



BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2023-082585
Article Type:	Original research
Date Submitted by the Author:	03-Dec-2023
Complete List of Authors:	Akagi, Takanobu; Asahikawa Medical University, Department of Social Medicine Saijo, Yasuaki; Asahikawa Medical University, Division of Public Health and Epidemiology, Department of Social Medicine
Keywords:	PUBLIC HEALTH, Maternal medicine < OBSTETRICS, Paediatric neurology < PAEDIATRICS

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Supérieur (ABES).

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

Author names

Takanobu Akagi^a, Yasuaki Saijo^a, Eiji Yoshioka^a, Yukihiro Sato^a, Kentaro Nakanishi^b, Yasuhito Kato^b, Ken Nagaya^c, Satoru Takahashi^d, Yoshiya Ito^e, Hiroyoshi Iwata^f, Takeshi Yamaguchi^f, Chihiro Miyashita^f, Sachiko Itoh^f, Reiko Kishi^f, the Japan Environment and Children's Study (JECS) Group^h

Author affiliations

^aDivision of Public Health and Epidemiology, Department of Social Medicine, Asahikawa Medical University, 1-1-1, Midorigaoka higashi2-jo, Asahikawa, Hokkaido 078-8510, Japan

^bDepartment of Obstetrics and Gynecology, Asahikawa Medical University, Asahikawa, 1-1-1, Midorigaoka higashi2-jo, Asahikawa, Hokkaido 078-8510, Japan

^cDivision of Neonatology, Perinatal Medical Center, Asahikawa Medical University Hospital, 1-1-1, Midorigaoka higashi2-jo, Asahikawa, Hokkaido 078-8510, Japan

19 ^dDepartment of Pediatrics, Asahikawa Medical University, 1-1-1, Midorigaoka higashi2-
20 jo, Asahikawa, Hokkaido 078-8510, Japan

21 ^eFaculty of Nursing, Japanese Red Cross Hokkaido College of Nursing, 664-1, Akebono-
22 cho, Kitami, Hokkaido 090-0011, Japan

23 ^fCenter for Environmental and Health Sciences, Hokkaido University, Kita12-jo, Nishi7-
24 chome, Kita-ku, Sapporo, Hokkaido 060-0812, Japan

25 ^aFaculty of Health Sciences, Hokkaido University, Kita12-jo, Nishi5-chome, Kita-ku,
26 Sapporo, Hokkaido 060-0812, Japan

27 ^hMembers of the Japan Environment and Children's Study Group are listed in the
28 Appendices.

30 **Corresponding author**

31 Yasuaki Saijo

32 Division of Public Health and Epidemiology, Department of Social Medicine, Asahikawa Medical
33 University

34 078-8510, 1-1-1, Midorigaoka higashi2-io, Asahikawa, Hokkaido, Japan

35 Tel: +81-166-68-2402

36 Email: y-saijo@asahikawa-med.ac.jp

37

38 **ABSTRACT**

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

42 **Design:** This study was a prospective birth cohort study.

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

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

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

73 References: 24 references

74

75 **Strengths and limitations of this study**

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

83

84 **INTRODUCTION**

85 Multimorbidity is defined as the coexistence of two or more chronic diseases, whether
86 physical or mental, in the same individual.(1) Multimorbidity is considered one of the
87 principal challenges in older people as the incidence of chronic diseases such as
88 hypertension, dyslipidemia, diabetes, cardiac disease, and malignant tumors, increases
89 with age. Therefore, many studies have focused on older patients with
90 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.

1
2
3
4
5 109 The present study aimed to investigate the association between multimorbidity
6
7
8 110 during pregnancy and neurodevelopmental delay in offspring (every 6 months from birth
9
10
11 111 to age 4 years) using data from an ongoing nationwide birth cohort, namely the Japan
12
13
14 112 Environment and Children's Study (JECS)(13); the neurodevelopment of the participants
15
16
17 113 was evaluated using the Japanese version of the Ages and Stages Questionnaires, Third
18
19
20 114 Edition: Infant Developmental Examination (ASQ-3).(14)
21
22
23
24
25
26
27
28
29
30
31

32 116 **METHODS**

33 117 **Study population**

34
35 118 The JECS is a nationwide and government-funded birth cohort study that started
36
37
38 119 recruiting expecting mothers in January 2011.(13); the primary objective was to
39
40
41 120 investigate environmental factors such as exposure to chemicals and airborne pollutants
42
43
44 121 that can affect children's health and development during the fetal stage and early
45
46
47 122 childhood, in order to help policymakers to formulate measures to safeguard the
48
49
50 123 environment for future generations.(15) The study population included 104,059 fetal
51
52
53 124 records who participated in JECS from 2011 to 2014. A flowchart of the study participants
54
55
56 125 is presented in the Figure 1 . The exclusion criteria included: miscarriage, stillbirth, or
57
58
59 126 unknown birth outcomes (n = 2,123). Second, participants with multiple births,
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19

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

20
21
22
23
24
25

132 **Figure 1. Fetal records selection flow chart**

26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43

134 **Ethics**

35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52

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

53
54
55
56
57
58
59
60

140 **Patient and Public Involvement statement**

56
57
58
59
60

141 This study did not involve patients or public.

53
54
55
56
57
58
59
60

143 **Assessment of pregnant multimorbidity**

56
57
58
59
60

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

1
2
3
4
5 145 mental, or social conditions in an individual according to previous reports.(7) Maternal
6
7
8 146 chronic conditions included in multimorbidity were defined as conditions with high
9
10
11 147 prevalence among women of reproductive age.(7) To identify pregnant women with
12
13
14 148 disease more rigorously, the diseases of pregnant women were defined as those that were
15
16
17 149 medically treated at the time of pregnancy. Information was collected through self-reports,
18
19
20 150 medical record transcripts, and medication interviews. The targeted diseases included
21
22
23 151 allergic diseases, such as asthma, anemia, diabetes mellitus, dyslipidemia, epilepsy,
24
25
26 152 gastric or duodenal ulcers, heart disease, hepatitis, human immunodeficiency virus (HIV)
27
28
29 153 infection, hypertension, inflammatory bowel disease, kidney disease, malignancy,
30
31
32 154 migraine, neurologic disease, other sexually transmitted diseases (Chlamydia trachomatis
33
34
35 155 and syphilis), mental disorders, rheumatic or collagen diseases, and thyroid disease.
36
37
38 156 Having an episode of domestic violence, substance abusing, being obese (BMI ≥ 25), and
39
40
41 157 being thin (BMI < 18.5) were each defined as one disease. Pregnant women with two or
42
43
44 158 more of these diseases during pregnancy were defined as having multimorbidities.
45
46
47
48
49

160 **Assessment of neurodevelopment of offspring**

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

169

170 **Covariates**

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

174

175 **Statistical analysis**

176 This study used the dataset jecs-ta-20190930 and jecs-qa-20210401 from JECS. STATA
177 ®(MP17) and R®(version 4.2.2) were used for statistical analysis. Multivariate logistic
178 regression analysis was performed to determine the adjusted odds ratios (ORs). The
179 objective variable was neurodevelopment of the offspring, and the explanatory variable
180 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				

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Ensignement Supérieur (ABES).

	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				5,54		2,78	3.			1,89	
	0	318	0.4	0	6.7	8	4	5,675	6.8	8	2.3
	1	123	0.1	3	3.1	7	5	2,596	3.1	891	1.1
	2	19	0.02	316	0.4	137	2	294	0.4	101	0.1
1 year				2,71		2,74	3.				
	0	54	0.1	1	3.3	3	3	2,478	3.0	566	0.7
	1	31	0.04	4	1.6	3	7	1,226	1.5	282	0.3

							0.				
	2	6	0.01	148	0.2	154	2	172	0.2	57	0.1
1 half				2,13		2,00	2.			1,20	
years	0	1,091	1.3	8	2.6	0	4	1,831	2.2	9	1.5
				1,10			1.				
	1	528	0.6	0	1.3	984	2	949	1.1	564	0.7
							0.				
	2	76	0.1	148	0.2	156	2	128	0.2	78	0.1
				2,81		1,06	1.			1,40	
2 years	0	1,851	2.2	6	3.4	0	3	2,106	2.5	0	1.7
				1,47			0.				
	1	1,048	1.3	4	1.8	590	7	1,004	1.2	706	0.9
							0.				
	2	147	0.2	176	0.2	84	1	122	0.1	99	0.1
2 half				2,04		2,69	3.			1,63	
years	0	2,445	3.0	2	2.5	6	3	2,708	3.3	4	2.0
				1,08		1,38	1.				
	1	1,376	1.7	6	1.3	9	7	1,445	1.7	860	1.0
							0.				
	2	199	0.2	132	0.2	186	2	187	0.2	112	0.1
				2,03		3,49	4.			1,60	
3 years	0	1,901	2.3	7	2.5	2	2	3,406	4.1	3	1.9
				1,10		1,84	2.				
	1	1,030	1.2	2	1.3	3	2	1,783	2.2	861	1.0
							0.				
	2	164	0.2	144	0.2	245	3	260	0.3	122	0.1
3 half				2,02		2,52	3.			2,13	
years	0	2,873	3.5	0	2.4	2	0	2,689	3.2	0	2.6
				1,09		1,34	1.			1,17	
	1	1,467	1.8	8	1.3	1	6	1,508	1.8	1	1.4
							0.				
	2	219	0.3	155	0.2	182	2	218	0.3	154	0.2
				2,59		3,03	3.			2,62	
4 years	0	2,157	2.6	7	3.1	8	7	1,733	2.1	9	3.2
				1,34		1,65	2.			1,36	
	1	1,118	1.3	7	1.6	1	0	977	1.2	2	1.6

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Ensignement Supérieur (ABES).

						0.					
	2	166	0.2	177	0.2	239	3	145	0.2	194	0.2

205

206 The results of the multivariate logistic regression analysis conducted on the

207 number of comorbidities in pregnant women and the neurodevelopment of offspring are

208 shown in Table 3 and Figure 2. Except at 6 months, the ORs were more than 1 for any of

209 the following items: communication, gross motor, fine motor, problem solving, and

210 personal and social. The ORs at 6 months were lower than those at other ages for all items,

211 both single disease comorbidity and multimorbidity. ORs tended to be higher with

212 increasing age of the offspring, and the ORs for all items were higher at 4 years than at 6

213 months for both single-disease coexistence and multimorbidity. The ORs for single

214 disease comorbidities ranged from 0.85 to 1.28. The OR range for multimorbidity was

215 0.95–2.29, and that at 4 years of age was 1.30–1.40 for all domains.

216 **Table 3. Adjusted odds ratio for developmental delay of offspring for**

217 **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)	0.99 (0.96 - 1.02)	0.95 (0.8 - 1.14)	1.01 (0.96 - 1.06)	1.02 (0.86 - 1.11)	0.99 (0.8 - 1.21)	1.02 (0.94 - 1.11)	0.99 (0.8 - 1.21)

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

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

221

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

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

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

227 *95% confidence interval: 0.98 – 5.3

228

229 **DISCUSSION**

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

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

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

Enseignement Supérieur (ABES) .
Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

1
2
3
4
5
6
7 262 vary depending on the target population.(23) Second, it was difficult in this study to
8
9 263 discuss the biological mechanisms of the association between multimorbidity and
10
11
12 264 neurodevelopmental delay. The association between various diseases and
13
14
15 265 neurodevelopmental delays has been reported in previous studies.(8,16–18,24) Further
16
17
18 266 studies on disease characteristics and disease combinations may allow for hypotheses to
19
20
21 267 be made regarding the biological mechanisms underlying the association between
22
23
24 268 multimorbidity and neurodevelopmental delay. Third, as participants in the JECS were
25
26
27 269 only collaborators, selection bias may have occurred.(15) The prevalence of
28
29
30 270 multimorbidity and the results of the association between multimorbidity and
31
32
33 271 neurodevelopmental delay might have been different if the study design included
34
35
36 272 pregnant women who did not participate in the JECS. The number of pregnant women
37
38
39 273 with multimorbidities would increase and the results of the effects on the
40
41
42 274 neurodevelopment of the children might be different if all pregnant women and children
43
44
45 275 registered in the administration were included in the study.

46
47
48 276 Previous reports on multimorbidities in pregnant women have focused on its
49
50
51 277 prevalence and impact on pregnant women themselves.(5–7) This study is a new report
52
53
54 278 in terms of the effect of multimorbidity in pregnant women on their offspring and
55
56
57 279 provides important recommendations regarding the health of pregnant women.
58
59
60

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 be done in other regions of the world.

Acknowledgments

We would like to express our gratitude to all the JECS study participants and staff members involved in data collection. Members of the JECS Group are as of 2023: Michihiro Kamijima (principal investigator, Nagoya City University, Nagoya, Japan); Shin Yamazaki (National Institute for Environmental Studies, Tsukuba, Japan); Yukihiro Ohya (National Center for Child Health and Development, Tokyo, Japan); Reiko Kishi (Hokkaido University, Sapporo, Japan); Nobuo Yaegashi (Tohoku University, Sendai, Japan); Koichi Hashimoto (Fukushima Medical University, Fukushima, Japan); Chisato Mori (Chiba University, Chiba, Japan); Shuichi Ito (Yokohama City University, Yokohama, Japan), Zentaro Yamagata (University of Yamanashi, Chuo, Japan), Hidekuni Inadera (University of Toyama, Toyama, Japan), Takeo Nakayama (Kyoto University, Kyoto, Japan), Tomotaka Sobue (Osaka University, Suita, Japan), Masayuki Shima (Hyogo Medical University, Nishinomiya, Japan), Seiji Kageyama (Tottori University, Yonago, Japan), Narufumi Suganuma (Kochi University, Nankoku, Japan),

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Ensignment Supérieur (ABES).

298 Shoichi Ohga (Kyushu University, Fukuoka, Japan), and Takahiko Katoh (Kumamoto
299 University, Kumamoto, Japan).

300 We would like to thank Editage (www.editage.com) for the English language editing.

301

302 **Contributors**

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

310

311 **Funding statement**

312 This study was funded by the Ministry of the Environment, Japan. The findings and
313 conclusions of this study are solely the responsibility of the authors and do not represent
314 the official views of the government.

315

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

316 **Competing interests**

317 The authors declare that they have no competing interests.

318

319 **Patient and public involvement**

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

322

323 **Patient consent for publication**

324 Not applicable.

325

326 **Ethics approval**

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

332

333 **Provenance and peer review**

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Supérieur (ABES)

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.

References

1. World Health Organization. *Multimorbidity*. World Health Organization; 2016. Accessed November 1, 2022. <https://apps.who.int/iris/handle/10665/252275>

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

2. McParland C, Johnston B, Cooper M. A mixed-methods systematic review of nurse-led interventions for people with multimorbidity. *Journal of Advanced Nursing*. 2022;78(12):3930-51. doi:10.1111/jan.15427

3. Salisbury C, Johnson L, Purdy S, et al. Epidemiology and impact of multimorbidity in primary care: a retrospective cohort study. *Br J Gen Pract*. 2011;61(582):e12-21. doi:10.3399/bjgp11X548929

4. Taylor AW, Price K, Gill TK, et al. Multimorbidity - not just an older person's issue. Results from an Australian biomedical study. *BMC Public Health*. 2010;10(1):718. doi:10.1186/1471-2458-10-718

5. Lee SI, Azcoaga-Lorenzo A, Agrawal U, et al. Epidemiology of pre-existing multimorbidity in pregnant women in the UK in 2018: a population-based cross-sectional study. *BMC Pregnancy Childbirth*. 2022;22(1):120. doi:10.1186/s12884-022-04442-3

6. McCauley M, Zafar S, van den Broek N. Maternal multimorbidity during pregnancy and after childbirth in women in low- and middle-income countries: a systematic literature review. *BMC Pregnancy Childbirth*. 2020;20(1):637. doi:10.1186/s12884-020-03303-1

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Supérieur (ABES)

- 1
2
3
4
5
6
7 369 7. Nakanishi K, Saijo Y, Yoshioka E, et al. Association between maternal
8
9 370 multimorbidity and preterm birth, low birth weight and small for gestational age: a
10
11
12 371 prospective birth cohort study from the Japan Environment and Children's Study.
13
14
15 372 *BMJ Open*. 2023;13(3):e069281. doi:10.1136/bmjopen-2022-069281
16
17
18
19 373 8. Gong T, Lundholm C, Rejnö G, et al. Parental asthma and risk of autism spectrum
20
21
22 374 disorder in offspring: A population and family-based case-control study. *Clin Exp*
23
24
25 375 *Allergy*. 2019;49(6):883-91. doi:10.1111/cea.13353
26
27
28
29 376 9. Lyall K, Munger KL, O'Reilly EJ, et al. Maternal Dietary Fat Intake in Association
30
31
32 377 With Autism Spectrum Disorders. *American Journal of Epidemiology*.
33
34
35 378 2013;178(2):209-20. doi:10.1093/aje/kws433
36
37
38
39 379 10. Yamamoto M, Eguchi A, Sakurai K, et al. Longitudinal analyses of maternal and cord
40
41
42 380 blood manganese levels and neurodevelopment in children up to 3 years of age: The
43
44
45 381 Japan Environment and Children's Study (JECS). *Environment International*.
46
47
48 382 2022;161:107126. doi:10.1016/j.envint.2022.107126
49
50
51
52 383 11. Cusick SE, Georgieff MK. The Role of Nutrition in Brain Development: The Golden
53
54
55 384 Opportunity of the "First 1000 Days." *The Journal of Pediatrics*. 2016;175:16-21.
56
57
58 385 doi:10.1016/j.jpeds.2016.05.013
59
60

12. Smythe T, Zuurmond M, Tann CJ, et al. Early intervention for children with developmental disabilities in low and middle-income countries – the case for action. *International Health*. 2021;13(3):222-231. doi:10.1093/inthealth/ihaa044

13. Working Group of the Epidemiological Research for Children’s Environmental Health, Kawamoto T, Nitta H, et al. Rationale and study design of the Japan environment and children’s study (JECS). *BMC Public Health*. 2014;14(1):25. doi:10.1186/1471-2458-14-25

14. Mezawa H, Aoki S, Nakayama SF, et al. Psychometric profile of the Ages and Stages Questionnaires, Japanese translation. *Pediatrics International*. 2019;61(11):1086-95. doi:10.1111/ped.13990

15. Michikawa T, Nitta H, Nakayama SF, et al. The Japan Environment and Children’s Study (JECS): A Preliminary Report on Selected Characteristics of Approximately 10 000 Pregnant Women Recruited During the First Year of the Study. *Journal of Epidemiology*. 2015;25(6):452-8. doi:10.2188/jea.JE20140186

16. Nattero-Chávez L, Luque-Ramírez M, Escobar-Morreale HF. Systemic endocrinopathies (thyroid conditions and diabetes): impact on postnatal life of the offspring. *Fertility and Sterility*. 2019;111(6):1076-91.

