.8–1.14)	0.99 (0.86–1.11)	0.99 (0.8–1.21)
1 year	1	1.28 (0.82–1.99)	1.09 (1.02–1.16)	1.10 (1.03–1.18)	1.08 (1.01–1.16)	1.08 (0.94–1.25)
	≥2	2.29 (0.98–5.36)	1.08 (0.91–1.28)	1.05 (0.89–1.24)	1.32 (1.12–1.55)	1.90 (1.44–2.50)
1 half years	1	1.04 (0.94–1.16)	1.13 (1.05–1.22)	1.05 (0.97–1.14)	1.13 (1.04–1.22)	1.02 (0.92–1.13)
	≥2	1.29 (1.02–1.64)	1.34 (1.13–1.59)	1.42 (1.20–1.68)	1.32 (1.09–1.57)	1.23 (0.97–1.56)
2 years	1	1.21 (1.12–1.30)	1.15 (1.08–1.23)	1.19 (1.08–1.32)	1.04 (0.96–1.12)	1.09 (0.99–1.19)
	≥2	1.42 (1.19–1.69)	1.21 (1.03–1.41)	1.42 (1.13–1.78)	1.09 (0.9–1.32)	1.31 (1.06–1.61)
2 half years	1	1.19 (1.11–1.27)	1.17 (1.09–1.26)	1.11 (1.04–1.19)	1.14 (1.07–1.22)	1.14 (1.04–1.24)
	≥2	1.42 (1.22–1.65)	1.26 (1.05–1.51)	1.28 (1.09–1.49)	1.23 (1.05–1.44)	1.26 (1.04–1.54)
3 years	1	1.14 (1.05–1.23)	1.19 (1.10–1.28)	1.13 (1.06–1.19)	1.12 (1.06–1.19)	1.13 (1.04–1.24)
	≥2	1.48 (1.25–1.75)	1.37 (1.15–1.63)	1.26 (1.10–1.45)	1.39 (1.22–1.59)	1.33 (1.10–1.61)
3 half years	1	1.04 (0.98–1.11)	1.18 (1.10–1.28)	1.12 (1.04–1.20)	1.19 (1.11–1.27)	1.18 (1.09–1.27)
	≥2	1.24 (1.07–1.44)	1.46 (1.23–1.73)	1.26 (1.07–1.47)	1.42 (1.22–1.64)	1.30 (1.09–1.54)
4 years	1	1.10 (1.02–1.18)	1.13 (1.06–1.21)	1.15 (1.08–1.22)	1.18 (1.08–1.27)	1.11 (1.03–1.18)
	≥2	1.35 (1.14–1.59)	1.30 (1.11–1.52)	1.37 (1.19–1.58)	1.42 (1.19–1.69)	1.32 (1.14–1.54)

Models were adjusted for maternal age at birth, parity, history of alcohol consumption, history of smoking, maternal educational attainment, sex of child, household income, and sex of child.

DISCUSSION

This investigation showed significant associations between multimorbidities in pregnant women and delayed neurodevelopment in the offspring. The ORs were higher for most of the neurodevelopmental items in pregnant women with multimorbidities than in those with a single disease. This study is the first to highlight the significance of the association between multimorbidity in pregnant women and the neurodevelopment in the offspring, despite the existence of reports on the association between specific diseases, such as asthma, chronic inflammatory arthritis, depression, thyroid conditions, diabetes, and epilepsy, in pregnant women and the neurodevelopment of their children.(8,16–18) As the number of comorbidities in pregnant women increases, the factors contributing to neurodevelopmental delay in the offspring may increase. In the future, health education and treatment in terms of the number of comorbidities during pregnancy should be considered.

