British Journal of Nutrition (2023), 130, 1973–1981 doi:10.1017/S0007114523000922

Maternal magnesium intake and childhood wheezing in offspring at 3 years of age: the Japan Environment and Children's Study

Tsuyoshi Murata[1,2]*, Hyo Kyozuka[1,2], Toma Fukuda[1,2], Karin Imaizumi[1,2], Hirotaka Isogami[1,2], Shun Yasuda[1,2], Akiko Yamaguchi[1,2], Akiko Sato[1], Yuka Ogata[1], Kosei Shinoki[1], Mitsuaki Hosoya[1,3], Seiji Yasumura[1,4], Koichi Hashimoto[1,3], Hidekazu Nishigori[1,5], Keiya Fujimori[1,2] and The Japan Environment and Children's Study (JECS) Group†

[1]*Fukushima Regional Center for the Japan Environment and Children's Study, 1 Hikarigaoka, Fukushima 960-1295, Japan*
[2]*Department of Obstetrics and Gynecology, Fukushima Medical University School of Medicine, 1 Hikarigaoka, Fukushima 960-1295, Japan*
[3]*Department of Pediatrics, Fukushima Medical University School of Medicine, 1 Hikarigaoka, Fukushima 960-1295, Japan*
[4]*Department of Public Health, Fukushima Medical University School of Medicine, 1 Hikarigaoka, Fukushima 960-1295, Japan*
[5]*Fukushima Medical Center for Children and Women, Fukushima Medical University, 1 Hikarigaoka, Fukushima 960-1295, Japan*

(Submitted 8 October 2022 – Final revision received 11 March 2023 – Accepted 30 March 2023 – First published online 26 May 2023)

Abstract

This study evaluated the association between maternal magnesium intake (MMI) and childhood wheezing incidence in 3-year-old offspring. We hypothesised that higher MMI imparts anti-inflammatory and antioxidant effects that decrease childhood wheezing incidence in offspring. Data of 79 907 women (singleton pregnancy, ≥ 22 weeks) from the Japan Environment and Children's Study (enrolled between 2011 and 2014) were analysed. Participants were categorised into quintiles of MMI (< 148·00, 148·00–187·99, 188·00–228·99, 229·00–289·99 and ≥ 290·00 mg/d), quintiles of adjusted MMI for daily energy intake (aMMI) (< 0·107, 0·107–0·119, 0·120–0·132, 0·133–0·149 and ≥ 0·150 mg/kcal) and MMI levels either below or above the ideal value (< 310·00 or ≥ 310·00 mg/d). Multivariable logistic regression analysis was performed to calculate OR for the incidence of childhood wheezing in offspring among participants in each MMI category, with the lowest MMI group considered the reference group. Maternal demographic, socio-economic, medical and other nutrient intake backgrounds were considered potential confounding factors. The adjusted OR (aOR) for childhood wheezing in the offspring of women with the highest MMI was 1·09 (95 % CI, 1·00, 1·20), whereas that calculated based on aMMI categories and offspring of women with above-ideal MMI levels remained unchanged. The highest MMI was associated with slightly increased childhood wheezing incidence in the offspring. MMI during pregnancy had an insignificant clinical impact on this incidence; moreover, modifying MMI would not significantly improve childhood wheezing incidence in offspring. Therefore, further studies should clarify the association between other prenatal factors and childhood wheezing incidence in offspring.

Key words: **Birth cohort study: Childhood wheezing: Magnesium: Offspring: Pregnancy**

Asthma and wheezing commonly occur during childhood, with a prevalence of approximately 10 % in Japan[1,2]. There is no exact method for predicting or preventing childhood wheezing. While environmental factors have been reported as causal factors for asthma and wheezing during childhood[3–5], pregnancy-associated factors have also been reported to influence the incidence of childhood asthma and wheezing[6–9]. According to our previous study, maternal ritodrine hydrochloride administration for the prolongation of pregnancy was associated with an increased incidence of childhood wheezing in the offspring[9]. There is no clear explanation for this association; however, the foetuses of mothers whose gestational period was prolonged by long-term maternal ritodrine hydrochloride administration may have experienced stress due to 'excessive' uterine contractions, and there might have been secretion of foetal pituitary adrenocorticotropic hormone,

Abbreviations: aMMI, adjusted MMI; aOR, adjusted OR; JECS, Japan Environment and Children's Study; MMI, maternal magnesium intake.