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Ensignement Supérieur (ABES).

doi:10.1016/j.fertnstert.2019.04.039

17. Nulman I, Koren G, Rovet J, et al. Neurodevelopment of Children Following Prenatal Exposure to Venlafaxine, Selective Serotonin Reuptake Inhibitors, or Untreated Maternal Depression. *AJP*. 2012;169(11):1165-74. doi:10.1176/appi.ajp.2012.11111721

18. Meador KJ, Baker GA, Browning N, et al. Cognitive Function at 3 Years of Age after Fetal Exposure to Antiepileptic Drugs. *N Engl J Med*. 2009;360(16):1597-605. doi:10.1056/NEJMoa0803531

19. Nolvi S, Merz EC, Kataja EL, et al. Prenatal Stress and the Developing Brain: Postnatal Environments Promoting Resilience. *Biological Psychiatry*. 2023;93(10):942-52. doi:10.1016/j.biopsych.2022.11.023

20. Premkumar A, Mele L, Casey BM, et al. Relationship Between Maternal Economic Vulnerability and Childhood Neurodevelopment at 2 and 5 Years of Life. *Obstetrics & Gynecology*. 2021;138(3):379-88. doi:10.1097/AOG.0000000000004503

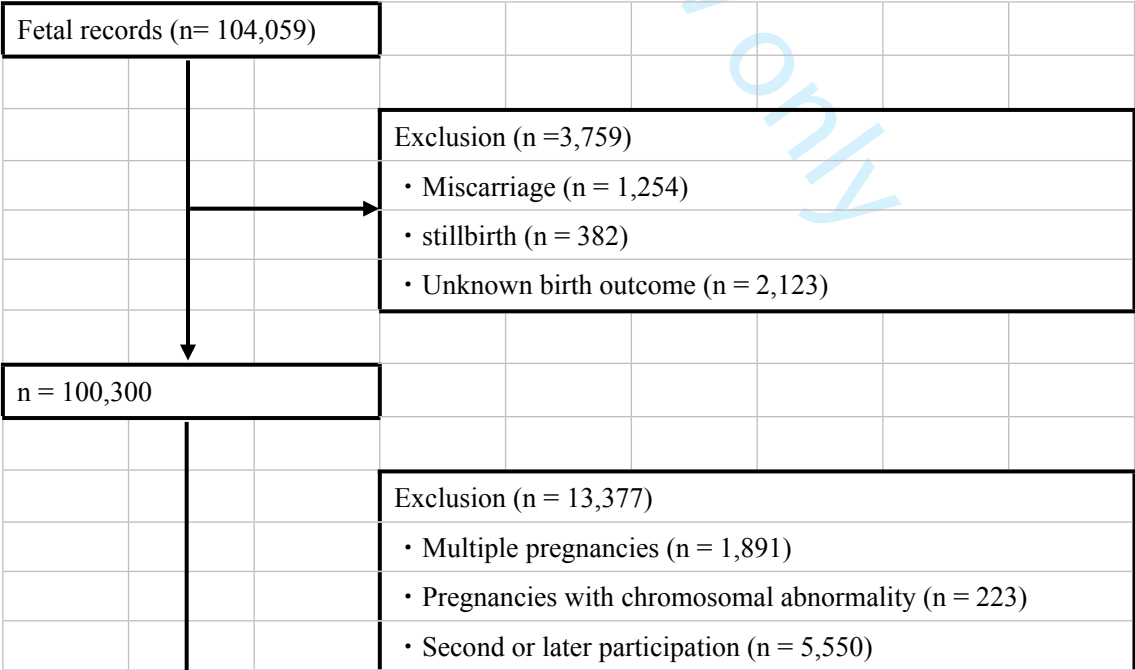
21. Kim-Cohen J, Moffitt TE, Taylor A, et al. Maternal Depression and Children's Antisocial Behavior. *ARCH GEN PSYCHIATRY*. 2005;62.

22. Harries CI, Smith DM, Gregg L, et al. Parenting and Serious Mental Illness (SMI): A Systematic Review and Metasynthesis. *Clin Child Fam Psychol Rev.* 2023;26(2):303-42. doi:10.1007/s10567-023-00427-6

23. Skou ST, Mair FS, Fortin M, et al. Multimorbidity. *Nat Rev Dis Primers.* 2022;8(1):48. doi:10.1038/s41572-022-00376-4

24. Nalli C, Galli J, Lini D, et al. The Influence of Treatment of Inflammatory Arthritis During Pregnancy on the Long-Term Children’s Outcome. *Front Pharmacol.* 2021;12:626258. doi:10.3389/fphar.2021.626258

Figure legends



Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Ensignement Supérieur (ABES).

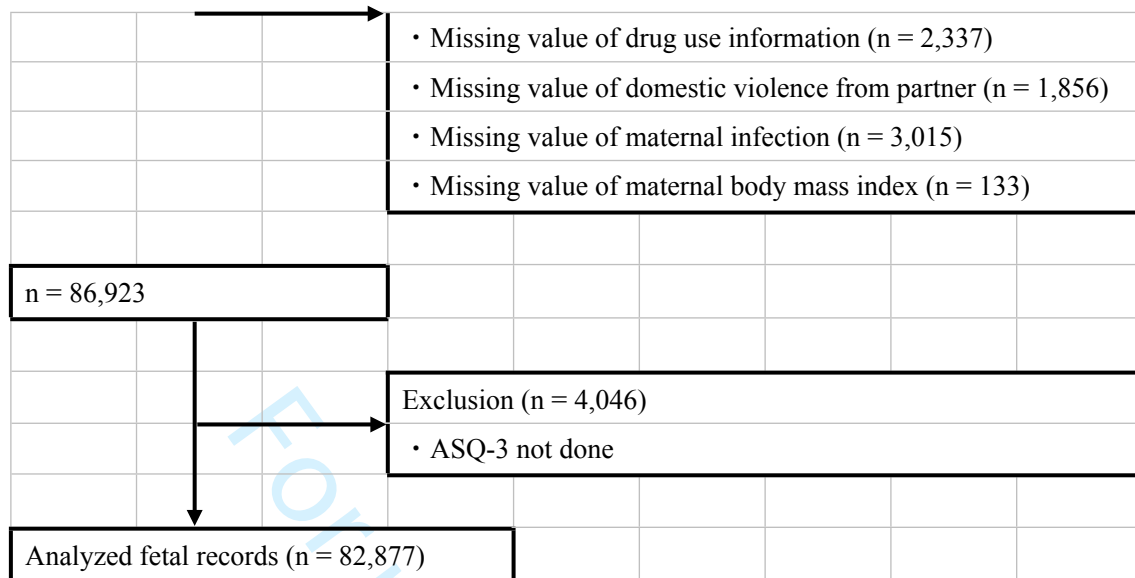


Figure 1. Participants selection flow chart

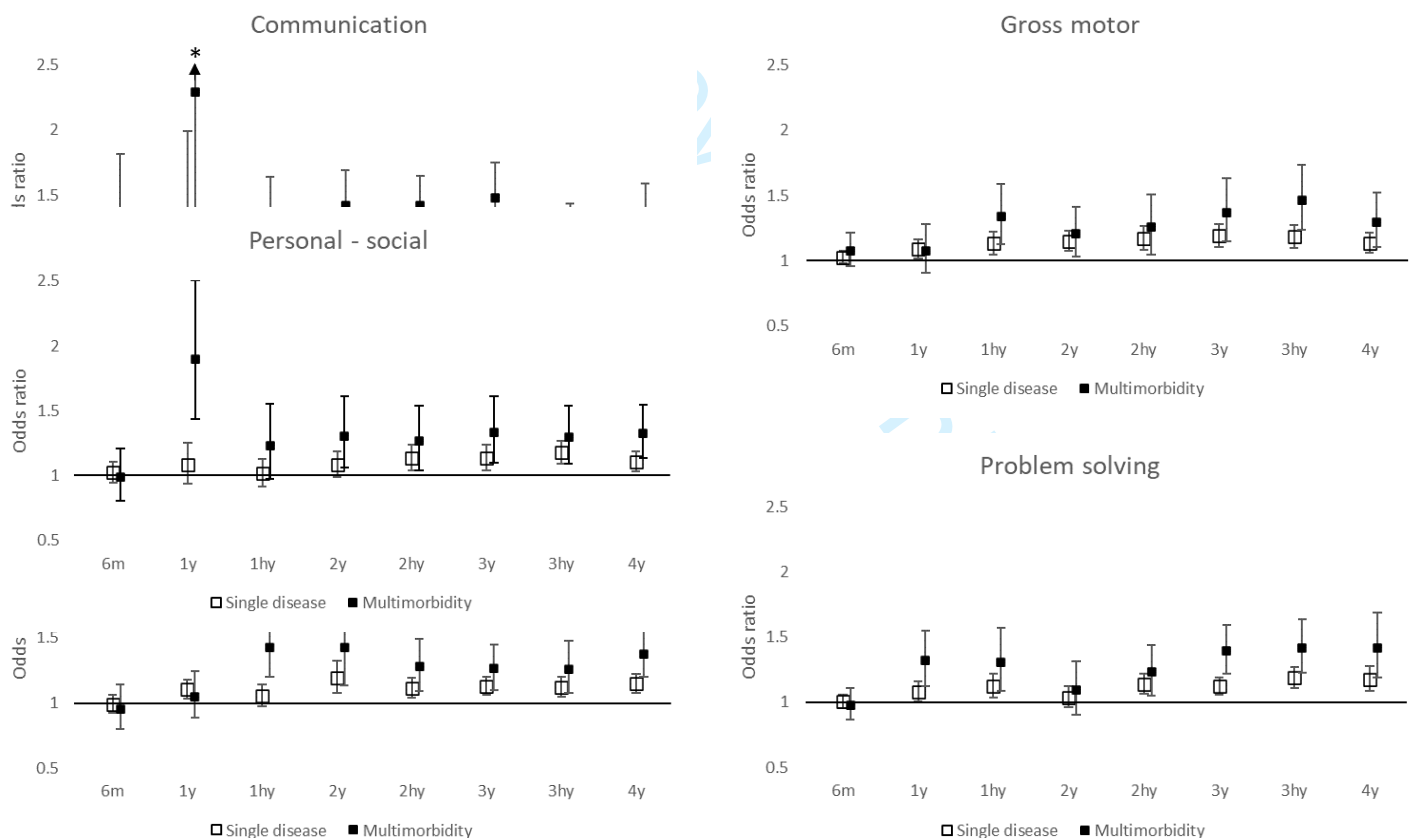


Figure 2. Adjusted odds ratio for developmental delay of offspring for

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

432 **multimorbidity during pregnancy by logistic regression.**

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

436 *95% confidence interval: 0.98 – 5.3

440

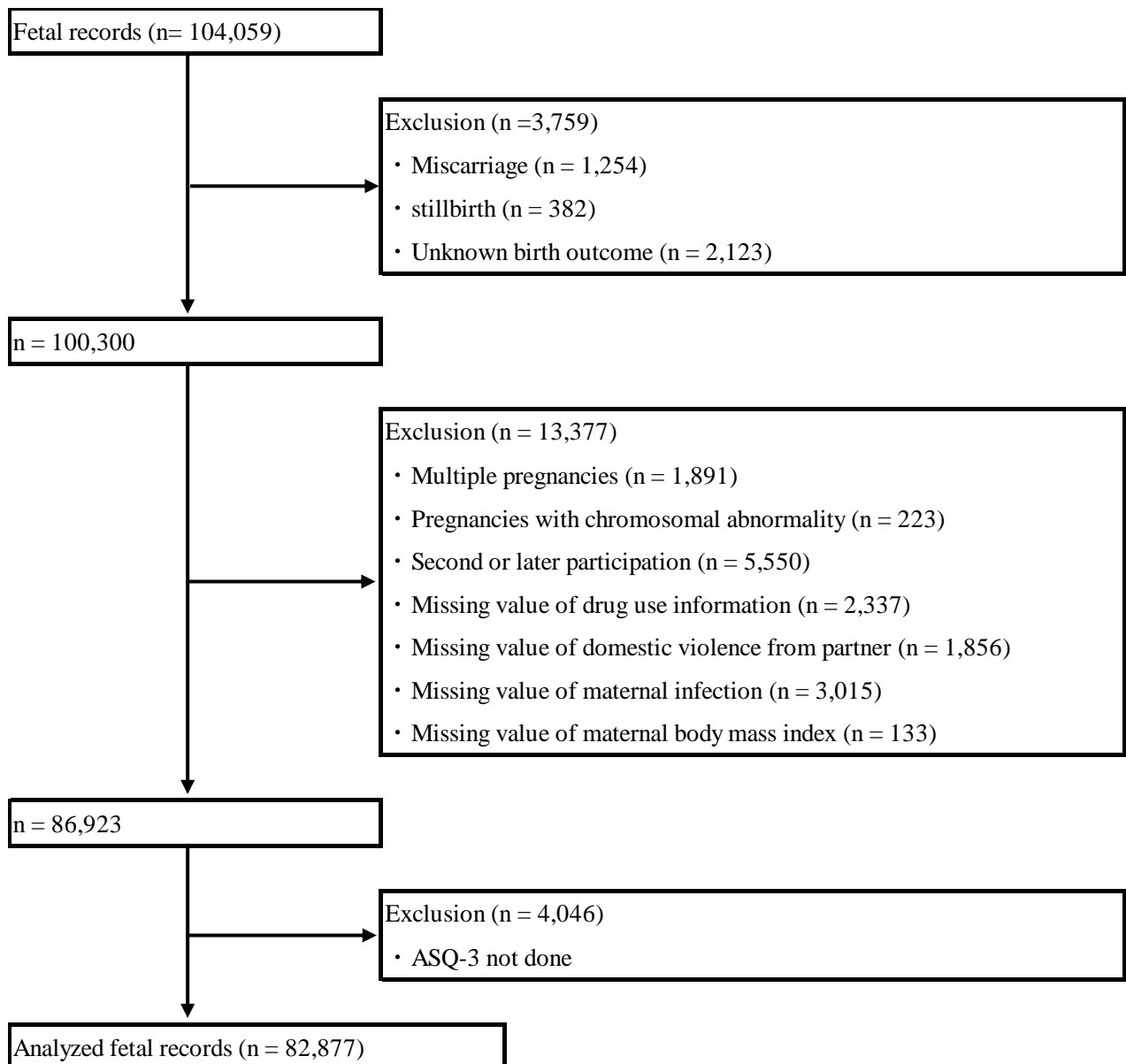


Figure 1. Fetal records selection flow chart

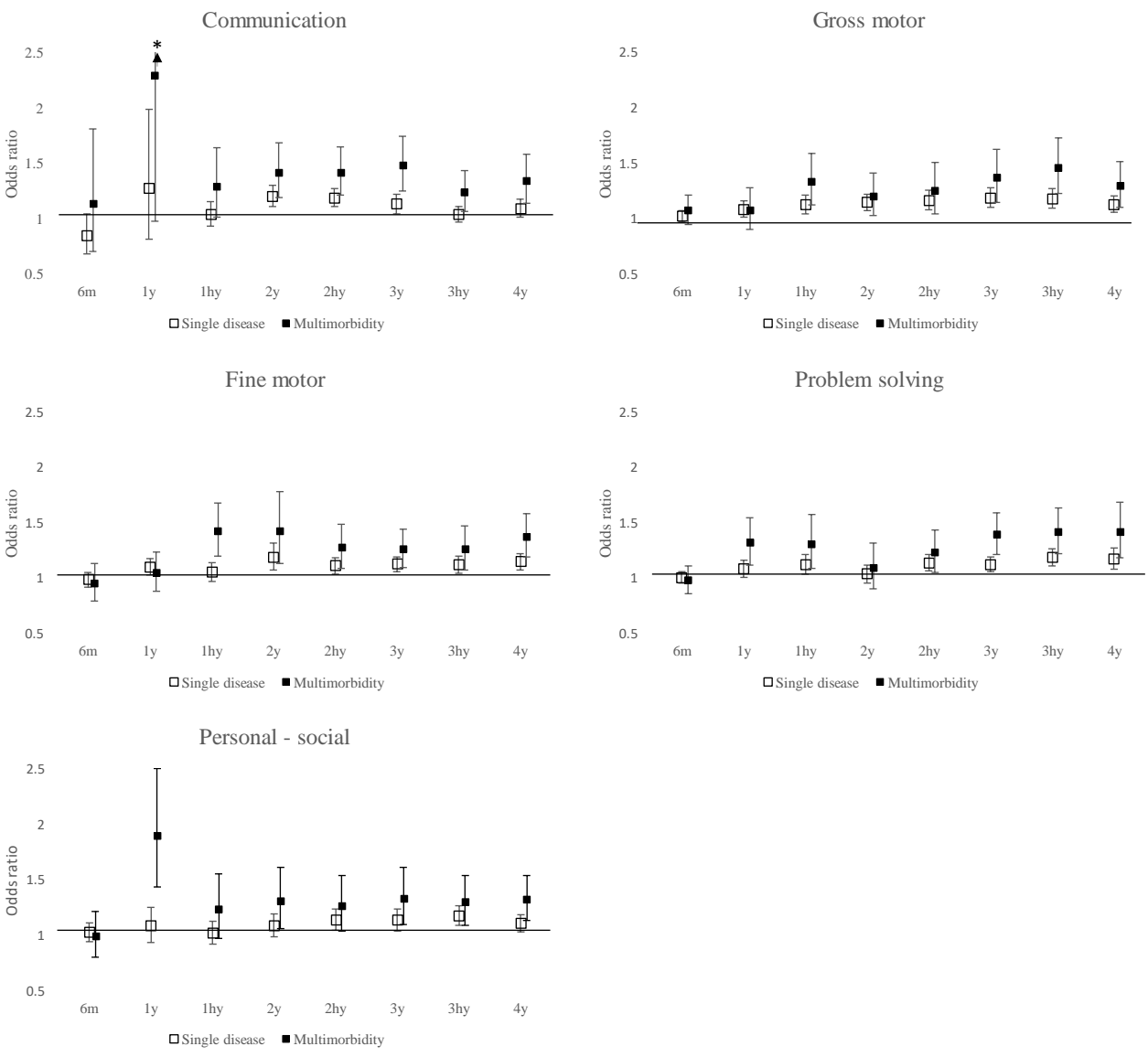


Figure 2. Adjusted odds ratio for developmental delay of offspring for multimorbidity during pregnancy by logistic regression.