The ORs for neurodevelopmental delay increased with the increase in the offspring's age. This may have been caused by the increasing accuracy of the assessment as the offspring aged. An accurate assessment of neurodevelopment cannot be made until the child has grown to a certain age.(19) Parents' assessments of their

children's neurodevelopment may not be established until a certain period of parenting time. Neurodevelopmental delays may have been caused by social factors.(20) It has been reported that depressed mothers tend to form family environments that are socially and economically disadvantageous to their children.(21) Pregnant women with multimorbidities and certain mental diseases may have tended to form socioeconomically undesirable family environments.(22) Further, a great deal of the brain's ultimate structure and capacity is shaped up to 3 years of age.(11) The maternal immune activation may be caused by comorbidities during pregnancy, and components of the maternal immune system such as microglia and cytokines produced by microglia may trigger inappropriate fetal immune responses and may lead to neurodevelopment delay in the future.(23) Neurodevelopmental delays in children may have gradually appeared as a result of multiple factors such as the postnatal brain development process, the undesirable family environment, and the caregiver's assessments of their children. Future research should take into account the prospect that factors such as children's birthweight and/or gestational age at birth, nutritional status, Apgar score, and maternal psychological status can be intermediate variables in the association between multimorbidity and neurodevelopmental delay.

This study has several limitations. First, Pregnant women with diagnoses but

no medication were not included in the disease sample in this study, with the exception of domestic violence, obese, and skinny women. The criterion for the disease was defined as the presence of medication; the number of pregnant women with the disease may have been higher if the study had been conducted using different criteria. Some have criticized the definition of multimorbidity as simply having more than one disease, which would include a large population.(24) In the future, a definition of multimorbidity that is suitable for the target community will be required since the significant diseases and conditions vary depending on the target population.(24) Second, it was difficult in this study to discuss the biological mechanisms of the association between multimorbidity and neurodevelopmental delay. The association between various diseases and neurodevelopmental delays has been reported in previous studies.(8,16–18,25) Further studies on disease characteristics and disease combinations may allow for hypotheses to be made regarding the biological mechanisms underlying the association between multimorbidity and neurodevelopmental delay. Third, as participants in the JECS were only collaborators, selection bias may have occurred.(15) The prevalence of multimorbidity and the results of the association between multimorbidity and neurodevelopmental delay might have been different if the study design included pregnant women who did not participate in the JECS. The number of

pregnant women with multimorbidities would increase and the results of the effects on the neurodevelopment of the children might be different if all pregnant women and children registered in the administration were included in the study. Fourth, we didn't use the data on maternal situation after delivery. Incomplete questionnaire responses were reported to be influenced by the maternal situation after delivery as health status, number of siblings, partner, and primary caregiver.(26,27) The ASQ-3 scores of the offspring who were excluded were lower than those of the offspring included in most time points. In the analyzed population, the changes in the ASQ-3 scores of the offspring tested less frequently differed from those of the offspring tested at all time points. Except for the group tested at all time points, the number of the offspring tested tended to decrease with age. It was difficult to examine the association between incomplete responses and the ASQ-3 scores in this study. In the future, we need to consider studies with regard to incomplete participants and neurodevelopmental delay of offspring. There was no analysis of data from offspring, such as birth weight, gestational age at birth, nutritional status, and Apgar score, but, as we mentioned above, they were not selected as adjusted variables because we considered them as intermediate variables in the association between multimorbidity and neurodevelopmental delay.

Previous reports on multimorbidities in pregnant women have focused on its

prevalence and impact on pregnant women themselves.(5–7) This study is a new report in terms of the effect of multimorbidity in pregnant women on their offspring and provides important recommendations regarding the health of pregnant women.

CONCLUSION

This study demonstrated an association between multimorbidities in pregnant women and neurodevelopmental delays in their offspring in Japan. To clarify its mechanisms and effects, more research needs to be done in many regions of the world with different economic, geographic, and racial conditions.

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Contributors

TA and YaS designed this study. JECS collected the data and obtained funding. YaS, EY, KNag, ST, YI, CM, SI, and RK collected the data. TA and YaS conducted the data analysis. TA, YaS, EY, YuS, KNak, YK, KNag, ST, YI, HI, TY, CM, SI, and RK contributed to data interpretation. TA, YaS, EY, YuS, KNak, YK, KNag, ST, YI, HI, TY, CM, SI, RK, and the JECS Group conducted critical reviews. TA drafted the manuscript. YaS made critical revisions. YaS is responsible for the overall content as guarantor. All the authors have reviewed and commented on the manuscript. All the

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Competing interests

The authors declare that they have no competing interests.