* **Corresponding author:** Tsuyoshi Murata, email tuyoshim@fmu.ac.jp

† Membership of the Japan Environment and Children's Study Group is provided in the Acknowledgments

leading to asthma development in the offspring in future[9,10]. The association between prenatal factors and incidence of childhood wheezing in the offspring should be clarified considering underlying mechanisms.

Mg is a common factor involved in the function of enzymes and acts as a cofactor in over 600 enzymatic reactions[11]. Mg is important during pregnancy because it also affects uterine smooth muscle activity[12], which could affect the pregnancy and offspring; additionally, it exerts various benefits, including anti-inflammatory and antioxidant effects[13]. Several studies have reported that adequate maternal magnesium intake (MMI) reduces preterm births, foetal growth restriction, small-for-gestational-age births and pre-eclampsia[14]. However, the association between MMI and offspring childhood health, including childhood wheezing, remains unclarified. A previous study did not report any association between MMI, which was estimated using a FFQ, and childhood asthma[15]; however, this study showed an association between MMI and the decreased incidence of childhood eczema in offspring[15]. Non-pregnant adults who received oral Mg supplements showed improved objective and subjective measures of bronchial reactivity, asthma control, and quality of life, respectively[16].

Therefore, we analysed the association between MMI and incidence of childhood wheezing in the offspring using data from a nationwide birth cohort study. Based on the above phenomenon[16], we hypothesised that higher MMI imparts anti-inflammatory and antioxidant effects that decrease childhood wheezing incidence in offspring.

Experimental methods

Study design

We analysed data from the Japan Environment and Children's Study (JECS), a nationwide, government-funded, prospective birth cohort study initiated in January 2011 – participants were enrolled during 2011–2014 – aimed to investigate the effects of environmental factors on children's health[17,18]. Expectant mothers who (1) resided within the study area at the time of recruitment, with plans to keep residing in Japan in the foreseeable future; (2) had their expected delivery date between August 2011 and mid-2014; and (3) could easily participate in the study (i.e. understood the Japanese language and completed a self-administered questionnaire) were considered eligible for inclusion in the JECS.

The two modes of recruitment were as follows: (1) at the time of first prepartum examination by cooperating healthcare providers and (2) at local government offices issuing a pregnancy journal (i.e. the Maternal and Child Health Handbook) to all expectant mothers before receiving municipal services. Pregnant women were contacted through healthcare providers, and those who were willing to participate were registered. Self-administered questionnaires were used to collect information on demographic factors, medical history, physical and mental health, lifestyle, occupation, environmental exposure at home and in the workplace, housing condition, and socio-economic status during the first and second/third trimesters[17,18].

Data collection

The current analysis used data released in October 2019 (dataset: jecs-ta-20190930). Women with singleton pregnancies were included in the present study, while those who experienced abortion or stillbirth or had missing information were excluded.

Exposure variables

We used the FFQ administered in the early stage of pregnancy and in the second/third trimester (median: 27·0 weeks of gestation) in the JECS. Participants were asked to answer questions about their 1-year dietary intake at the early stage of pregnancy and between awareness of pregnancy and the second or third trimester. The FFQ used in this study was validated in a large-scale epidemiological study in Japan, and its details have been reported[19]. Briefly, the long-type FFQ asked about the respondents' habitual consumption of the listed food items using nine frequency and three portion sizes categories[19–21]. Frequencies ranged from less than once per month to more than seven times per d, and portions ranged from small, 0·5; medium, 1·0; and large, 1·5, compared with standard units[19–21]. Eating habits, including breakfast frequency, eating out and eating speed, were also assessed[19–21]. The validity of nutrient intake assessment using a FFQ in Japanese pregnant women has been previously reported[20–22].