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/m ²)	12,889	15.6
Obesity (BMI >25.0 kg/m ²)	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 (b) Provide in the abstract an informative and balanced summary of what was done and what was found	1 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 (b) For matched studies, give matching criteria and number of exposed and unexposed	7,8 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 (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	10 10 10,11 - -
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	7,8 7,8 7,8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	11,12 - 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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2023-082585.R1
Article Type:	Original research
Date Submitted by the Author:	24-Apr-2024
Complete List of Authors:	Akagi, Takanobu; Asahikawa Medical University, Division of Public Health and Epidemiology, Department of Social Medicine Saijo, Yasuaki; Asahikawa Medical University, Division of Public Health and Epidemiology, Department of Social Medicine Yoshioka, Eiji ; Asahikawa Medical University, Division of Public Health and Epidemiology, Department of Social Medicine Sato, Yukihiro; Asahikawa Medical University, Division of Public Health and Epidemiology, Department of Social Medicine Nakanishi, Kentaro; Asahikawa Medical University, Department of Obstetrics and Gynecology Kato, Yasuhito; Asahikawa Medical University, Department of Obstetrics and Gynecology; Asahikawa Medical University, Department of Social Medicine Nagaya, Ken; Asahikawa Medical University Hospital, Division of Neonatology, Perinatal Medical Center Takahashi, Satoru; Asahikawa Medical University, Department of Pediatrics Ito, Yoshiya; Japanese Red Cross Hokkaido College of Nursing, Faculty of Nursing Iwata, Hiroyoshi; Hokkaido University, Center for Environmental and Health Sciences Yamaguchi, Takeshi; Hokkaido University, Center for Environmental and Health Sciences; Hokkaido University Hospital, Department of Pediatrics Miyashita, Chihiro; Hokkaido University, Center for Environmental and Health Sciences Ito, Sachiko; Hokkaido University, Center for Environmental and Health Sciences Kishi, Reiko; Hokkaido University, Center for Environmental and Health Sciences group, The Japan Environment ; National Institute for Environmental Studies, Tsukuba city, Ibaraki, Japan
Primary Subject Heading:	Public health
Secondary Subject Heading:	Obstetrics and gynaecology, Paediatrics
Keywords:	PUBLIC HEALTH, Maternal medicine < OBSTETRICS, Paediatric neurology < PAEDIATRICS, Multimorbidity, Pregnant Women

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 **Title: Association between maternal multimorbidity and neurodevelopment of**
2 **offspring: a prospective birth cohort study from the Japan Environment and**
3 **Children’s Study**

5 **Author names**

6 Takanobu Akagi^a, Yasuaki Saijo^a, Eiji Yoshioka^a, Yukihiro Sato^a, Kentaro Nakanishi^b,
7 Yasuhito Kato^b, Ken Nagaya^c, Satoru Takahashi^d, Yoshiya Ito^e, Hiroyoshi Iwata^f,
8 Takeshi Yamaguchi^f, Chihiro Miyashita^f, Sachiko Itoh^f, Reiko Kishi^f, the Japan
9 Environment and Children’s Study (JECS) Group^g

11 **Author affiliations**

12 ^aDivision of Public Health and Epidemiology, Department of Social Medicine,
13 Asahikawa Medical University, 1-1-1, Midorigaoka higashi2-jo, Asahikawa, Hokkaido
14 078-8510, Japan

15 ^bDepartment of Obstetrics and Gynecology, Asahikawa Medical University, Asahikawa,
16 1-1-1, Midorigaoka higashi2-jo, Asahikawa, Hokkaido 078-8510, Japan

17 ^cDivision of Neonatology, Perinatal Medical Center, Asahikawa Medical University
18 Hospital, 1-1-1, Midorigaoka higashi2-jo, Asahikawa, Hokkaido 078-8510, Japan

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Ensignment Superior (ABES).

^dDepartment of Pediatrics, Asahikawa Medical University, 1-1-1, Midorigaoka
higashi2-jo, Asahikawa, Hokkaido 078-8510, Japan

^eFaculty of Nursing, Japanese Red Cross Hokkaido College of Nursing, 664-1,
Akebono-cho, Kitami, Hokkaido 090-0011, Japan

^fCenter for Environmental and Health Sciences, Hokkaido University, Kita12-jo,
Nishi7-chome, Kita-ku, Sapporo, Hokkaido 060-0812, Japan

^gMembers of the Japan Environment and Children's Study Group are listed in the
Appendices.

27

Corresponding author

Yasuaki Saijo

Division of Public Health and Epidemiology, Department of Social Medicine,
Asahikawa Medical University

078-8510, 1-1-1, Midorigaoka higashi2-jo, Asahikawa, Hokkaido, Japan

Tel: +81-166-68-2402

Email: y-saijo@asahikawa-med.ac.jp

35

ABSTRAT

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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% CI 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

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Ensignment Supérieur (ABES).

1
2
3
4
5 91 as hypertension, kidney disease, and systemic lupus erythematosus, are potential risk
6
7
8 92 factors for preterm birth (PTB) and low birth weight infants (LBW).(7) Moreover,
9
10
11 93 maternal mental and social morbidities have also been associated with PTB and
12
13
14 94 LBW.(7) Previous studies also reported the relationship between maternal environment
15
16
17 95 such as maternal asthma, maternal intake of fats, maternal and cord blood Manganese
18
19
20 96 levels and child development.(8–10)
21
22

23 97 Infancy is considered to be the period in which language, cognition, motor
24
25
26 98 skills, and socioemotional domains form the basis for subsequent social
27
28
29 99 participation.(11) It is essential to receive appropriate support, early detection, and
30
31
32 100 intervention during this period.(12) Although maternal nutritional status, certain
33
34
35 101 diseases, and blood substances can affect the neurodevelopment of offspring(8–11), the
36
37
38 102 impacts of multimorbidity in pregnant women on the neurodevelopment of offspring
39
40
41 103 has not been extensively studied.(5,6) A major difference between previous reports and
42
43
44 104 this study was the investigation of the association between multiple diseases of pregnant
45
46
47 105 women and child neurodevelopment; previous reports have mainly focused on the
48
49
50 106 relationship between a single disease or single substance in pregnant women and child
51
52
53 107 neurodevelopment.
54

55
56 108 The present study aimed to investigate the association between multimorbidity
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

115 **METHODS**

116 **Study population**

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

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Supérieur (ABES).

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

145 chronic conditions included in multimorbidity were defined as conditions with high
146 prevalence among women of reproductive age.(7) To identify pregnant women with
147 disease more rigorously, the diseases of pregnant women were defined as those that
148 were medically treated at the time of pregnancy. Information was collected through self-
149 reports, medical record transcripts, and medication interviews. The targeted diseases
150 included allergic diseases, such as asthma, anemia, diabetes mellitus, dyslipidemia,
151 epilepsy, gastric or duodenal ulcers, heart disease, hepatitis, human immunodeficiency
152 virus (HIV) infection, hypertension, inflammatory bowel disease, kidney disease,
153 malignancy, migraine, neurologic disease, other sexually transmitted diseases
154 (Chlamydia trachomatis and syphilis), mental disorders, rheumatic or collagen diseases,
155 and thyroid disease. Having an episode of domestic violence, substance abusing, being
156 obese (BMI ≥ 25), and being thin (BMI < 18.5) were each defined as one disease. We
157 used maternal pre-pregnancy body weight data for analysis. Pregnant women with two
158 or more of these diseases during pregnancy were defined as having multimorbidities.

159

160 **Assessment of neurodevelopment of offspring**

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

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Supérieur (ABES).

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

194

195

196

197

198

199

200

201

202

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 (6.8)	1,898 (2.3)
	1	123 (0.1)	2,603 (3.1)	1,237 (1.5)	6 (3.1)	891 (1.1)
	≥2	19 (0.02)	316 (0.4)	137 (0.2)	4 (0.4)	101 (0.1)
1 year	0	54 (0.1)	2,711 (3.3)	2,743 (3.3)	8 (3.0)	566 (0.7)
	1	31 (0.04)	1,324 (1.6)	1,383 (1.7)	6 (1.5)	282 (0.3)
	≥2	6 (0.01)	148 (0.2)	154 (0.2)	2 (0.2)	57 (0.1)
1 half years	0	1,091 (1.3)	2,138 (2.6)	2,000 (2.4)	1 (2.2)	1,209 (1.5)
	1	528 (0.6)	1,100 (1.3)	984 (1.2)	9 (1.1)	564 (0.7)
	≥2	76 (0.1)	148 (0.2)	156 (0.2)	3 (0.2)	78 (0.1)
2 years	0	1,851 (2.2)	2,816 (3.4)	1,060 (1.3)	2,166 (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)	112 (0.1)	99 (0.1)
2 half years	0	2,445 (3.0)	2,042 (2.5)	2,696 (3.3)	2,788 (3.3)	1,634 (2.0)
	1	1,376 (1.7)	1,086 (1.3)	1,389 (1.7)	1,455 (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)	3,466 (4.1)	1,603 (1.9)
	1	1,030 (1.2)	1,102 (1.3)	1,843 (2.2)	1,733 (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)	2,609 (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)	238 (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)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

204

205

206

207

208

209

210

211

212

213

214

215

216

217

218

219

220

221

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% CI 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)	0.86 (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)	1.01 (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)	1.12 (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)	1.04 (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)	1.09 (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)	1.06 (1.06–1.12)	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.

237

238 **DISCUSSION**

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

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

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

1
2
3
4
5 273 medication were not included in the disease sample in this study, with the exception of
6
7
8 274 domestic violence, obese, and skinny women. The criterion for disease was defined as
9
10
11 275 the presence of medication; the number of pregnant women with disease may have been
12
13
14 276 higher if the study had been conducted using different criteria. Some have criticized the
15
16
17 277 definition of multimorbidity as simply having more than one disease, which would
18
19
20 278 include a large population.(24) In the future, a definition of multimorbidity that is
21
22
23 279 suitable for the target community will be required since the significant diseases and
24
25
26 280 conditions vary depending on the target population.(24) Second, it was difficult in this
27
28
29 281 study to discuss the biological mechanisms of the association between multimorbidity
30
31
32 282 and neurodevelopmental delay. The association between various diseases and
33
34
35 283 neurodevelopmental delays has been reported in previous studies.(8,16–18,25) Further
36
37
38 284 studies on disease characteristics and disease combinations may allow for hypotheses to
39
40
41 285 be made regarding the biological mechanisms underlying the association between
42
43
44 286 multimorbidity and neurodevelopmental delay. Third, as participants in the JECS were
45
46
47 287 only collaborators, selection bias may have occurred.(15) The prevalence of
48
49
50 288 multimorbidity and the results of the association between multimorbidity and
51
52
53 289 neurodevelopmental delay might have been different if the study design included
54
55
56 290 pregnant women who did not participate in the JECS. The number of pregnant women
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

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

308 This study demonstrated an association between multimorbidities in pregnant

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Supérieur (ABES)

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.

Acknowledgments

We would like to express our gratitude to all the JECS study participants and staff members involved in data collection. Members of the JECS Group are as of 2023: Michihiro Kamijima (principal investigator, Nagoya City University, Nagoya, Japan); Shin Yamazaki (National Institute for Environmental Studies, Tsukuba, Japan); Yukihiro Ohya (National Center for Child Health and Development, Tokyo, Japan); Reiko Kishi (Hokkaido University, Sapporo, Japan); Nobuo Yaegashi (Tohoku University, Sendai, Japan); Koichi Hashimoto (Fukushima Medical University, Fukushima, Japan); Chisato Mori (Chiba University, Chiba, Japan); Shuichi Ito (Yokohama City University, Yokohama, Japan), Zentaro Yamagata (University of Yamanashi, Chuo, Japan), Hidekuni Inadera (University of Toyama, Toyama, Japan), Takeo Nakayama (Kyoto University, Kyoto, Japan), Tomotaka Sobue (Osaka University, Suita, Japan), Masayuki Shima (Hyogo Medical University, Nishinomiya, Japan), Seiji Kageyama (Tottori University, Yonago, Japan), Narufumi Suganuma

(Kochi University, Nankoku, Japan), Shoichi Ohga (Kyushu University, Fukuoka, Japan), and Takahiko Katoh (Kumamoto University, Kumamoto, Japan).

We would like to thank Editage (www.editage.com) for the English language editing.

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.

Funding statement

This study was funded by the Ministry of the Environment, Japan. The findings and conclusions of this study are solely the responsibility of the authors and do not represent the official views of the government. (N/A)

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Ensignement Supérieur (ABES).

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

363 Not commissioned; externally peer reviewed.

364

365 **Data availability statement**

366 Data are unsuitable for public deposition due to ethical restrictions and legal framework
367 of Japan. It is prohibited by the Act on the Protection of Personal Information (Act No.
368 57 of 30 May 2003, amendment on 9 September 2015) to publicly deposit the data
369 containing personal information. Ethical Guidelines for Medical and Health Research
370 Involving Human Subjects enforced by the Japan Ministry of Education, Culture,
371 Sports, Science and Technology and the Ministry of Health, Labour and Welfare also
372 restricts the open sharing of the epidemiologic data. All inquiries about access to data
373 should be sent to: jecs-en@nies.go.jp. The person responsible for handling enquiries
374 sent to this e-mail address is Dr Shoji F. Nakayama, JECS Programme Office, National
375 Institute for Environmental Studies.

376

377 **References**

378

- 379 1. World Health Organization. Multimorbidity. World Health Organization; 2016.
380 Accessed November 1, 2022. <https://apps.who.int/iris/handle/10665/252275>
381
382 2. McParland C, Johnston B, Cooper M. A mixed-methods systematic review of

- nurse-led interventions for people with multimorbidity. *Journal of Advanced Nursing*. 2022;78(12):3930-51. doi:10.1111/jan.15427
3. Salisbury C, Johnson L, Purdy S, et al. Epidemiology and impact of multimorbidity in primary care: a retrospective cohort study. *Br J Gen Pract*. 2011;61(582):e12-21. doi:10.3399/bjgp11X548929
4. Taylor AW, Price K, Gill TK, et al. Multimorbidity - not just an older person's issue. Results from an Australian biomedical study. *BMC Public Health*. 2010;10(1):718. doi:10.1186/1471-2458-10-718
5. Lee SI, Azcoaga-Lorenzo A, Agrawal U, et al. Epidemiology of pre-existing multimorbidity in pregnant women in the UK in 2018: a population-based cross-sectional study. *BMC Pregnancy Childbirth*. 2022;22(1):120. doi:10.1186/s12884-022-04442-3
6. McCauley M, Zafar S, van den Broek N. Maternal multimorbidity during pregnancy and after childbirth in women in low- and middle-income countries: a systematic literature review. *BMC Pregnancy Childbirth*. 2020;20(1):637. doi:10.1186/s12884-020-03303-1
7. Nakanishi K, Saijo Y, Yoshioka E, et al. Association between maternal multimorbidity and preterm birth, low birth weight and small for gestational age: a prospective birth cohort study from the Japan Environment and Children's Study. *BMJ Open*. 2023;13(3):e069281. doi:10.1136/bmjopen-2022-069281
8. Gong T, Lundholm C, Rejnö G, et al. Parental asthma and risk of autism spectrum disorder in offspring: A population and family-based case-control study. *Clin Exp Allergy*. 2019;49(6):883-91. doi:10.1111/cea.13353
9. Lyall K, Munger KL, O'Reilly EJ, et al. Maternal Dietary Fat Intake in Association With Autism Spectrum Disorders. *American Journal of Epidemiology*. 2013;178(2):209-20. doi:10.1093/aje/kws433
10. Yamamoto M, Eguchi A, Sakurai K, et al. Longitudinal analyses of maternal and cord blood manganese levels and neurodevelopment in children up to 3 years of age:

The Japan Environment and Children’s Study (JECS). *Environment International*. 2022;161:107126. doi:10.1016/j.envint.2022.107126

11. Cusick SE, Georgieff MK. The Role of Nutrition in Brain Development: The Golden Opportunity of the “First 1000 Days.” *The Journal of Pediatrics*. 2016;175:16-21. doi:10.1016/j.jpeds.2016.05.013

12. Smythe T, Zuurmond M, Tann CJ, et al. Early intervention for children with developmental disabilities in low and middle-income countries – the case for action. *International Health*. 2021;13(3):222-231. doi:10.1093/inthealth/ihaa044

13. Working Group of the Epidemiological Research for Children’s Environmental Health, Kawamoto T, Nitta H, et al. Rationale and study design of the Japan environment and children’s study (JECS). *BMC Public Health*. 2014;14(1):25. doi:10.1186/1471-2458-14-25

14. Mezawa H, Aoki S, Nakayama SF, et al. Psychometric profile of the Ages and Stages Questionnaires, Japanese translation. *Pediatrics International*. 2019;61(11):1086-95. doi:10.1111/ped.13990

15. Michikawa T, Nitta H, Nakayama SF, et al. The Japan Environment and Children’s Study (JECS): A Preliminary Report on Selected Characteristics of Approximately 10 000 Pregnant Women Recruited During the First Year of the Study. *Journal of Epidemiology*. 2015;25(6):452-8. doi:10.2188/jea.JE20140186

16. Nattero-Chávez L, Luque-Ramírez M, Escobar-Morreale HF. Systemic endocrinopathies (thyroid conditions and diabetes): impact on postnatal life of the offspring. *Fertility and Sterility*. 2019;111(6):1076-91. doi:10.1016/j.fertnstert.2019.04.039

17. Nulman I, Koren G, Rovet J, et al. Neurodevelopment of Children Following Prenatal Exposure to Venlafaxine, Selective Serotonin Reuptake Inhibitors, or Untreated Maternal Depression. *AJP*. 2012;169(11):1165-74. doi:10.1176/appi.ajp.2012.11111721

18. Meador KJ, Baker GA, Browning N, et al. Cognitive Function at 3 Years of Age

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Ensignment Supérieur (ABES).

- after Fetal Exposure to Antiepileptic Drugs. *N Engl J Med*. 2009 Apr 16;360(16):1597–605. doi:10.1056/NEJMoa0803531
19. Nolvi S, Merz EC, Kataja EL, et al. Prenatal Stress and the Developing Brain: Postnatal Environments Promoting Resilience. *Biological Psychiatry*. 2023;93(10):942-52. doi:10.1016/j.biopsych.2022.11.023
20. Premkumar A, Mele L, Casey BM, et al. Relationship Between Maternal Economic Vulnerability and Childhood Neurodevelopment at 2 and 5 Years of Life. *Obstetrics & Gynecology*. 2021;138(3):379-88. doi:10.1097/AOG.0000000000004503
21. Kim-Cohen J, Moffitt TE, Taylor A, et al. Maternal Depression and Children's Antisocial Behavior. *ARCH GEN PSYCHIATRY*. 2005;62.
22. Harries CI, Smith DM, Gregg L, et al. Parenting and Serious Mental Illness (SMI): A Systematic Review and Metasynthesis. *Clin Child Fam Psychol Rev*. 2023;26(2):303-42. doi:10.1007/s10567-023-00427-6
23. H.K. Hughes, R.J. Moreno, P. Ashwood et al. Innate immune dysfunction and neuroinflammation in autism spectrum disorder (ASD). *Brain Behav Immun*. 2023 Feb;108:245-254. doi: 10.1016/j.bbi.2022.12.001.
24. Skou ST, Mair FS, Fortin M, et al. Multimorbidity. *Nat Rev Dis Primers*. 2022;8(1):48. doi:10.1038/s41572-022-00376-4
25. Nalli C, Galli J, Lini D, et al. The Influence of Treatment of Inflammatory Arthritis During Pregnancy on the Long-Term Children's Outcome. *Front Pharmacol*. 2021;12:626258. doi:10.3389/fphar.2021.626258
26. Kigawa M, Tsuchida A, Miura K, et al. Analysis of non-respondent pregnant women who were registered in the Japan Environment and Children's Study: a longitudinal cohort study. *BMJ Open*. 2019 Jun;9(6):e025562. doi: 10.1136/bmjopen-2018-025562
27. Kigawa M, Tsuchida A, Matsumura K, et al. Predictors of non-response to

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

490 successive waves of surveys in the Japan Environment and Children’s Study during the
491 3-year postpartum period: a longitudinal cohort study. BMJ Open. 2022
492 Jul;12(7):e050087. doi: 10.1136/bmjopen-2021-050087

493

494 **Figure legends**

495

496 **Figure 1. Fetal records selection flow chart.**

497

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

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

503 *** 95% confidence interval: 0.98–5.3**

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Ensignement Supérieur (ABES).