Patient and public involvement

The patients and/or the public were not involved in the design, conduct, reporting, or dissemination of this study.

Patient consent for publication

Not applicable.

Ethics approval

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

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

Data are unsuitable for public deposition due to ethical restrictions and legal framework of Japan. It is prohibited by the Act on the Protection of Personal Information (Act No. 57 of 30 May 2003, amendment on 9 September 2015) to publicly deposit the data containing personal information. Ethical Guidelines for Medical and Health Research Involving Human Subjects enforced by the Japan Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare also restricts the open sharing of the epidemiologic data. All inquiries about access to data should be sent to: jecs-en@nies.go.jp. The person responsible for handling enquiries

sent to this e-mail address is Dr Shoji F. Nakayama, JECS Programme Office, National Institute for Environmental Studies.

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Figure legends

Figure 1. Fetal records selection flow chart.

Figure 2. Adjusted odds ratio for developmental delay of offspring for multimorbidity during pregnancy by logistic regression. Models were adjusted for maternal age at birth, parity, history of alcohol consumption, history of smoking, maternal educational

attainment, household income, and sex of child. Error bars indicate 95% confidence intervals. The 95% confidence interval for communication at 1 year with multimorbidity was 0.98-5.3.

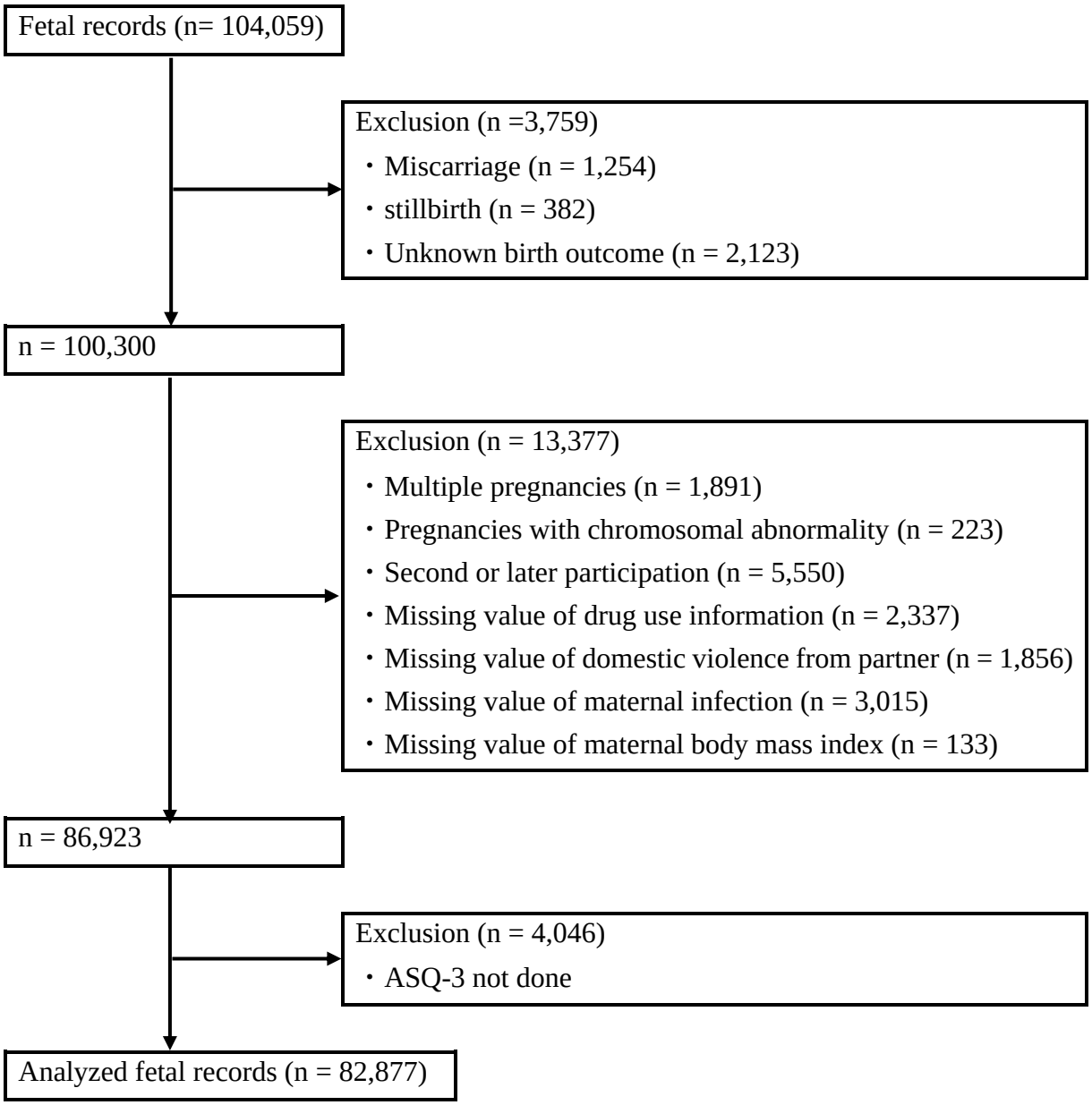

Figure 1. Fetal records selection flow chart.