The nutrient contents of each food were determined based on the Japanese food composition tables, 5th revised revision, while the daily intakes of nutrients were calculated by summing the contents from the food items after multiplying by the frequency of consumption[21]; MMI was also computed using FFQ data. We performed two analyses to adjust for the effects of maternal daily energy intake in assessing the association between MMI and the incidence of childhood wheezing in offspring: a standard model adjustment and nutrient density model adjustment[23]. For the standard model adjustment, we focused on maternal daily energy intake as a confounding factor, after confirming the multicollinearity. For nutrient density model adjustment, we calculated adjusted MMI (aMMI) by rescaling the MMI as a proportion of total energy (MMI (mg/d)/maternal daily energy intake (kcal/d)). We plotted a histogram and performed the Shapiro–Wilk test, which showed that MMI and aMMI were not normally distributed. Participants were categorised based on (1) their MMI levels quintiles (< 148·00, 148·00–187·99, 188·00–228·99, 229·00–289·99 and ≥ 290·00 mg/d), (2) their aMMI levels quintiles (< 0·107, 0·107–0·119, 0·120–0·132, 0·133–0·149 and ≥ 0·150 mg/kcal), and (3) whether they had below- or above-ideal MMI levels (< 310·00 or ≥ 310·00 mg/d) according to the Reference Intakes for the Japanese population.

Main outcome measures and confounding factors

The main outcome measure was 'wheezing ever' at 3 years of age, which was assessed based on the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire[24–26]. Information on 'wheezing ever' was obtained using self-reported questions from caregivers, including 'Has your child ever had wheezing or whistling in the chest at any time in the past?'

Maternal age, BMI before pregnancy, parity, smoking status, educational status, annual household income, maternal daily energy intake, mode of delivery, preterm birth (before 37 weeks), low birth weight (< 2500 g), severe hypertensive disorders of pregnancy, maternal asthma, intra-uterine infection, MMI estimated at the early stage of pregnancy and maternal intake of other minerals during pregnancy, including Ca and Zn, that affect maternal Mg absorption via the digestive system were analysed as potential confounding factors. These factors were selected based on clinical importance[9,15,27–30].