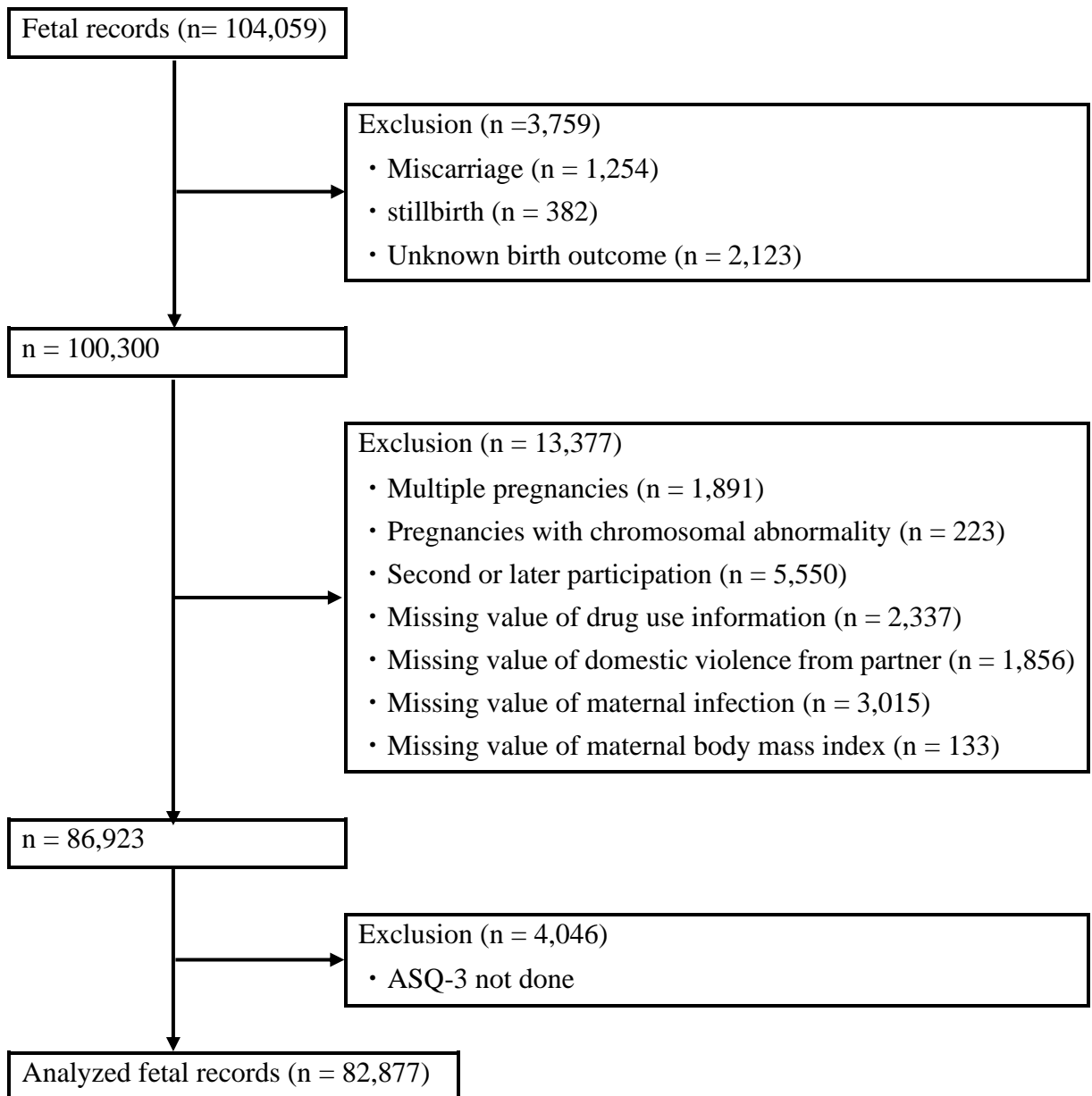


Figure 1. Fetal records selection flow chart.

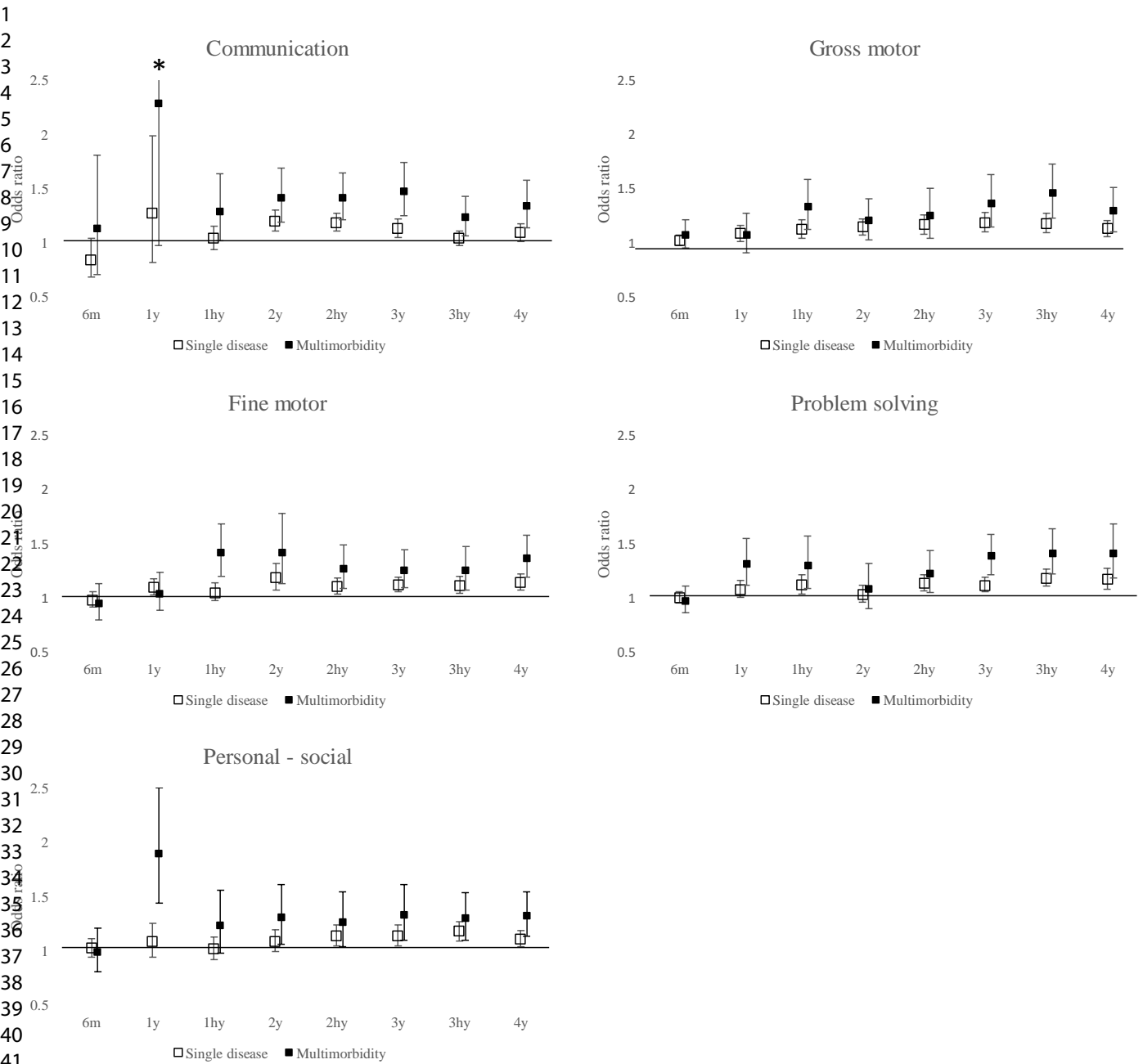


Figure 2. Adjusted odds ratio for developmental delay of offspring for multimorbidity during pregnancy by logistic regression.

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/m ²)	12,889	15.6
Obesity (BMI >25.0 kg/m ²)	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	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	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	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	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	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	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	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	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	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
4 years	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 (b) Provide in the abstract an informative and balanced summary of what was done and what was found	1 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 (b) For matched studies, give matching criteria and number of exposed and unexposed	7,8 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 (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	10 10 10,11 - -
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	7,8 7,8 7,8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	11,12 - 8
Outcome data	15*	Report numbers of outcome events or summary measures over time	13-15

1	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	15,16
2			(b) Report category boundaries when continuous variables were categorized	-
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
4	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
5	Discussion			
6	Key results	18	Summarise key results with reference to study objectives	17
7	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
8	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
9	Generalisability	21	Discuss the generalisability (external validity) of the study results	20
10	Other information			
11	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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2023-082585.R2
Article Type:	Original research
Date Submitted by the Author:	30-May-2024
Complete List of Authors:	Akagi, Takanobu; Asahikawa Medical University, Division of Public Health and Epidemiology, Department of Social Medicine Saijo, Yasuaki; Asahikawa Medical University, Division of Public Health and Epidemiology, Department of Social Medicine Yoshioka, Eiji ; Asahikawa Medical University, Division of Public Health and Epidemiology, Department of Social Medicine Sato, Yukihiro; Asahikawa Medical University, Division of Public Health and Epidemiology, Department of Social Medicine Nakanishi, Kentaro; Asahikawa Medical University, Department of Obstetrics and Gynecology Kato, Yasuhito; Asahikawa Medical University, Department of Obstetrics and Gynecology; Asahikawa Medical University, Department of Social Medicine Nagaya, Ken; Asahikawa Medical University Hospital, Division of Neonatology, Perinatal Medical Center Takahashi, Satoru; Asahikawa Medical University, Department of Pediatrics Ito, Yoshiya; Japanese Red Cross Hokkaido College of Nursing, Faculty of Nursing Iwata, Hiroyoshi; Hokkaido University, Center for Environmental and Health Sciences Yamaguchi, Takeshi; Hokkaido University, Center for Environmental and Health Sciences; Hokkaido University Hospital, Department of Pediatrics Miyashita, Chihiro; Hokkaido University, Center for Environmental and Health Sciences Ito, Sachiko; Hokkaido University, Center for Environmental and Health Sciences Kishi, Reiko; Hokkaido University, Center for Environmental and Health Sciences group, The Japan Environment ; National Institute for Environmental Studies, Tsukuba city, Ibaraki, Japan
Primary Subject Heading:	Public health
Secondary Subject Heading:	Obstetrics and gynaecology, Paediatrics
Keywords:	PUBLIC HEALTH, Maternal medicine < OBSTETRICS, Paediatric neurology < PAEDIATRICS, Multimorbidity, Pregnant Women

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 **Title: Association between maternal multimorbidity and neurodevelopment of**
2 **offspring: a prospective birth cohort study from the Japan Environment and**
3 **Children’s Study**

5 **Author names**

6 Takanobu Akagi^a, Yasuaki Saijo^a, Eiji Yoshioka^a, Yukihiro Sato^a, Kentaro Nakanishi^b,
7 Yasuhito Kato^b, Ken Nagaya^c, Satoru Takahashi^d, Yoshiya Ito^e, Hiroyoshi Iwata^f,
8 Takeshi Yamaguchi^f, Chihiro Miyashita^f, Sachiko Itoh^f, Reiko Kishi^f, the Japan
9 Environment and Children’s Study (JECS) Group^g

11 **Author affiliations**

12 ^aDivision of Public Health and Epidemiology, Department of Social Medicine,
13 Asahikawa Medical University, 1-1-1, Midorigaoka higashi2-jo, Asahikawa, Hokkaido
14 078-8510, Japan

15 ^bDepartment of Obstetrics and Gynecology, Asahikawa Medical University, Asahikawa,
16 1-1-1, Midorigaoka higashi2-jo, Asahikawa, Hokkaido 078-8510, Japan

17 ^cDivision of Neonatology, Perinatal Medical Center, Asahikawa Medical University
18 Hospital, 1-1-1, Midorigaoka higashi2-jo, Asahikawa, Hokkaido 078-8510, Japan

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Ensignment Superior (ABES) .

^dDepartment of Pediatrics, Asahikawa Medical University, 1-1-1, Midorigaoka
higashi2-jo, Asahikawa, Hokkaido 078-8510, Japan

^eFaculty of Nursing, Japanese Red Cross Hokkaido College of Nursing, 664-1,
Akebono-cho, Kitami, Hokkaido 090-0011, Japan

^fCenter for Environmental and Health Sciences, Hokkaido University, Kita12-jo,
Nishi7-chome, Kita-ku, Sapporo, Hokkaido 060-0812, Japan

^gMembers of the Japan Environment and Children's Study Group are listed in the
Appendices.

27

Corresponding author

Yasuaki Saijo

Division of Public Health and Epidemiology, Department of Social Medicine,
Asahikawa Medical University

078-8510, 1-1-1, Midorigaoka higashi2-jo, Asahikawa, Hokkaido, Japan

Tel: +81-166-68-2402

Email: y-saijo@asahikawa-med.ac.jp

35

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

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Ensignment Supérieur (ABES).

1
2
3
4
5 91 as hypertension, kidney disease, and systemic lupus erythematosus, are potential risk
6
7
8 92 factors for preterm birth (PTB) and low birth weight infants (LBW).(7) Moreover,
9
10
11 93 maternal mental and social morbidities have also been associated with PTB and
12
13
14 94 LBW.(7) Previous studies also reported the relationship between maternal environment
15
16
17 95 such as maternal asthma, maternal intake of fats, maternal and cord blood Manganese
18
19
20 96 levels and child development.(8–10)
21
22

23 97 Infancy is considered to be the period in which language, cognition, motor
24
25
26 98 skills, and socioemotional domains form the basis for subsequent social
27
28
29 99 participation.(11) It is essential to receive appropriate support, early detection, and
30
31
32 100 intervention during this period.(12) Although maternal nutritional status, certain
33
34
35 101 diseases, and blood substances can affect the neurodevelopment of offspring(8–11), the
36
37
38 102 impacts of multimorbidity in pregnant women on the neurodevelopment of offspring
39
40
41 103 has not been extensively studied.(5,6) A major difference between previous reports and
42
43
44 104 this study was the investigation of the association between multiple diseases of pregnant
45
46
47 105 women and child neurodevelopment; previous reports have mainly focused on the
48
49
50 106 relationship between a single disease or single substance in pregnant women and child
51
52
53 107 neurodevelopment.
54

55
56 108 The present study aimed to investigate the association between multimorbidity
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

114

115 **METHODS**

116 **Study population**

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

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Supérieur (ABES) .

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

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Supérieur (ABES).

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

145 chronic conditions included in multimorbidity were defined as conditions with high
146 prevalence among women of reproductive age.(7) To identify pregnant women with
147 disease more rigorously, the diseases of pregnant women were defined as those that
148 were medically treated at the time of pregnancy. Information was collected through self-
149 reports, medical record transcripts, and medication interviews. The targeted diseases
150 included allergic diseases, such as asthma, anemia, diabetes mellitus, dyslipidemia,
151 epilepsy, gastric or duodenal ulcers, heart disease, hepatitis, human immunodeficiency
152 virus (HIV) infection, hypertension, inflammatory bowel disease, kidney disease,
153 malignancy, migraine, neurologic disease, other sexually transmitted diseases
154 (Chlamydia trachomatis and syphilis), mental disorders, rheumatic or collagen diseases,
155 and thyroid disease. Having an episode of domestic violence, substance abusing, being
156 obese (BMI ≥ 25), and being thin (BMI < 18.5) were each defined as one disease. We
157 used maternal pre-pregnancy body weight data for analysis. Pregnant women with two
158 or more of these diseases during pregnancy were defined as having multimorbidities.

159

160 **Assessment of neurodevelopment of offspring**

161 Score results from the Japanese version of the ASQ-3 (Ages and Stages Questionnaires,
162 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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

194

195

196

197

198

199

200

201

202

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 (6.8)	1,898 (2.3)
	1	123 (0.1)	2,603 (3.1)	1,237 (1.5)	6 (3.1)	891 (1.1)
	≥2	19 (0.02)	316 (0.4)	137 (0.2)	4 (0.4)	101 (0.1)
1 year	0	54 (0.1)	2,711 (3.3)	2,743 (3.3)	8 (3.0)	566 (0.7)
	1	31 (0.04)	1,324 (1.6)	1,383 (1.7)	6 (1.5)	282 (0.3)
	≥2	6 (0.01)	148 (0.2)	154 (0.2)	2 (0.2)	57 (0.1)
1 half years	0	1,091 (1.3)	2,138 (2.6)	2,000 (2.4)	1 (2.2)	1,209 (1.5)
	1	528 (0.6)	1,100 (1.3)	984 (1.2)	9 (1.1)	564 (0.7)
	≥2	76 (0.1)	148 (0.2)	156 (0.2)	3 (0.2)	78 (0.1)
2 years	0	1,851 (2.2)	2,816 (3.4)	1,060 (1.3)	2,166 (2.5)	1,400 (1.7)
	1	1,048 (1.3)	1,474 (1.8)	590 (0.7)	1,064 (1.2)	706 (0.9)
	≥2	147 (0.2)	176 (0.2)	84 (0.1)	112 (0.1)	99 (0.1)
2 half years	0	2,445 (3.0)	2,042 (2.5)	2,696 (3.3)	2,788 (3.3)	1,634 (2.0)
	1	1,376 (1.7)	1,086 (1.3)	1,389 (1.7)	1,455 (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)	3,466 (4.1)	1,603 (1.9)
	1	1,030 (1.2)	1,102 (1.3)	1,843 (2.2)	1,733 (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)	2,669 (3.2)	2,130 (2.6)
	1	1,467 (1.8)	1,098 (1.3)	1,341 (1.6)	1,588 (1.8)	1,171 (1.4)
	≥2	219 (0.3)	155 (0.2)	182 (0.2)	238 (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)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

204

205

206

207

208

209

210

211

212

213

214

215

216

217

218

219

220

221

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

1
2
3
4
5
6 222 decrease in the group tested 1 to 3 times. The difference in ASQ-3 scores of the groups
7
8
9 223 tested less frequently from those of the group tested in all time points ranged from -1.62
10
11
12 224 to 3.37. Comparing the group tested in all time points, the groups tested less frequently
13
14
15 225 tended to have higher scores until 2 years and lower scores after 2.5 years. The results
16
17
18 226 of the multivariate logistic regression analysis conducted on the number of
19
20
21 227 comorbidities in pregnant women and the neurodevelopment of offspring are shown in
22
23
24 228 Table 3 and Figure 2. Except at 6 months, the ORs were more than 1 for any of the
25
26
27 229 following items: communication, gross motor, fine motor, problem solving, and
28
29
30 230 personal and social. The ORs at 6 months were lower than those at other ages for all
31
32
33 231 items, both single disease comorbidity and multimorbidity. ORs tended to be higher
34
35
36 232 with increasing age of the offspring, and the ORs for all items were higher at 4 years
37
38
39 233 than at 6 months for both single-disease coexistence and multimorbidity. The ORs for
40
41
42 234 single disease comorbidities ranged from 0.85 (95% CI 0.69–1.05) to 1.28 (95% CI
43
44
45 235 0.82–1.99). The OR range for multimorbidity was 0.95 (95% CI 0.80–1.14) to 2.29
46
47
48 236 (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
49
50
51 237 (95% CI 1.19–1.69) for all domains.
52
53
54
55
56
57
58
59
60

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)	0.86 (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)	1.01 (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)	1.12 (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)	1.04 (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)	1.09 (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)	1.06 (1.06–1.12)	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.