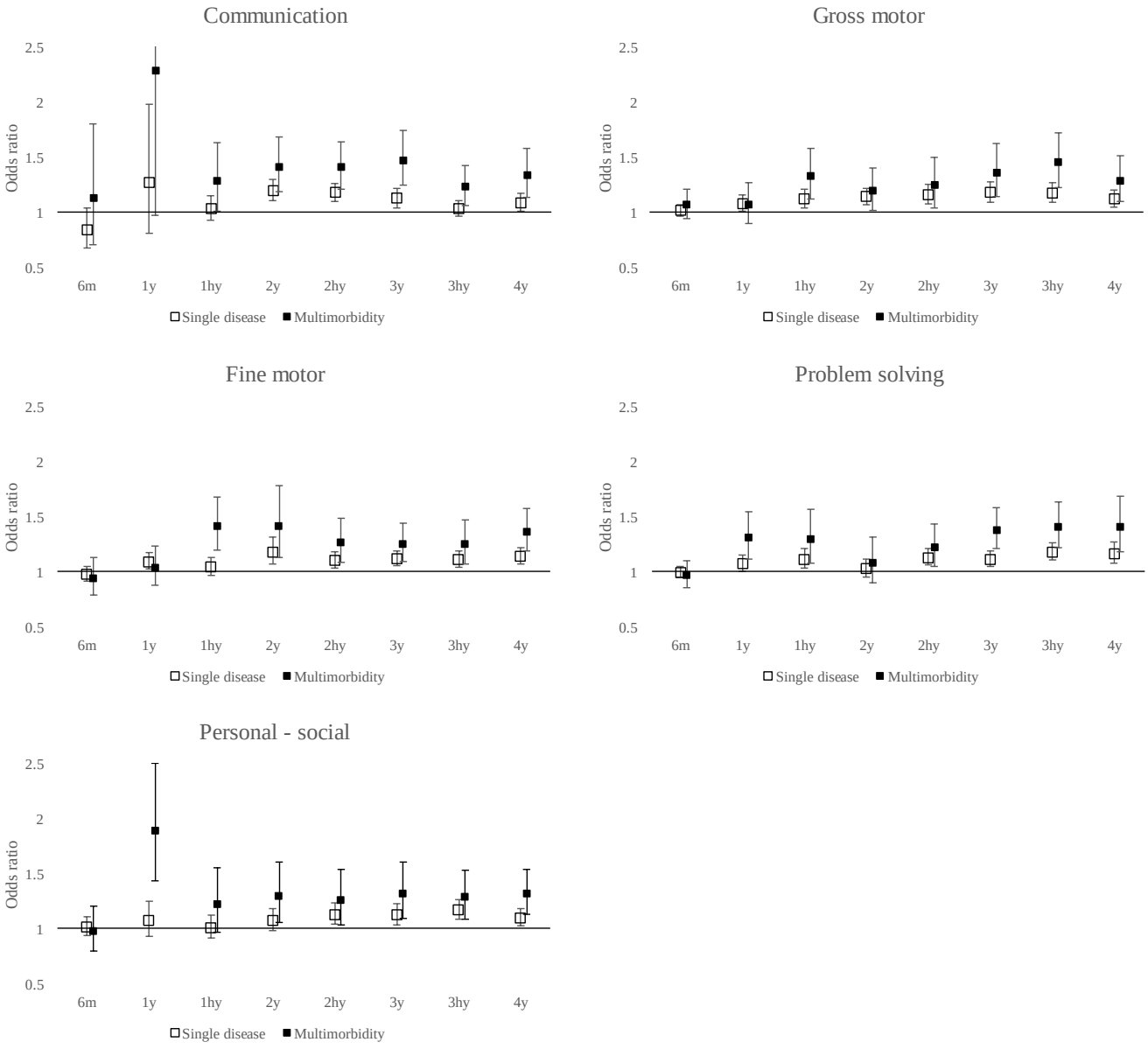

Figure 2. Adjusted odds ratio for developmental delay of offspring for multimorbidity during pregnancy by logistic regression. Models were adjusted for maternal age at birth, parity, history of alcohol consumption, history of smoking, maternal educational attainment, household income, and sex of child. Error bars indicate 95% confidence intervals. The 95% confidence interval for communication at 1 year with multimorbidity was 0.98-5.3.

Supplemental Table 1. Prevalence of 23 maternal diseases

Condition	n	%
Abnormal pre-pregnancy BMI		
Underweight (BMI <18.5 kg/m2)	12,889	15.6
Obesity (BMI >25.0 kg/m2)	8,848	10.7
Allergic disease	2,557	3.1
Anaemia	592	0.7
Diabetes mellitus	124	0.2
Domestic violence	3,632	4.4
Dyslipidaemia	6	0.01
Epilepsy	122	0.2
Gastric or duodenal ulcer	285	0.3
Heart disease	7	0.01
Hepatitis	5	0.01
HIV infection	7	0.01
Hypertension	83	0.1
Inflammatory bowel disease	16	0.02
Kidney disease	17	0.02
Malignancy	0	0
Migraine	41	0.05
Neurological disease	0	0
Other sexually transmitted diseases	1,089	1.3
Mental disorder	550	0.7
Rheumatic or collagen disease	91	0.1
Substance abuse	1	0.001
Thyroid disease	614	0.7

BMI, body mass index.

Supplemental Table 2. The mean ASQ-3 scores and the number of offspring analyzed (n = 82,877) and those excluded (n = 11,927)

Age	Group	Communication				Gross motor				Fine motor				problem solving				Personal-social			
		Mean score	δ*	n	%**	Mean score	δ*	n	%**	Mean score	δ*	n	%**	Mean score	δ*	n	%**	Mean score	δ*	n	%**
6 months	Excluded	46.14	-0.55	9,636	80.8	32.54	-1.07	9,637	80.8	39.81	-1.11	9,605	80.5	42.80	-1.44	9,629	80.7	32.03	-2.44	9,611	80.6
	Included	46.69		74,135	89.5	33.61		74,126	89.4	40.92		73,928	89.2	44.24		74,137	89.5	34.47		74,043	89.3
1 year	Excluded	36.57	-1.30	9,236	77.4	42.01	-0.90	9,241	77.5	47.16	-1.19	9,227	77.4	42.47	-1.89	9,223	77.3	35.88	-1.34	9,204	77.2
	Included	37.86		70,443	85.0	42.90		70,445	85.0	48.35		70,416	85.0	42.36		70,347	84.9	37.22		70,229	84.7
1.5 years	Excluded	32.27	-0.79	8,669	72.7	53.98	-0.61	8,669	72.7	49.36	-0.54	8,664	72.6	42.06	-1.44	8,613	72.2	47.86	-0.08	8,659	72.6
	Included	33.06		66,543	80.3	54.60		66,563	80.3	49.90		66,525	80.3	42.48		66,133	79.8	47.94		66,528	80.3
2 years	Excluded	43.91	-1.19	9,632	80.8	52.81	-0.94	9,630	80.7	49.47	-0.35	9,626	80.7	48.58	-1.25	9,603	80.5	46.14	-0.20	9,620	80.7
	Included	45.11		69,541	83.9	53.75		69,542	83.9	49.82		69,478	83.8	48.83		69,346	83.7	46.34		69,435	83.8
2.5 years	Excluded	51.99	-0.94	9,377	78.6	53.86	-0.90	9,389	78.7	46.34	-0.90	9,337	78.3	49.79	-1.74	9,360	78.5	50.07	0.01	9,370	78.6
	Included	52.92		67,899	81.9	54.75		67,915	81.9	47.25		67,597	81.6	50.52		67,749	81.7	50.06		67,809	81.8
3 years	Excluded	52.28	-0.88	9,663	81.0	54.50	-0.96	9,657	81.1	48.07	-1.15	9,645	80.9	51.14	-1.69	9,597	80.5	50.36	0.03	9,661	81.0
	Included	53.16		69,466	83.8	55.47		69,566	83.9	49.21		69,291	83.6	51.83		68,907	83.1	50.33		69,404	83.7
3.5 years	Excluded	53.44	-0.65	9,222	77.3	55.77	-0.67	9,226	77.4	52.36	-0.69	9,211	77.2	53.91	-1.61	9,163	76.8	54.52	-0.18	9,214	77.3
	Included	54.09		67,447	81.4	56.44		67,398	81.3	53.05		67,361	81.3	54.53		67,140	81.0	54.70		67,358	81.3
4 years	Excluded	52.99	-0.81	8,939	74.9	53.76	-0.58	8,982	75.3	50.91	-0.77	8,983	75.3	54.06	-1.45	8,966	75.2	53.25	-0.27	9,002	75.5
	Included	53.80		65,162	78.6	54.34		65,426	78.9	51.68		65,429	78.9	54.51		65,311	78.8	53.52		65,505	79.0