239

240 DISCUSSION

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

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

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

1
2
3
4
5 275 medication were not included in the disease sample in this study, with the exception of
6
7
8 276 domestic violence, obese, and skinny women. The criterion for disease was defined as
9
10
11 277 the presence of medication; the number of pregnant women with disease may have been
12
13
14 278 higher if the study had been conducted using different criteria. Some have criticized the
15
16
17 279 definition of multimorbidity as simply having more than one disease, which would
18
19
20 280 include a large population.(24) In the future, a definition of multimorbidity that is
21
22
23 281 suitable for the target community will be required since the significant diseases and
24
25
26 282 conditions vary depending on the target population.(24) Second, it was difficult in this
27
28
29 283 study to discuss the biological mechanisms of the association between multimorbidity
30
31
32 284 and neurodevelopmental delay. The association between various diseases and
33
34
35 285 neurodevelopmental delays has been reported in previous studies.(8,16–18,25) Further
36
37
38 286 studies on disease characteristics and disease combinations may allow for hypotheses to
39
40
41 287 be made regarding the biological mechanisms underlying the association between
42
43
44 288 multimorbidity and neurodevelopmental delay. Third, as participants in the JECS were
45
46
47 289 only collaborators, selection bias may have occurred.(15) The prevalence of
48
49
50 290 multimorbidity and the results of the association between multimorbidity and
51
52
53 291 neurodevelopmental delay might have been different if the study design included
54
55
56 292 pregnant women who did not participate in the JECS. The number of pregnant women
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

310 Previous reports on multimorbidities in pregnant women have focused on its

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Supérieur (ABES) .

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.

Acknowledgments

We would like to express our gratitude to all the JECS study participants and staff members involved in data collection. Members of the JECS Group are as of 2023: Michihiro Kamijima (principal investigator, Nagoya City University, Nagoya, Japan); Shin Yamazaki (National Institute for Environmental Studies, Tsukuba, Japan); Yukihiro Ohya (National Center for Child Health and Development, Tokyo, Japan); Reiko Kishi (Hokkaido University, Sapporo, Japan); Nobuo Yaegashi (Tohoku University, Sendai, Japan); Koichi Hashimoto (Fukushima Medical University, Fukushima, Japan); Chisato Mori (Chiba University, Chiba, Japan); Shuichi Ito (Yokohama City University, Yokohama, Japan), Zentaro Yamagata (University of

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

329 Yamanashi, Chuo, Japan), Hidekuni Inadera (University of Toyama, Toyama, Japan),
330 Takeo Nakayama (Kyoto University, Kyoto, Japan), Tomotaka Sobue (Osaka
331 University, Suita, Japan), Masayuki Shima (Hyogo Medical University, Nishinomiya,
332 Japan), Seiji Kageyama (Tottori University, Yonago, Japan), Narufumi Suganuma
333 (Kochi University, Nankoku, Japan), Shoichi Ohga (Kyushu University, Fukuoka,
334 Japan), and Takahiko Katoh (Kumamoto University, Kumamoto, Japan).

335 We would like to thank Editage (www.editage.com) for the English language editing.

336

337 **Contributors**

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

345

346 **Funding statement**

1
2
3
4
5 347 This study was funded by the Ministry of the Environment, Japan. The findings and
6
7
8 348 conclusions of this study are solely the responsibility of the authors and do not represent
9
10
11 349 the official views of the government. (N/A)
12
13

14 350

17 351 **Competing interests**

18
19
20 352 The authors declare that they have no competing interests.
21
22

23 353

26 354 **Patient and public involvement**

27
28
29 355 The patients and/or the public were not involved in the design, conduct, reporting, or
30
31
32 356 dissemination of this study.
33
34

35 357

38 358 **Patient consent for publication**

39
40
41 359 Not applicable.
42
43

44 360

47 361 **Ethics approval**

48
49
50 362 The JECS protocol was reviewed and approved by the Ministry of the Environment's
51
52
53 363 Institutional Review Board on Epidemiological Studies and the Ethics Committees of
54
55
56 364 all participating institutions (No. 100910001). The JECS protocol was conducted
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

367
368 **Provenance and peer review**

369 Not commissioned; externally peer reviewed.

370
371 **Data availability statement**

372 Data are unsuitable for public deposition due to ethical restrictions and legal framework
373 of Japan. It is prohibited by the Act on the Protection of Personal Information (Act No.
374 57 of 30 May 2003, amendment on 9 September 2015) to publicly deposit the data
375 containing personal information. Ethical Guidelines for Medical and Health Research
376 Involving Human Subjects enforced by the Japan Ministry of Education, Culture,
377 Sports, Science and Technology and the Ministry of Health, Labour and Welfare also
378 restricts the open sharing of the epidemiologic data. All inquiries about access to data
379 should be sent to: jecs-en@nies.go.jp. The person responsible for handling enquiries
380 sent to this e-mail address is Dr Shoji F. Nakayama, JECS Programme Office, National
381 Institute for Environmental Studies.

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Supérieur (ABES).

References

1. World Health Organization. Multimorbidity. World Health Organization; 2016. Accessed November 1, 2022. <https://apps.who.int/iris/handle/10665/252275>
2. McParland C, Johnston B, Cooper M. A mixed-methods systematic review of nurse-led interventions for people with multimorbidity. *Journal of Advanced Nursing*. 2022;78(12):3930-51. doi:10.1111/jan.15427
3. Salisbury C, Johnson L, Purdy S, et al. Epidemiology and impact of multimorbidity in primary care: a retrospective cohort study. *Br J Gen Pract*. 2011;61(582):e12-21. doi:10.3399/bjgp11X548929
4. Taylor AW, Price K, Gill TK, et al. Multimorbidity - not just an older person's issue. Results from an Australian biomedical study. *BMC Public Health*. 2010;10(1):718. doi:10.1186/1471-2458-10-718
5. Lee SI, Azcoaga-Lorenzo A, Agrawal U, et al. Epidemiology of pre-existing multimorbidity in pregnant women in the UK in 2018: a population-based cross-sectional study. *BMC Pregnancy Childbirth*. 2022;22(1):120. doi:10.1186/s12884-022-04442-3
6. McCauley M, Zafar S, van den Broek N. Maternal multimorbidity during pregnancy and after childbirth in women in low- and middle-income countries: a systematic literature review. *BMC Pregnancy Childbirth*. 2020;20(1):637. doi:10.1186/s12884-020-03303-1
7. Nakanishi K, Saijo Y, Yoshioka E, et al. Association between maternal multimorbidity and preterm birth, low birth weight and small for gestational age: a prospective birth cohort study from the Japan Environment and Children's Study. *BMJ Open*. 2023;13(3):e069281. doi:10.1136/bmjopen-2022-069281
8. Gong T, Lundholm C, Rejnö G, et al. Parental asthma and risk of autism spectrum disorder in offspring: A population and family-based case-control study. *Clin Exp*

Allergy. 2019;49(6):883-91. doi:10.1111/cea.13353

9. Lyall K, Munger KL, O'Reilly EJ, et al. Maternal Dietary Fat Intake in Association With Autism Spectrum Disorders. American Journal of Epidemiology. 2013;178(2):209-20. doi:10.1093/aje/kws433

10. Yamamoto M, Eguchi A, Sakurai K, et al. Longitudinal analyses of maternal and cord blood manganese levels and neurodevelopment in children up to 3 years of age: The Japan Environment and Children's Study (JECS). Environment International. 2022;161:107126. doi:10.1016/j.envint.2022.107126

11. Cusick SE, Georgieff MK. The Role of Nutrition in Brain Development: The Golden Opportunity of the "First 1000 Days." The Journal of Pediatrics. 2016;175:16-21. doi:10.1016/j.jpeds.2016.05.013

12. Smythe T, Zuurmond M, Tann CJ, et al. Early intervention for children with developmental disabilities in low and middle-income countries – the case for action. International Health. 2021;13(3):222-231. doi:10.1093/inthealth/ihaa044

13. Working Group of the Epidemiological Research for Children's Environmental Health, Kawamoto T, Nitta H, et al. Rationale and study design of the Japan environment and children's study (JECS). BMC Public Health. 2014;14(1):25. doi:10.1186/1471-2458-14-25

14. Mezawa H, Aoki S, Nakayama SF, et al. Psychometric profile of the Ages and Stages Questionnaires, Japanese translation. Pediatrics International. 2019;61(11):1086-95. doi:10.1111/ped.13990

15. Michikawa T, Nitta H, Nakayama SF, et al. The Japan Environment and Children's Study (JECS): A Preliminary Report on Selected Characteristics of Approximately 10 000 Pregnant Women Recruited During the First Year of the Study. Journal of Epidemiology. 2015;25(6):452-8. doi:10.2188/jea.JE20140186

16. Nattero-Chávez L, Luque-Ramírez M, Escobar-Morreale HF. Systemic endocrinopathies (thyroid conditions and diabetes): impact on postnatal life of the offspring. Fertility and Sterility. 2019;111(6):1076-91.

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Ensignement Supérieur (ABES).

- doi:10.1016/j.fertnstert.2019.04.039
17. Nulman I, Koren G, Rovet J, et al. Neurodevelopment of Children Following Prenatal Exposure to Venlafaxine, Selective Serotonin Reuptake Inhibitors, or Untreated Maternal Depression. *AJP*. 2012;169(11):1165-74. doi:10.1176/appi.ajp.2012.11111721
18. Meador KJ, Baker GA, Browning N, et al. Cognitive Function at 3 Years of Age after Fetal Exposure to Antiepileptic Drugs. *N Engl J Med*. 2009 Apr 16;360(16):1597–605. doi:10.1056/NEJMoa0803531
19. Nolvi S, Merz EC, Kataja EL, et al. Prenatal Stress and the Developing Brain: Postnatal Environments Promoting Resilience. *Biological Psychiatry*. 2023;93(10):942-52. doi:10.1016/j.biopsych.2022.11.023
20. Premkumar A, Mele L, Casey BM, et al. Relationship Between Maternal Economic Vulnerability and Childhood Neurodevelopment at 2 and 5 Years of Life. *Obstetrics & Gynecology*. 2021;138(3):379-88. doi:10.1097/AOG.0000000000004503
21. Kim-Cohen J, Moffitt TE, Taylor A, et al. Maternal Depression and Children's Antisocial Behavior. *ARCH GEN PSYCHIATRY*. 2005;62.
22. Harries CI, Smith DM, Gregg L, et al. Parenting and Serious Mental Illness (SMI): A Systematic Review and Metasynthesis. *Clin Child Fam Psychol Rev*. 2023;26(2):303-42. doi:10.1007/s10567-023-00427-6
23. H.K. Hughes, R.J. Moreno, P. Ashwood et al. Innate immune dysfunction and neuroinflammation in autism spectrum disorder (ASD). *Brain Behav Immun*. 2023 Feb;108:245-254. doi: 10.1016/j.bbi.2022.12.001.
24. Skou ST, Mair FS, Fortin M, et al. Multimorbidity. *Nat Rev Dis Primers*. 2022;8(1):48. doi:10.1038/s41572-022-00376-4
25. Nalli C, Galli J, Lini D, et al. The Influence of Treatment of Inflammatory Arthritis During Pregnancy on the Long-Term Children's Outcome. *Front Pharmacol*. 2021;12:626258. doi:10.3389/fphar.2021.626258

26. Kigawa M, Tsuchida A, Miura K, et al. Analysis of non-respondent pregnant women who were registered in the Japan Environment and Children's Study: a longitudinal cohort study. *BMJ Open*. 2019 Jun;9(6):e025562. doi: 10.1136/bmjopen-2018-025562

27. Kigawa M, Tsuchida A, Matsumura K, et al. Predictors of non-response to successive waves of surveys in the Japan Environment and Children's Study during the 3-year postpartum period: a longitudinal cohort study. *BMJ Open*. 2022 Jul;12(7):e050087. doi: 10.1136/bmjopen-2021-050087

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.

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Engagement Superior (ABES).

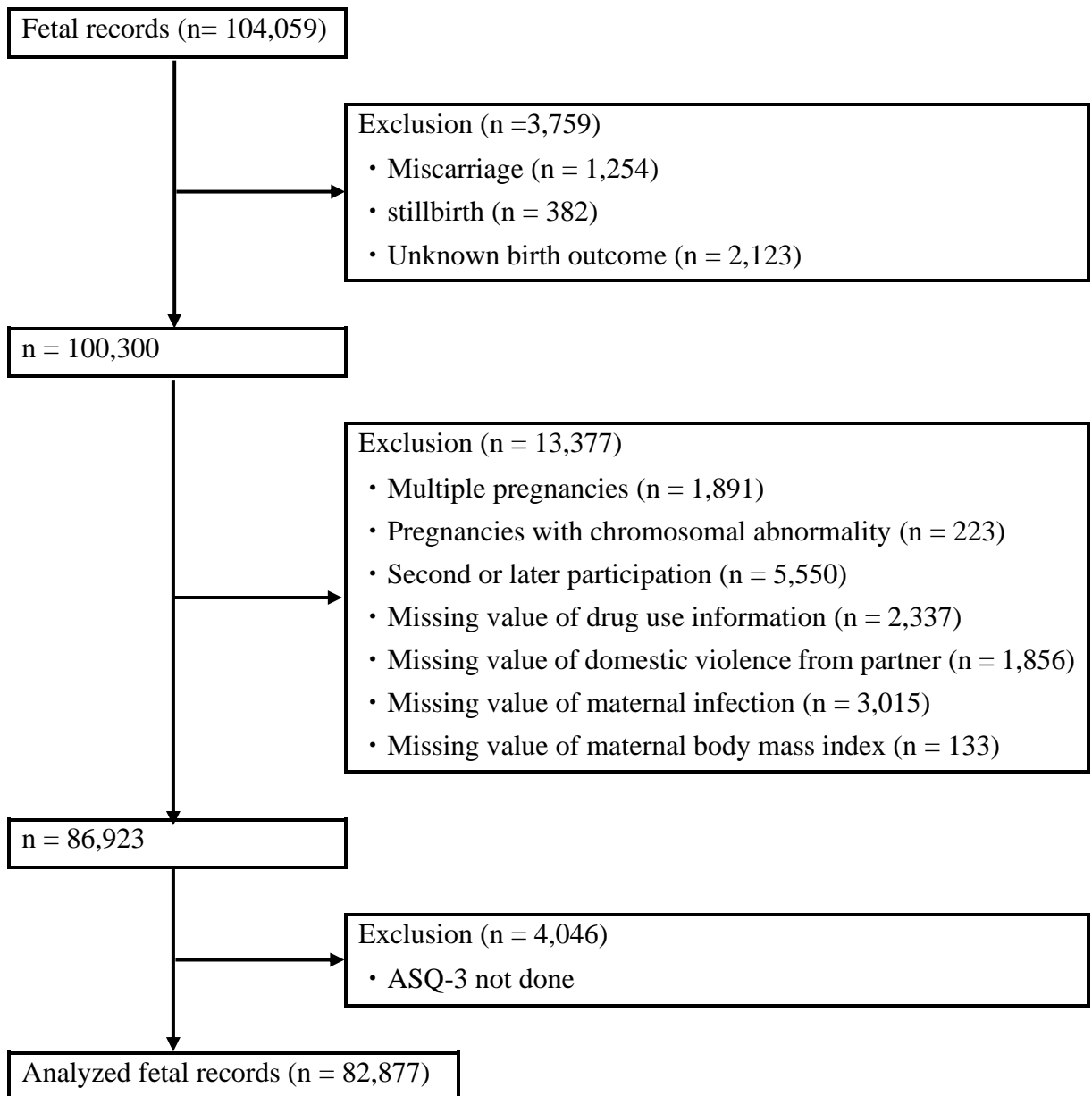


Figure 1. Fetal records selection flow chart.