*Difference in the mean scores from those of the offspring included at each point. **Percentage of total group population.

Supplemental Table 3. The ASQ scores and the number of offspring by testing times from 6 months to 4 years

Age	Testing times	Communication				Gross motor				Fine motor				Problem solving				Personal-social			
		Mean score	n	δ*	%**	Mean score	n	δ*	%**	Mean score	n	δ*	%**	Mean score	n	δ*	%**	Mean score	n	δ*	%**
6 months	1-3	47.39	6,285	0.94	65.9	35.57	6,284	2.57	65.9	43.51	6,271	3.37	65.8	46.40	6,290	2.76	66.0	36.69	6,281	2.90	65.9
	4-7	46.98	21,111	0.52	79.4	34.39	21,110	1.39	79.4	41.86	21,043	1.73	79.2	44.93	21,117	1.30	79.5	35.32	21,072	1.53	79.3
	8	46.46	46,739		99.9	33.00	46,732		99.9	40.14	46,614		99.7	43.64	46,730		99.9	33.79	46,690		99.8
1 year	1-3	40.28	4,028	3.01	42.3	44.55	4,025	2.07	42.2	49.27	4,028	1.15	42.3	44.09	4,018	2.22	42.2	39.19	4,004	2.47	42.0
	4-7	38.78	19,665	1.52	74.0	43.58	19,666	1.10	74.0	48.70	19,645	0.58	73.9	43.18	19,614	1.32	73.8	37.99	19,582	1.26	73.7
	8	37.27	46,750		99.9	42.48	46,754		99.9	48.12	46,743		99.9	41.86	46,715		99.9	36.73	46,643		99.7
1.5 years	1-3	35.21	2,367	2.55	24.8	54.84	2,368	0.36	24.8	50.46	2,364	0.70	24.8	43.53	2,342	1.34	24.6	49.52	2,363	1.91	24.8
	4-7	33.86	17,431	1.20	65.6	54.85	17,434	0.37	65.6	50.19	17,427	0.43	65.6	43.10	17,278	0.91	65.0	48.60	17,424	0.99	65.6
	8	32.65	46,745		99.9	54.49	46,761		100.0	49.76	46,734		99.9	42.19	46,513		99.5	47.61	46,741		99.9
2 years	1-3	45.71	1,719	0.72	18.0	54.29	1,717	0.56	18.0	50.42	1,720	0.68	18.0	49.42	1,710	0.60	17.9	47.14	1,714	0.91	18.0
	4-7	45.30	21,067	0.31	79.3	53.75	21,066	0.02	79.3	49.94	21,048	0.20	79.2	48.80	20,982	-0.01	78.9	46.52	21,028	0.29	79.1
	8	44.99	46,755		99.9	53.73	46,759		99.9	49.74	46,710		99.9	48.82	46,654		99.8	46.23	46,693		99.8
2.5 years	1-3	52.41	1,217	-0.62	12.8	54.66	1,217	-0.12	12.8	47.09	1,200	-0.23	12.6	50.68	1,206	0.12	12.7	50.75	1,211	0.77	12.7
	4-7	52.70	19,941	-0.33	75.0	54.69	19,945	-0.09	75.0	47.08	19,809	-0.24	74.5	50.44	19,873	-0.11	74.8	50.21	19,912	0.22	74.9
	8	53.03	46,741		99.9	54.78	46,753		99.9	47.32	46,588		99.6	50.55	46,670		99.8	49.98	46,686		99.8
3 years	1-3	52.96	1,369	-0.29	14.4	55.69	1,374	0.21	14.4	49.17	1,355	-0.12	14.2	52.17	1,336	0.29	14.0	51.13	1,365	0.89	14.3
	4-7	52.98	21,417	-0.26	80.6	55.44	21,462	-0.03	80.8	49.06	21,339	-0.22	80.3	51.70	21,184	-0.18	79.7	50.47	21,406	0.22	80.5
	8	53.25	46,680		99.8	55.48	46,730		99.9	49.29	46,597		99.6	51.88	46,387		99.2	50.24	46,633		99.7
3.5 years	1-3	53.78	1,080	-0.31	11.3	56.25	1,078	-0.20	11.3	52.58	1,077	-0.53	11.3	53.88	1,065	-0.70	11.2	54.51	1,079	-0.15	11.3
	4-7	54.13	19,641	0.04	73.9	56.41	19,618	-0.05	73.8	52.93	19,593	-0.18	73.7	54.44	19,480	-0.13	73.3	54.83	19,613	0.17	73.8