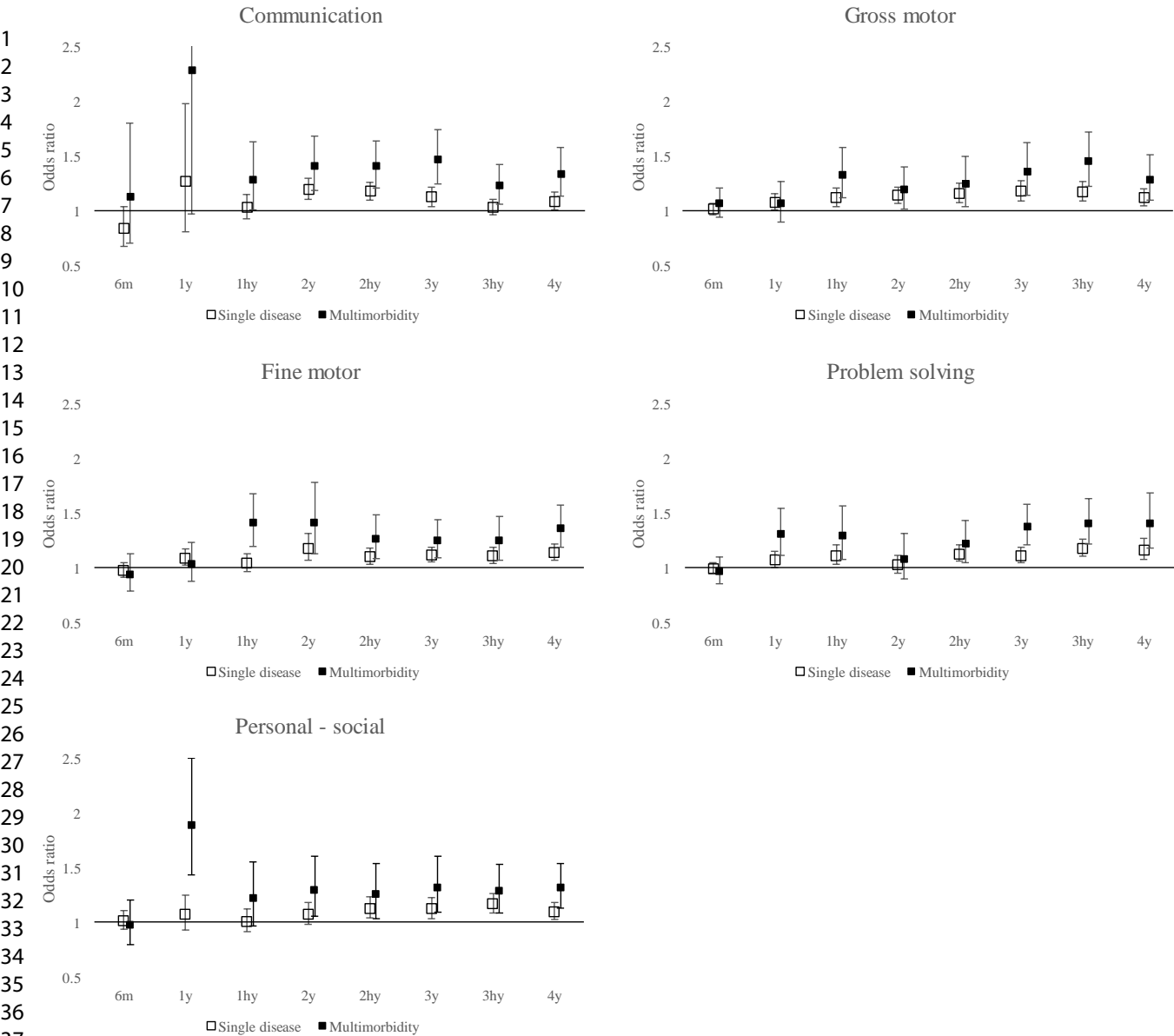


Figure 2. Adjusted odds ratio for developmental delay of offspring for multimorbidity during pregnancy by logistic regression. Models were adjusted for maternal age at birth, parity, history of alcohol consumption, history of smoking, maternal educational attainment, household income, and sex of child. 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/m ²)	12,889	15.6
Obesity (BMI >25.0 kg/m ²)	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	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	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	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	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	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	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	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	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	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
4 years	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 (b) Provide in the abstract an informative and balanced summary of what was done and what was found	1 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 (b) For matched studies, give matching criteria and number of exposed and unexposed	7,8 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 (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	10 10 10,11 - -
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	7,8 7,8 7,8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	11,12 - 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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2023-082585.R3
Article Type:	Original research
Date Submitted by the Author:	25-Jun-2024
Complete List of Authors:	Akagi, Takanobu; Asahikawa Medical University, Division of Public Health and Epidemiology, Department of Social Medicine Saijo, Yasuaki; Asahikawa Medical University, Division of Public Health and Epidemiology, Department of Social Medicine Yoshioka, Eiji ; Asahikawa Medical University, Division of Public Health and Epidemiology, Department of Social Medicine Sato, Yukihiro; Asahikawa Medical University, Division of Public Health and Epidemiology, Department of Social Medicine Nakanishi, Kentaro; Asahikawa Medical University, Department of Obstetrics and Gynecology Kato, Yasuhito; Asahikawa Medical University, Department of Obstetrics and Gynecology; Asahikawa Medical University, Department of Social Medicine Nagaya, Ken; Asahikawa Medical University Hospital, Division of Neonatology, Perinatal Medical Center Takahashi, Satoru; Asahikawa Medical University, Department of Pediatrics Ito, Yoshiya; Japanese Red Cross Hokkaido College of Nursing, Faculty of Nursing Iwata, Hiroyoshi; Hokkaido University, Center for Environmental and Health Sciences Yamaguchi, Takeshi; Hokkaido University, Center for Environmental and Health Sciences; Hokkaido University Hospital, Department of Pediatrics Miyashita, Chihiro; Hokkaido University, Center for Environmental and Health Sciences Ito, Sachiko; Hokkaido University, Center for Environmental and Health Sciences Kishi, Reiko; Hokkaido University, Center for Environmental and Health Sciences group, The Japan Environment ; National Institute for Environmental Studies, Tsukuba city, Ibaraki, Japan
Primary Subject Heading:	Public health
Secondary Subject Heading:	Obstetrics and gynaecology, Paediatrics
Keywords:	PUBLIC HEALTH, Maternal medicine < OBSTETRICS, Paediatric neurology < PAEDIATRICS, Multimorbidity, Pregnant Women

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 **Title: Association between maternal multimorbidity and neurodevelopment of**
2 **offspring: a prospective birth cohort study from the Japan Environment and**
3 **Children’s Study**

5 **Author names**

6 Takanobu Akagi^a, Yasuaki Saijo^a, Eiji Yoshioka^a, Yukihiro Sato^a, Kentaro Nakanishi^b,
7 Yasuhito Kato^b, Ken Nagaya^c, Satoru Takahashi^d, Yoshiya Ito^e, Hiroyoshi Iwata^f,
8 Takeshi Yamaguchi^f, Chihiro Miyashita^f, Sachiko Itoh^f, Reiko Kishi^f, the Japan
9 Environment and Children’s Study (JECS) Group^g

11 **Author affiliations**

12 ^aDivision of Public Health and Epidemiology, Department of Social Medicine,
13 Asahikawa Medical University, 1-1-1, Midorigaoka higashi2-jo, Asahikawa, Hokkaido
14 078-8510, Japan

15 ^bDepartment of Obstetrics and Gynecology, Asahikawa Medical University, Asahikawa,
16 1-1-1, Midorigaoka higashi2-jo, Asahikawa, Hokkaido 078-8510, Japan

17 ^cDivision of Neonatology, Perinatal Medical Center, Asahikawa Medical University
18 Hospital, 1-1-1, Midorigaoka higashi2-jo, Asahikawa, Hokkaido 078-8510, Japan

^dDepartment of Pediatrics, Asahikawa Medical University, 1-1-1, Midorigaoka
higashi2-jo, Asahikawa, Hokkaido 078-8510, Japan

^eFaculty of Nursing, Japanese Red Cross Hokkaido College of Nursing, 664-1,
Akebono-cho, Kitami, Hokkaido 090-0011, Japan

^fCenter for Environmental and Health Sciences, Hokkaido University, Kita12-jo,
Nishi7-chome, Kita-ku, Sapporo, Hokkaido 060-0812, Japan

^gMembers of the Japan Environment and Children's Study Group are listed in the
Appendices.

27

Corresponding author

Yasuaki Saijo

Division of Public Health and Epidemiology, Department of Social Medicine,
Asahikawa Medical University

078-8510, 1-1-1, Midorigaoka higashi2-jo, Asahikawa, Hokkaido, Japan

Tel: +81-166-68-2402

Email: y-saijo@asahikawa-med.ac.jp

35

ABSTRACT

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3
4
5 91 as hypertension, kidney disease, and systemic lupus erythematosus, are potential risk
6
7
8 92 factors for preterm birth (PTB) and low birth weight infants (LBW).(7) Moreover,
9
10
11 93 maternal mental and social morbidities have also been associated with PTB and
12
13
14 94 LBW.(7) Previous studies also reported the relationship between maternal environments
15
16
17 95 such as maternal asthma, maternal intake of fats, maternal and cord blood Manganese
18
19
20 96 levels and child development.(8–10)
21
22

23 97 Infancy is considered to be the period in which language, cognition, motor
24
25
26 98 skills, and socioemotional domains form the basis for subsequent social
27
28
29 99 participation.(11) It is essential to receive appropriate support, early detection, and
30
31
32 100 intervention during this period.(12) Although maternal nutritional status, certain
33
34
35 101 diseases, and blood substances can affect the neurodevelopment of offspring(8–11), the
36
37
38 102 impacts of multimorbidity in pregnant women on the neurodevelopment of offspring
39
40
41 103 have not been extensively studied.(5,6) A major difference between previous reports
42
43
44 104 and this study was the investigation of the association between multiple diseases of
45
46
47 105 pregnant women and child neurodevelopment; previous reports have mainly focused on
48
49
50 106 the relationship between a single disease or single substance in pregnant women and
51
52
53 107 child neurodevelopment.
54

55
56 108 The present study aimed to investigate the association between multimorbidity
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

115 **METHODS**

116 **Study population**

117 The JECS is a nationwide and government-funded birth cohort study that started
118 recruiting expecting mothers in January 2011.(13); the primary objective was to
119 investigate environmental factors such as exposure to chemicals and airborne pollutants
120 that can affect children’s health and development during the fetal stage and early
121 childhood, in order to help policymakers to formulate measures to safeguard the
122 environment for future generations.(15) The study population included 104,059 fetal
123 records who participated in JECS from 2011 to 2014. A flowchart of the study
124 participants is presented in Figure 1. The exclusion criteria included: miscarriage,
125 stillbirth, or unknown birth outcomes (n = 2,123). Second, participants with multiple
126 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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

145 chronic conditions included in multimorbidity were defined as conditions with high
146 prevalence among women of reproductive age.(7) To identify pregnant women with the
147 disease more rigorously, the diseases of pregnant women were defined as those that
148 were medically treated at the time of pregnancy. Information was collected through self-
149 reports, medical record transcripts, and medication interviews. The targeted diseases
150 included allergic diseases, such as asthma, anemia, diabetes mellitus, dyslipidemia,
151 epilepsy, gastric or duodenal ulcers, heart disease, hepatitis, human immunodeficiency
152 virus (HIV) infection, hypertension, inflammatory bowel disease, kidney disease,
153 malignancy, migraine, neurologic disease, other sexually transmitted diseases
154 (Chlamydia trachomatis and syphilis), mental disorders, rheumatic or collagen diseases,
155 and thyroid disease. Having an episode of domestic violence, substance abuse, being
156 obese (BMI ≥ 25), and being thin (BMI < 18.5) were each defined as one disease. We
157 used maternal pre-pregnancy body weight data for analysis. Pregnant women with two
158 or more of these diseases during pregnancy were defined as having multimorbidities.

159

160 **Assessment of neurodevelopment of offspring**

161 Score results from the Japanese version of the ASQ-3 (Ages and Stages Questionnaires,
162 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

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Ensignement Supérieur (ABES).

	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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

194

195 The prevalence of 23 maternal diseases is described in supplemental table 1.

196 Maternal underweight (BMI <18.5) (15.6%) was the most frequently observed chronic
197 condition, followed by maternal obesity (BMI ≥25) (10.7%). The most frequent diseases
198 on medication were allergic diseases (3.1%), other sexually transmitted diseases (1.3%),
199 anemia (0.7%), mental disorders (0.7%) and thyroid disease (0.7%).

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

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Supérieur (ABES) .

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 (6.8)	1,898 (2.3)
	1	123 (0.1)	2,603 (3.1)	1,237 (1.5)	6 (3.1)	891 (1.1)
	≥2	19 (0.02)	316 (0.4)	137 (0.2)	0 (0.4)	101 (0.1)
1 year	0	54 (0.1)	2,711 (3.3)	2,743 (3.3)	8 (3.0)	566 (0.7)
	1	31 (0.04)	1,324 (1.6)	1,383 (1.7)	6 (1.5)	282 (0.3)
	≥2	6 (0.01)	148 (0.2)	154 (0.2)	2 (0.2)	57 (0.1)
1 half years	0	1,091 (1.3)	2,138 (2.6)	2,000 (2.4)	1 (2.2)	1,209 (1.5)
	1	528 (0.6)	1,100 (1.3)	984 (1.2)	9 (1.1)	564 (0.7)
	≥2	76 (0.1)	148 (0.2)	156 (0.2)	3 (0.2)	78 (0.1)
2 years	0	1,851 (2.2)	2,816 (3.4)	1,060 (1.3)	2,166 (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)	112 (0.1)	99 (0.1)
2 half years	0	2,445 (3.0)	2,042 (2.5)	2,696 (3.3)	2,788 (3.3)	1,634 (2.0)
	1	1,376 (1.7)	1,086 (1.3)	1,389 (1.7)	1,455 (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)	3,466 (4.1)	1,603 (1.9)
	1	1,030 (1.2)	1,102 (1.3)	1,843 (2.2)	1,733 (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)	2,609 (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)	238 (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)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

204

205

206

207

208

209

210

211

212

213

214

215

216

217

218

219

220

221

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% CI 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)	0.86 (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)	1.01 (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)	1.12 (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)	1.04 (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)	1.09 (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)	1.06 (1.06–1.12)	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.

239

240 **DISCUSSION**

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

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

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

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Supérieur (ABES)

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

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Ensignement Supérieur (ABES).

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.

Acknowledgments

We would like to express our gratitude to all the JECS study participants and staff members involved in data collection. Members of the JECS Group are as of 2023: Michihiro Kamijima (principal investigator, Nagoya City University, Nagoya, Japan); Shin Yamazaki (National Institute for Environmental Studies, Tsukuba, Japan); Yukihiro Ohya (National Center for Child Health and Development, Tokyo, Japan); Reiko Kishi (Hokkaido University, Sapporo, Japan); Nobuo Yaegashi (Tohoku University, Sendai, Japan); Koichi Hashimoto (Fukushima Medical University,

Fukushima, Japan); Chisato Mori (Chiba University, Chiba, Japan); Shuichi Ito (Yokohama City University, Yokohama, Japan), Zentaro Yamagata (University of Yamanashi, Chuo, Japan), Hidekuni Inadera (University of Toyama, Toyama, Japan), Takeo Nakayama (Kyoto University, Kyoto, Japan), Tomotaka Sobue (Osaka University, Suita, Japan), Masayuki Shima (Hyogo Medical University, Nishinomiya, Japan), Seiji Kageyama (Tottori University, Yonago, Japan), Narufumi Suganuma (Kochi University, Nankoku, Japan), Shoichi Ohga (Kyushu University, Fukuoka, Japan), and Takahiko Katoh (Kumamoto University, Kumamoto, Japan).

We would like to thank Editage (www.editage.com) for the English language editing.

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.

Funding statement

This study was funded by the Ministry of the Environment, Japan. The findings and conclusions of this study are solely the responsibility of the authors and do not represent the official views of the government. (N/A)

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

371 **Provenance and peer review**

372 Not commissioned; externally peer reviewed.

374 **Data availability statement**

375 Data are unsuitable for public deposition due to ethical restrictions and legal framework
376 of Japan. It is prohibited by the Act on the Protection of Personal Information (Act No.
377 57 of 30 May 2003, amendment on 9 September 2015) to publicly deposit the data
378 containing personal information. Ethical Guidelines for Medical and Health Research
379 Involving Human Subjects enforced by the Japan Ministry of Education, Culture,
380 Sports, Science and Technology and the Ministry of Health, Labour and Welfare also
381 restricts the open sharing of the epidemiologic data. All inquiries about access to data
382 should be sent to: jecs-en@nies.go.jp. The person responsible for handling enquiries

Enseignement Supérieur (ABES) .
Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

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

References

1. World Health Organization. Multimorbidity. World Health Organization; 2016. Accessed November 1, 2022. <https://apps.who.int/iris/handle/10665/252275>
2. McParland C, Johnston B, Cooper M. A mixed-methods systematic review of nurse-led interventions for people with multimorbidity. *Journal of Advanced Nursing*. 2022;78(12):3930-51. doi:10.1111/jan.15427
3. Salisbury C, Johnson L, Purdy S, et al. Epidemiology and impact of multimorbidity in primary care: a retrospective cohort study. *Br J Gen Pract*. 2011;61(582):e12-21. doi:10.3399/bjgp11X548929
4. Taylor AW, Price K, Gill TK, et al. Multimorbidity - not just an older person's issue. Results from an Australian biomedical study. *BMC Public Health*. 2010;10(1):718. doi:10.1186/1471-2458-10-718
5. Lee SI, Azcoaga-Lorenzo A, Agrawal U, et al. Epidemiology of pre-existing multimorbidity in pregnant women in the UK in 2018: a population-based cross-sectional study. *BMC Pregnancy Childbirth*. 2022;22(1):120. doi:10.1186/s12884-022-04442-3
6. McCauley M, Zafar S, van den Broek N. Maternal multimorbidity during pregnancy and after childbirth in women in low- and middle-income countries: a systematic literature review. *BMC Pregnancy Childbirth*. 2020;20(1):637. doi:10.1186/s12884-020-03303-1
7. Nakanishi K, Saijo Y, Yoshioka E, et al. Association between maternal

multimorbidity and preterm birth, low birth weight and small for gestational age: a prospective birth cohort study from the Japan Environment and Children's Study. *BMJ Open*. 2023;13(3):e069281. doi:10.1136/bmjopen-2022-069281

8. Gong T, Lundholm C, Rejnö G, et al. Parental asthma and risk of autism spectrum disorder in offspring: A population and family-based case-control study. *Clin Exp Allergy*. 2019;49(6):883-91. doi:10.1111/cea.13353

9. Lyall K, Munger KL, O'Reilly EJ, et al. Maternal Dietary Fat Intake in Association With Autism Spectrum Disorders. *American Journal of Epidemiology*. 2013;178(2):209-20. doi:10.1093/aje/kws433

10. Yamamoto M, Eguchi A, Sakurai K, et al. Longitudinal analyses of maternal and cord blood manganese levels and neurodevelopment in children up to 3 years of age: The Japan Environment and Children's Study (JECS). *Environment International*. 2022;161:107126. doi:10.1016/j.envint.2022.107126

11. Cusick SE, Georgieff MK. The Role of Nutrition in Brain Development: The Golden Opportunity of the "First 1000 Days." *The Journal of Pediatrics*. 2016;175:16-21. doi:10.1016/j.jpeds.2016.05.013

12. Smythe T, Zuurmond M, Tann CJ, et al. Early intervention for children with developmental disabilities in low and middle-income countries – the case for action. *International Health*. 2021;13(3):222-231. doi:10.1093/inthealth/ihaa044

13. Working Group of the Epidemiological Research for Children's Environmental Health, Kawamoto T, Nitta H, et al. Rationale and study design of the Japan environment and children's study (JECS). *BMC Public Health*. 2014;14(1):25. doi:10.1186/1471-2458-14-25

14. Mezawa H, Aoki S, Nakayama SF, et al. Psychometric profile of the Ages and Stages Questionnaires, Japanese translation. *Pediatrics International*. 2019;61(11):1086-95. doi:10.1111/ped.13990

15. Michikawa T, Nitta H, Nakayama SF, et al. The Japan Environment and Children's Study (JECS): A Preliminary Report on Selected Characteristics

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Ensignement Supérieur (ABES).

- of Approximately 10 000 Pregnant Women Recruited During the First Year of the Study. *Journal of Epidemiology*. 2015;25(6):452-8. doi:10.2188/jea.JE20140186
16. Nattero-Chávez L, Luque-Ramírez M, Escobar-Morreale HF. Systemic endocrinopathies (thyroid conditions and diabetes): impact on postnatal life of the offspring. *Fertility and Sterility*. 2019;111(6):1076-91. doi:10.1016/j.fertnstert.2019.04.039
17. Nulman I, Koren G, Rovet J, et al. Neurodevelopment of Children Following Prenatal Exposure to Venlafaxine, Selective Serotonin Reuptake Inhibitors, or Untreated Maternal Depression. *AJP*. 2012;169(11):1165-74. doi:10.1176/appi.ajp.2012.11111721
18. Meador KJ, Baker GA, Browning N, et al. Cognitive Function at 3 Years of Age after Fetal Exposure to Antiepileptic Drugs. *N Engl J Med*. 2009 Apr 16;360(16):1597-605. doi:10.1056/NEJMoa0803531
19. Nolvi S, Merz EC, Kataja EL, et al. Prenatal Stress and the Developing Brain: Postnatal Environments Promoting Resilience. *Biological Psychiatry*. 2023;93(10):942-52. doi:10.1016/j.biopsych.2022.11.023
20. Premkumar A, Mele L, Casey BM, et al. Relationship Between Maternal Economic Vulnerability and Childhood Neurodevelopment at 2 and 5 Years of Life. *Obstetrics & Gynecology*. 2021;138(3):379-88. doi:10.1097/AOG.0000000000004503
21. Kim-Cohen J, Moffitt TE, Taylor A, et al. Maternal Depression and Children's Antisocial Behavior: nature and nurture effects. *Arch Gen Psychiatry*. 2005 Feb;62(2):173-81. doi: 10.1001/archpsyc.62.2.173.
22. Harries CI, Smith DM, Gregg L, et al. Parenting and Serious Mental Illness (SMI): A Systematic Review and Metasynthesis. *Clin Child Fam Psychol Rev*. 2023;26(2):303-42. doi:10.1007/s10567-023-00427-6
23. H.K. Hughes, R.J. Moreno, P. Ashwood et al. Innate immune dysfunction and neuroinflammation in autism spectrum disorder (ASD). *Brain Behav Immun*. 2023 Feb;108:245-254. doi: 10.1016/j.bbi.2022.12.001.

24. Skou ST, Mair FS, Fortin M, et al. Multimorbidity. *Nat Rev Dis Primers*. 2022;8(1):48. doi:10.1038/s41572-022-00376-4

25. Nalli C, Galli J, Lini D, et al. The Influence of Treatment of Inflammatory Arthritis During Pregnancy on the Long-Term Children's Outcome. *Front Pharmacol*. 2021;12:626258. doi:10.3389/fphar.2021.626258

26. Kigawa M, Tsuchida A, Miura K, et al. Analysis of non-respondent pregnant women who were registered in the Japan Environment and Children's Study: a longitudinal cohort study. *BMJ Open*. 2019 Jun;9(6):e025562. doi: 10.1136/bmjopen-2018-025562

27. Kigawa M, Tsuchida A, Matsumura K, et al. Predictors of non-response to successive waves of surveys in the Japan Environment and Children's Study during the 3-year postpartum period: a longitudinal cohort study. *BMJ Open*. 2022 Jul;12(7):e050087. doi: 10.1136/bmjopen-2021-050087

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

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Ensignement Supérieur (ABES).

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.

For peer review only

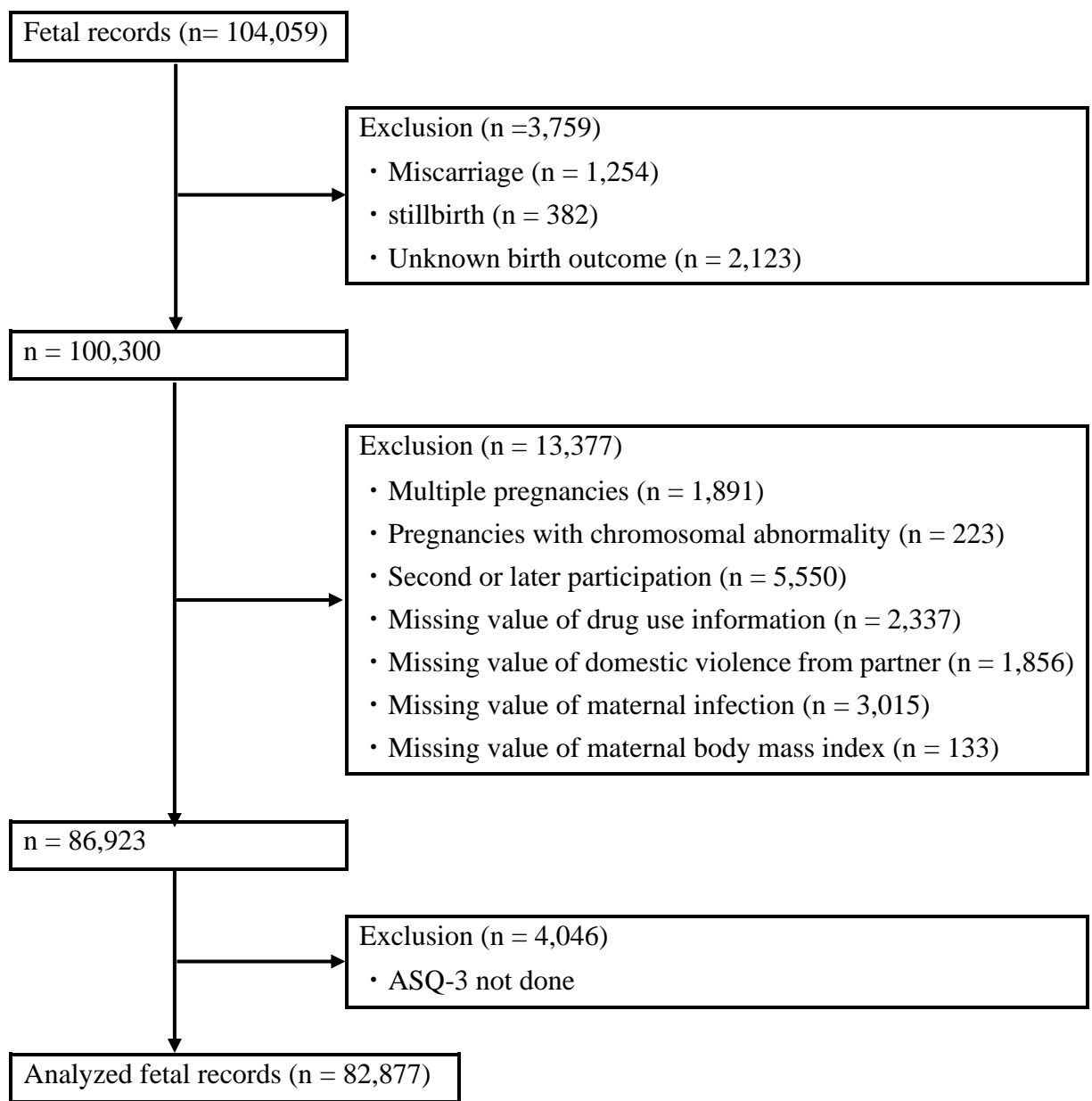


Figure 1. Fetal records selection flow chart.

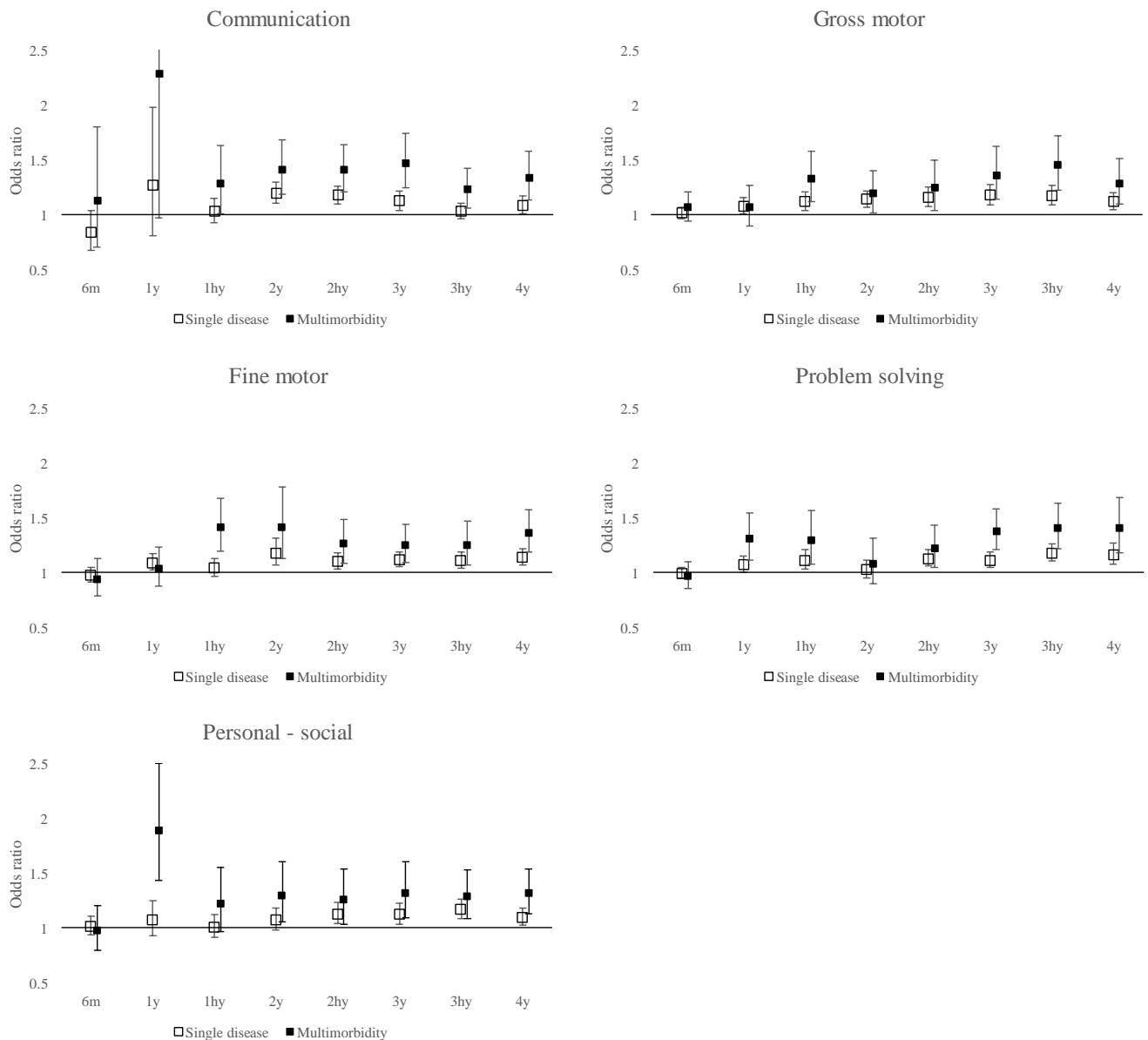


Figure 2. Adjusted odds ratio for developmental delay of offspring for multimorbidity during pregnancy by logistic regression. Models were adjusted for maternal age at birth, parity, history of alcohol consumption, history of smoking, maternal educational attainment, household income, and sex of child. 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	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	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	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	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	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	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	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	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	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
4 years		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 (b) Provide in the abstract an informative and balanced summary of what was done and what was found	1 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 (b) For matched studies, give matching criteria and number of exposed and unexposed	7,8 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 (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	10 10 10,11 - -
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	7,8 7,8 7,8
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	11,12 - 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>.

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Supérieur (ABES)

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2023-082585.R4
Article Type:	Original research
Date Submitted by the Author:	04-Jul-2024
Complete List of Authors:	Akagi, Takanobu; Asahikawa Medical University, Division of Public Health and Epidemiology, Department of Social Medicine Saijo, Yasuaki; Asahikawa Medical University, Division of Public Health and Epidemiology, Department of Social Medicine Yoshioka, Eiji ; Asahikawa Medical University, Division of Public Health and Epidemiology, Department of Social Medicine Sato, Yukihiro; Asahikawa Medical University, Division of Public Health and Epidemiology, Department of Social Medicine Nakanishi, Kentaro; Asahikawa Medical University, Department of Obstetrics and Gynecology Kato, Yasuhito; Asahikawa Medical University, Department of Obstetrics and Gynecology; Asahikawa Medical University, Department of Social Medicine Nagaya, Ken; Asahikawa Medical University Hospital, Division of Neonatology, Perinatal Medical Center Takahashi, Satoru; Asahikawa Medical University, Department of Pediatrics Ito, Yoshiya; Japanese Red Cross Hokkaido College of Nursing, Faculty of Nursing Iwata, Hiroyoshi; Hokkaido University, Center for Environmental and Health Sciences Yamaguchi, Takeshi; Hokkaido University, Center for Environmental and Health Sciences; Hokkaido University Hospital, Department of Pediatrics Miyashita, Chihiro; Hokkaido University, Center for Environmental and Health Sciences Ito, Sachiko; Hokkaido University, Center for Environmental and Health Sciences Kishi, Reiko; Hokkaido University, Center for Environmental and Health Sciences group, The Japan Environment ; National Institute for Environmental Studies, Tsukuba city, Ibaraki, Japan
Primary Subject Heading:	Public health
Secondary Subject Heading:	Obstetrics and gynaecology, Paediatrics
Keywords:	PUBLIC HEALTH, Maternal medicine < OBSTETRICS, Paediatric neurology < PAEDIATRICS, Multimorbidity, Pregnant Women

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1 **Title: Association between maternal multimorbidity and neurodevelopment of**
2 **offspring: a prospective birth cohort study from the Japan Environment and**
3 **Children’s Study**

5 **Author names**

6 Takanobu Akagi^a, Yasuaki Saijo^a, Eiji Yoshioka^a, Yukihiro Sato^a, Kentaro Nakanishi^b,
7 Yasuhito Kato^b, Ken Nagaya^c, Satoru Takahashi^d, Yoshiya Ito^e, Hiroyoshi Iwata^f,
8 Takeshi Yamaguchi^f, Chihiro Miyashita^f, Sachiko Itoh^f, Reiko Kishi^f, the Japan
9 Environment and Children’s Study (JECS) Group^g

11 **Author affiliations**

12 ^aDivision of Public Health and Epidemiology, Department of Social Medicine,
13 Asahikawa Medical University, 1-1-1, Midorigaoka higashi2-jo, Asahikawa, Hokkaido
14 078-8510, Japan

15 ^bDepartment of Obstetrics and Gynecology, Asahikawa Medical University, Asahikawa,
16 1-1-1, Midorigaoka higashi2-jo, Asahikawa, Hokkaido 078-8510, Japan

17 ^cDivision of Neonatology, Perinatal Medical Center, Asahikawa Medical University
18 Hospital, 1-1-1, Midorigaoka higashi2-jo, Asahikawa, Hokkaido 078-8510, Japan

^dDepartment of Pediatrics, Asahikawa Medical University, 1-1-1, Midorigaoka
higashi2-jo, Asahikawa, Hokkaido 078-8510, Japan

^eFaculty of Nursing, Japanese Red Cross Hokkaido College of Nursing, 664-1,
Akebono-cho, Kitami, Hokkaido 090-0011, Japan

^fCenter for Environmental and Health Sciences, Hokkaido University, Kita12-jo,
Nishi7-chome, Kita-ku, Sapporo, Hokkaido 060-0812, Japan

^gMembers of the Japan Environment and Children's Study Group are listed in the
Appendices.

27

Corresponding author

Yasuaki Saijo

Division of Public Health and Epidemiology, Department of Social Medicine,
Asahikawa Medical University

078-8510, 1-1-1, Midorigaoka higashi2-jo, Asahikawa, Hokkaido, Japan

Tel: +81-166-68-2402

Email: y-saijo@asahikawa-med.ac.jp

35

ABSTRACT

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

114

115 **METHODS**

116 **Study population**

117 The JECS is a nationwide and government-funded birth cohort study that started
118 recruiting expecting mothers in January 2011.(13); the primary objective was to
119 investigate environmental factors such as exposure to chemicals and airborne pollutants
120 that can affect children’s health and development during the fetal stage and early
121 childhood, in order to help policymakers to formulate measures to safeguard the
122 environment for future generations.(15) The study population included 104,059 fetal
123 records who participated in JECS from 2011 to 2014. A flowchart of the study
124 participants is presented in Figure 1. The exclusion criteria included: miscarriage,
125 stillbirth, or unknown birth outcomes (n = 2,123). Second, participants with multiple
126 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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

145 chronic conditions included in multimorbidity were defined as conditions with high
146 prevalence among women of reproductive age.(7) To identify pregnant women with the
147 disease more rigorously, the diseases of pregnant women were defined as those that
148 were medically treated at the time of pregnancy. Information was collected through self-
149 reports, medical record transcripts, and medication interviews. The targeted diseases
150 included allergic diseases, such as asthma, anemia, diabetes mellitus, dyslipidemia,
151 epilepsy, gastric or duodenal ulcers, heart disease, hepatitis, human immunodeficiency
152 virus (HIV) infection, hypertension, inflammatory bowel disease, kidney disease,
153 malignancy, migraine, neurologic disease, other sexually transmitted diseases
154 (Chlamydia trachomatis and syphilis), mental disorders, rheumatic or collagen diseases,
155 and thyroid disease. Having an episode of domestic violence, substance abuse, being
156 obese (BMI ≥ 25), and being thin (BMI < 18.5) were each defined as one disease. We
157 used maternal pre-pregnancy body weight data for analysis. Pregnant women with two
158 or more of these diseases during pregnancy were defined as having multimorbidities.

159

160 **Assessment of neurodevelopment of offspring**

161 Score results from the Japanese version of the ASQ-3 (Ages and Stages Questionnaires,
162 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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

194

195 The prevalence of 23 maternal diseases is described in supplemental table 1.

196 Maternal underweight (BMI <18.5) (15.6%) was the most frequently observed chronic
197 condition, followed by maternal obesity (BMI ≥25) (10.7%). The most frequent diseases
198 on medication were allergic diseases (3.1%), other sexually transmitted diseases (1.3%),
199 anemia (0.7%), mental disorders (0.7%) and thyroid disease (0.7%).

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

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Supérieur (ABES) .