	8	54.09	46,726		99.9	56.46	46,702		99.9	53.11	46,691		99.8	54.58	46,595		99.6	54.66	46,666		99.8
4y ears	1-3	53.77	909	0.01	9.5	54.40	912	0.09	9.6	51.30	913	-0.46	9.6	53.99	899	-0.57	9.4	53.36	913	-0.12	9.6
	4-7	53.93	17,807	0.17	67.0	54.41	17,900	0.09	67.3	51.51	17,895	-0.25	67.3	54.42	17,862	-0.14	67.2	53.63	17,946	0.14	67.5
	8	53.76	46,446		99.3	54.32	46,614		99.7	51.76	46,621		99.7	54.56	46,550		99.5	53.49	46,646		99.7

*Difference in the mean scores from those of the offspring tested all at each point. **Percentage of total group population.

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	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2, 3, 4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5, 6
Objectives	3	State specific objectives, including any prespecified hypotheses	6, 7
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	7, 8
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	7–9
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8–10
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	7–11
Bias	9	Describe any efforts to address potential sources of bias	8–10
Study size	10	Explain how the study size was arrived at	7, 8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10, 11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10, 11
		(*b*) Describe any methods used to examine subgroups and interactions	10, 11
		(*c*) Explain how missing data were addressed	10, 11
		(*d*) If applicable, explain how loss to follow-up was addressed	Not Applicable
		(*e*) Describe any sensitivity analyses	Not Applicable
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	7, 8
		(b) Give reasons for non-participation at each stage	Not Applicable
		(c) Consider use of a flow diagram	7, 8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11, 12
		(b) Indicate number of participants with missing data for each variable of interest	15, 16
		(c) Summarise follow-up time (eg, average and total amount)	7

Outcome data	15*	Report numbers of outcome events or summary measures over time	13–16
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	10, 16–17
		(*b*) Report category boundaries when continuous variables were categorized	Not Applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not Applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Not Applicable
Discussion			
Key results	18	Summarise key results with reference to study objectives	18
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	19–21
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18–19
Generalisability	21	Discuss the generalisability (external validity) of the study results	22
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	24

*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.