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 (6.8)	1,898 (2.3)
	1	123 (0.1)	2,603 (3.1)	1,237 (1.5)	6 (3.1)	891 (1.1)
	≥2	19 (0.02)	316 (0.4)	137 (0.2)	4 (0.4)	101 (0.1)
1 year	0	54 (0.1)	2,711 (3.3)	2,743 (3.3)	8 (3.0)	566 (0.7)
	1	31 (0.04)	1,324 (1.6)	1,383 (1.7)	6 (1.5)	282 (0.3)
	≥2	6 (0.01)	148 (0.2)	154 (0.2)	2 (0.2)	57 (0.1)
1 half years	0	1,091 (1.3)	2,138 (2.6)	2,000 (2.4)	1 (2.2)	1,209 (1.5)
	1	528 (0.6)	1,100 (1.3)	984 (1.2)	9 (1.1)	564 (0.7)
	≥2	76 (0.1)	148 (0.2)	156 (0.2)	3 (0.2)	78 (0.1)
2 years	0	1,851 (2.2)	2,816 (3.4)	1,060 (1.3)	2,166 (2.5)	1,400 (1.7)
	1	1,048 (1.3)	1,474 (1.8)	590 (0.7)	1,064 (1.2)	706 (0.9)
	≥2	147 (0.2)	176 (0.2)	84 (0.1)	112 (0.1)	99 (0.1)
2 half years	0	2,445 (3.0)	2,042 (2.5)	2,696 (3.3)	2,788 (3.3)	1,634 (2.0)
	1	1,376 (1.7)	1,086 (1.3)	1,389 (1.7)	1,455 (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)	3,466 (4.1)	1,603 (1.9)
	1	1,030 (1.2)	1,102 (1.3)	1,843 (2.2)	1,733 (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)	2,669 (3.2)	2,130 (2.6)
	1	1,467 (1.8)	1,098 (1.3)	1,341 (1.6)	1,588 (1.8)	1,171 (1.4)
	≥2	219 (0.3)	155 (0.2)	182 (0.2)	238 (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)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

204

205

206

207

208

209

210

211

212

213

214

215

216

217

218

219

220

221

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% CI 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)	0.86 (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)	1.01 (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)	1.12 (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)	1.04 (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)	1.09 (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)	1.06 (1.06–1.12)	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.

239

240 DISCUSSION

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

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

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

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Enseignement Supérieur (ABES)

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

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Ensignement Supérieur (ABES).

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.

Acknowledgments

We would like to express our gratitude to all the JECS study participants and staff members involved in data collection. Members of the JECS Group are as of 2023: Michihiro Kamijima (principal investigator, Nagoya City University, Nagoya, Japan); Shin Yamazaki (National Institute for Environmental Studies, Tsukuba, Japan); Yukihiro Ohya (National Center for Child Health and Development, Tokyo, Japan); Reiko Kishi (Hokkaido University, Sapporo, Japan); Nobuo Yaegashi (Tohoku University, Sendai, Japan); Koichi Hashimoto (Fukushima Medical University,

Fukushima, Japan); Chisato Mori (Chiba University, Chiba, Japan); Shuichi Ito (Yokohama City University, Yokohama, Japan), Zentaro Yamagata (University of Yamanashi, Chuo, Japan), Hidekuni Inadera (University of Toyama, Toyama, Japan), Takeo Nakayama (Kyoto University, Kyoto, Japan), Tomotaka Sobue (Osaka University, Suita, Japan), Masayuki Shima (Hyogo Medical University, Nishinomiya, Japan), Seiji Kageyama (Tottori University, Yonago, Japan), Narufumi Suganuma (Kochi University, Nankoku, Japan), Shoichi Ohga (Kyushu University, Fukuoka, Japan), and Takahiko Katoh (Kumamoto University, Kumamoto, Japan).

We would like to thank Editage (www.editage.com) for the English language editing.

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.

Funding statement

This study was funded by the Ministry of the Environment, Japan. The findings and conclusions of this study are solely the responsibility of the authors and do not represent the official views of the government. (N/A)

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

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

371 **Provenance and peer review**

372 Not commissioned; externally peer reviewed.

374 **Data availability statement**

375 Data are unsuitable for public deposition due to ethical restrictions and legal framework
376 of Japan. It is prohibited by the Act on the Protection of Personal Information (Act No.
377 57 of 30 May 2003, amendment on 9 September 2015) to publicly deposit the data
378 containing personal information. Ethical Guidelines for Medical and Health Research
379 Involving Human Subjects enforced by the Japan Ministry of Education, Culture,
380 Sports, Science and Technology and the Ministry of Health, Labour and Welfare also
381 restricts the open sharing of the epidemiologic data. All inquiries about access to data
382 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.

References

1. World Health Organization. Multimorbidity. World Health Organization; 2016. Accessed November 1, 2022. <https://apps.who.int/iris/handle/10665/252275>
2. McParland C, Johnston B, Cooper M. A mixed-methods systematic review of nurse-led interventions for people with multimorbidity. *Journal of Advanced Nursing*. 2022;78(12):3930-51. doi:10.1111/jan.15427
3. Salisbury C, Johnson L, Purdy S, et al. Epidemiology and impact of multimorbidity in primary care: a retrospective cohort study. *Br J Gen Pract*. 2011;61(582):e12-21. doi:10.3399/bjgp11X548929
4. Taylor AW, Price K, Gill TK, et al. Multimorbidity - not just an older person's issue. Results from an Australian biomedical study. *BMC Public Health*. 2010;10(1):718. doi:10.1186/1471-2458-10-718
5. Lee SI, Azcoaga-Lorenzo A, Agrawal U, et al. Epidemiology of pre-existing multimorbidity in pregnant women in the UK in 2018: a population-based cross-sectional study. *BMC Pregnancy Childbirth*. 2022;22(1):120. doi:10.1186/s12884-022-04442-3
6. McCauley M, Zafar S, van den Broek N. Maternal multimorbidity during pregnancy and after childbirth in women in low- and middle-income countries: a systematic literature review. *BMC Pregnancy Childbirth*. 2020;20(1):637. doi:10.1186/s12884-020-03303-1
7. Nakanishi K, Saijo Y, Yoshioka E, et al. Association between maternal

multimorbidity and preterm birth, low birth weight and small for gestational age: a prospective birth cohort study from the Japan Environment and Children's Study. *BMJ Open*. 2023;13(3):e069281. doi:10.1136/bmjopen-2022-069281

8. Gong T, Lundholm C, Rejnö G, et al. Parental asthma and risk of autism spectrum disorder in offspring: A population and family-based case-control study. *Clin Exp Allergy*. 2019;49(6):883-91. doi:10.1111/cea.13353

9. Lyall K, Munger KL, O'Reilly ÉJ, et al. Maternal Dietary Fat Intake in Association With Autism Spectrum Disorders. *American Journal of Epidemiology*. 2013;178(2):209-20. doi:10.1093/aje/kws433

10. Yamamoto M, Eguchi A, Sakurai K, et al. Longitudinal analyses of maternal and cord blood manganese levels and neurodevelopment in children up to 3 years of age: The Japan Environment and Children's Study (JECS). *Environment International*. 2022;161:107126. doi:10.1016/j.envint.2022.107126

11. Cusick SE, Georgieff MK. The Role of Nutrition in Brain Development: The Golden Opportunity of the "First 1000 Days." *The Journal of Pediatrics*. 2016;175:16-21. doi:10.1016/j.jpeds.2016.05.013

12. Smythe T, Zuurmond M, Tann CJ, et al. Early intervention for children with developmental disabilities in low and middle-income countries – the case for action. *International Health*. 2021;13(3):222-231. doi:10.1093/inthealth/ihaa044

13. Working Group of the Epidemiological Research for Children's Environmental Health, Kawamoto T, Nitta H, et al. Rationale and study design of the Japan environment and children's study (JECS). *BMC Public Health*. 2014;14(1):25. doi:10.1186/1471-2458-14-25

14. Mezawa H, Aoki S, Nakayama SF, et al. Psychometric profile of the Ages and Stages Questionnaires, Japanese translation. *Pediatrics International*. 2019;61(11):1086-95. doi:10.1111/ped.13990

15. Michikawa T, Nitta H, Nakayama SF, et al. The Japan Environment and Children's Study (JECS): A Preliminary Report on Selected Characteristics

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Ensignement Supérieur (ABES).

- of Approximately 10 000 Pregnant Women Recruited During the First Year of the Study. *Journal of Epidemiology*. 2015;25(6):452-8. doi:10.2188/jea.JE20140186
16. Nattero-Chávez L, Luque-Ramírez M, Escobar-Morreale HF. Systemic endocrinopathies (thyroid conditions and diabetes): impact on postnatal life of the offspring. *Fertility and Sterility*. 2019;111(6):1076-91. doi:10.1016/j.fertnstert.2019.04.039
17. Nulman I, Koren G, Rovet J, et al. Neurodevelopment of Children Following Prenatal Exposure to Venlafaxine, Selective Serotonin Reuptake Inhibitors, or Untreated Maternal Depression. *AJP*. 2012;169(11):1165-74. doi:10.1176/appi.ajp.2012.11111721
18. Meador KJ, Baker GA, Browning N, et al. Cognitive Function at 3 Years of Age after Fetal Exposure to Antiepileptic Drugs. *N Engl J Med*. 2009 Apr 16;360(16):1597-605. doi:10.1056/NEJMoa0803531
19. Nolvi S, Merz EC, Kataja EL, et al. Prenatal Stress and the Developing Brain: Postnatal Environments Promoting Resilience. *Biological Psychiatry*. 2023;93(10):942-52. doi:10.1016/j.biopsych.2022.11.023
20. Premkumar A, Mele L, Casey BM, et al. Relationship Between Maternal Economic Vulnerability and Childhood Neurodevelopment at 2 and 5 Years of Life. *Obstetrics & Gynecology*. 2021;138(3):379-88. doi:10.1097/AOG.0000000000004503
21. Kim-Cohen J, Moffitt TE, Taylor A, et al. Maternal Depression and Children's Antisocial Behavior: nature and nurture effects. *Arch Gen Psychiatry*. 2005 Feb;62(2):173-81. doi: 10.1001/archpsyc.62.2.173.
22. Harries CI, Smith DM, Gregg L, et al. Parenting and Serious Mental Illness (SMI): A Systematic Review and Metasynthesis. *Clin Child Fam Psychol Rev*. 2023;26(2):303-42. doi:10.1007/s10567-023-00427-6
23. H.K. Hughes, R.J. Moreno, P. Ashwood et al. Innate immune dysfunction and neuroinflammation in autism spectrum disorder (ASD). *Brain Behav Immun*. 2023 Feb;108:245-254. doi: 10.1016/j.bbi.2022.12.001.

24. Skou ST, Mair FS, Fortin M, et al. Multimorbidity. *Nat Rev Dis Primers*. 2022;8(1):48. doi:10.1038/s41572-022-00376-4

25. Nalli C, Galli J, Lini D, et al. The Influence of Treatment of Inflammatory Arthritis During Pregnancy on the Long-Term Children's Outcome. *Front Pharmacol*. 2021;12:626258. doi:10.3389/fphar.2021.626258

26. Kigawa M, Tsuchida A, Miura K, et al. Analysis of non-respondent pregnant women who were registered in the Japan Environment and Children's Study: a longitudinal cohort study. *BMJ Open*. 2019 Jun;9(6):e025562. doi: 10.1136/bmjopen-2018-025562

27. Kigawa M, Tsuchida A, Matsumura K, et al. Predictors of non-response to successive waves of surveys in the Japan Environment and Children's Study during the 3-year postpartum period: a longitudinal cohort study. *BMJ Open*. 2022 Jul;12(7):e050087. doi: 10.1136/bmjopen-2021-050087

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

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Ensignement Supérieur (ABES).

1
2
3
4
5 511 attainment, household income, and sex of child. Error bars indicate 95% confidence
6
7
8 512 intervals. The 95% confidence interval for communication at 1 year with
9
10
11 513 multimorbidity was 0.98-5.3.
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

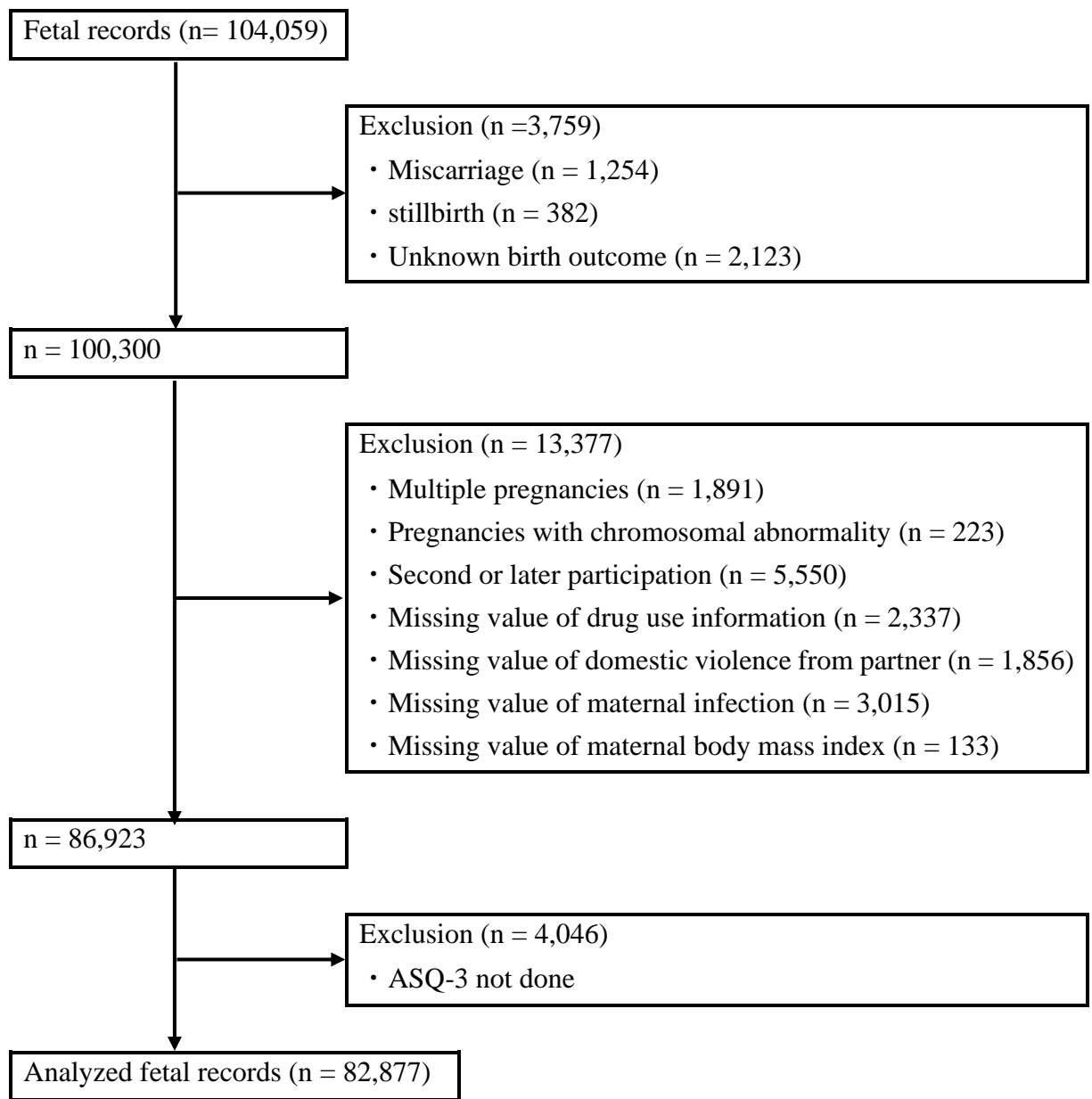


Figure 1. Fetal records selection flow chart.

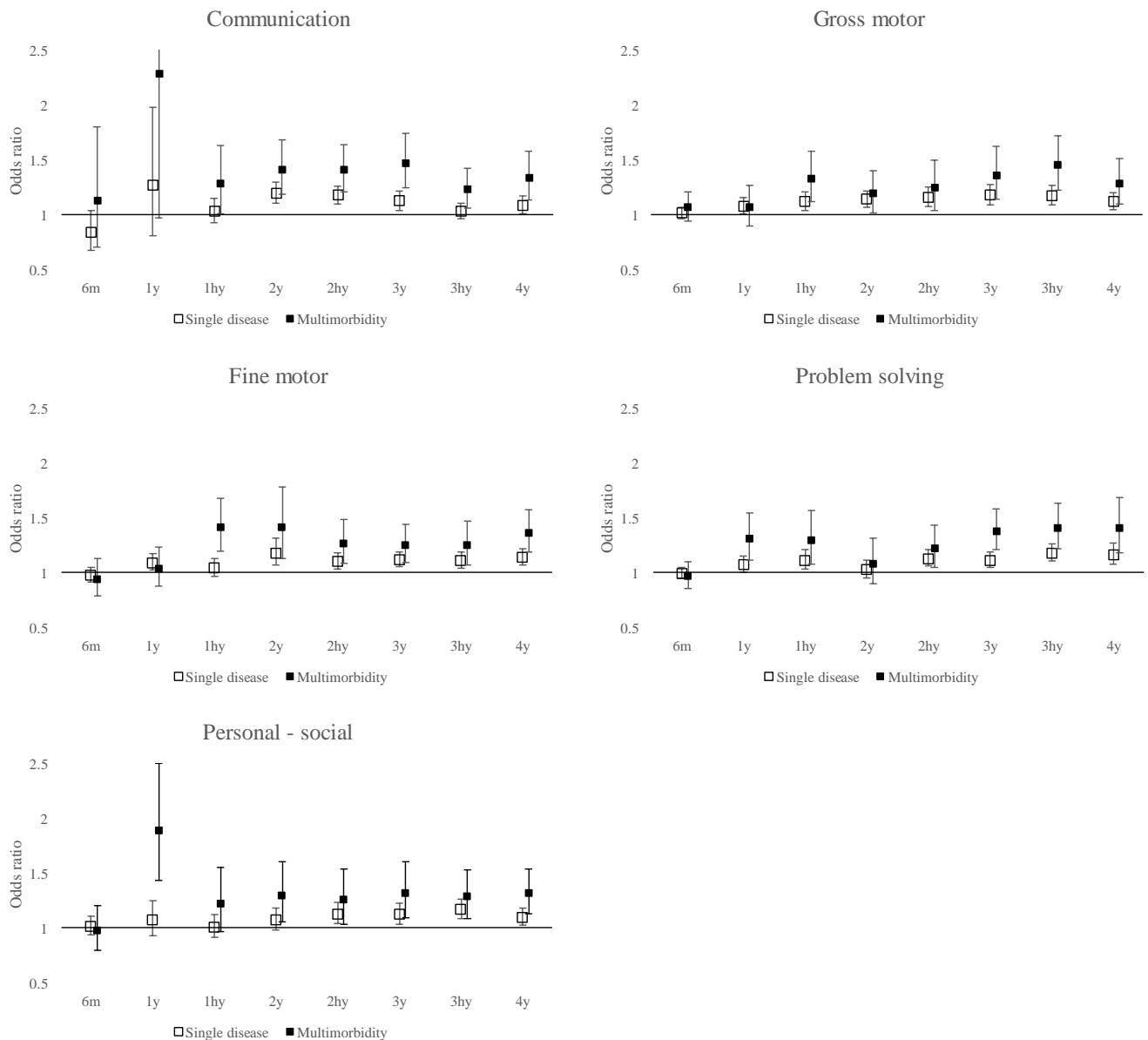


Figure 2. Adjusted odds ratio for developmental delay of offspring for multimorbidity during pregnancy by logistic regression. Models were adjusted for maternal age at birth, parity, history of alcohol consumption, history of smoking, maternal educational attainment, household income, and sex of child. 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	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	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	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	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	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	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	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	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	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
4 years		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 (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	10, 16–17 Not Applicable 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>.

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Enseignement Supérieur (ABES).