Participants were divided into four age groups: < 20, 20–29, 30–39 and ≥ 40 years. Maternal BMI before pregnancy was categorised as follows[31]: < 18·5, 18·5–19·9, 20·0–22·9, 23·0–24·9 and ≥ 25·0 kg/m^2. Participant parity was categorised as nulliparous and multiparous. Participants were requested to provide information on their smoking status by choosing one of the following: 'Currently smoking', 'Never', 'Previously did, but quit before realising current pregnancy' and 'Previously did, but quit after realising current pregnancy'. Participants who chose 'Currently smoking' were included in the 'smoking' group; otherwise, participants were assigned to the 'non-smoking' group[9]. Maternal educational status was categorised into four groups as follows: junior high school, < 10 years; high school, 10–12 years; technical junior college, technical/vocational college, associate degree, or bachelor's degree, 13–16 years; and graduate degree (master's/doctorate), ≥ 17 years[9]. Annual household income was categorised into four levels as follows: < 2 000 000; 2 000 000–5 999 999; 6 000 000–9 999 999 and ≥ 10 000 000 Japanese yen[9]. Maternal daily energy intake was evaluated using a FFQ that was validated in previous cohort studies[19,21] and calculated based on the Japan Standard Tables of Food Composition, 5th Revised Edition. Mode of delivery was divided into vaginal delivery and caesarean section based on medical record transcripts. Severe hypertensive disorders of pregnancy were defined as a persistently elevated blood pressure (≥ 160/110 mmHg) after 20 gestational weeks in an otherwise normotensive woman[32]. Maternal asthma was diagnosed based on the information in the questionnaire issued during the first trimester. Paternal asthma was not considered owing to a large amount of missing data. Intra-uterine infection was clinically diagnosed by the attending physician, and the corresponding data were retrieved from medical record transcripts. MMI via daily diet at the early stage of pregnancy was determined using the FFQ[19,21]. After combining the second and third groups to form the moderate group, the participants were categorised into low-MMI (< 167·00 mg/d), moderate-MMI (167·00–287·99 mg/d) and high-MMI (≥ 288·00 mg/d) groups according to the quartiles of the MMI distribution in the early stage of pregnancy. Maternal intake of other minerals during pregnancy via the daily diet was determined using the FFQ[19,21]. The participants were categorised into groups according to the quartiles of the distribution of maternal Ca intake in the second/third trimester. After combining the second and third quartiles to form the moderate group, we analysed the following three groups: low maternal Ca intake (< 320·00 mg/d), moderate maternal Ca intake (320·00–652·99 mg/d) and high maternal Ca intake (≥ 653·00 mg/d). Participants were likewise categorised into low, moderate and high maternal Zn intake groups according to the quartiles of the distribution of maternal Zn intake in the second/third trimester (< 5·40, 5·40–8·59 and ≥ 8·60 mg/d, respectively). For each confounder, 'no answer' was analysed as a single item.

Statistical analysis

Participant characteristics were summarised based on their daily MMI status. Univariable and multivariable logistic regression models were used to calculate the crude OR (cOR), adjusted OR (aOR) and 95 % CI for offspring childhood wheezing among participants (1) in each MMI, (2) aMMI and (3) above-ideal MMI categories, with the lowest MMI group used as the reference group for each classification criteria. Multivariable logistic regression analyses were adjusted for maternal age, BMI before pregnancy, parity, maternal smoking status, educational status, annual household income, maternal daily energy intake, mode of delivery, preterm birth, low birth weight, severe hypertensive disorders of pregnancy, maternal asthma, intra-uterine infection, MMI estimated at the early stage of pregnancy, and maternal intake of Ca and Zn during pregnancy. However, in analysis (2), multivariable logistic regression did not adjust maternal daily energy intake.

All statistical analyses were performed using SPSS version 26 (IBM Corp.). The model fitness of the multivariable logistic regression was confirmed using Hosmer and Lemeshow analysis. There was no multicollinearity, which was deemed present should there be an association between independent variables with a correlation coefficient of r > 0·8 and/or a variance inflation factor > 10.

Results

The total number of foetal records in the JECS was 104 062, and 79 907 individuals met the inclusion criteria (Fig. 1).

Table 1 summarises participant characteristics stratified by MMI status. Differences were noted between the groups with respect to demographic, socio-economic, medical and other nutrient intake data. The incidence of preterm birth in the present study was relatively higher in the high-MMI group than in the remaining groups. Specifically, maternal daily energy intake, MMI estimated at the early stage of pregnancy, and maternal intake of Ca and Zn during pregnancy were the highest in the highest-MMI group. The ratio of wheezing ever was also the highest in this group. The median values of MMI in the early stage of pregnancy, maternal Ca intake during pregnancy and maternal Zn intake during pregnancy were 221·00 mg/d, 465·00 mg/d and 6·80 mg/d, respectively.

Table 2 summarises the cOR, aOR and 95 % CI for childhood wheezing in the offspring of participants in each MMI group. The aOR for childhood wheezing in the offspring of participants in the highest MMI group was 1·09 (95 % CI, 1·00, 1·20), and no significant difference was found in the aOR between other groups.

Table 3 summarises the cOR, aOR and 95 % CI for childhood wheezing in the offspring of participants in each aMMI group. The aOR for childhood wheezing in the offspring of participants

British Journal of Nutrition

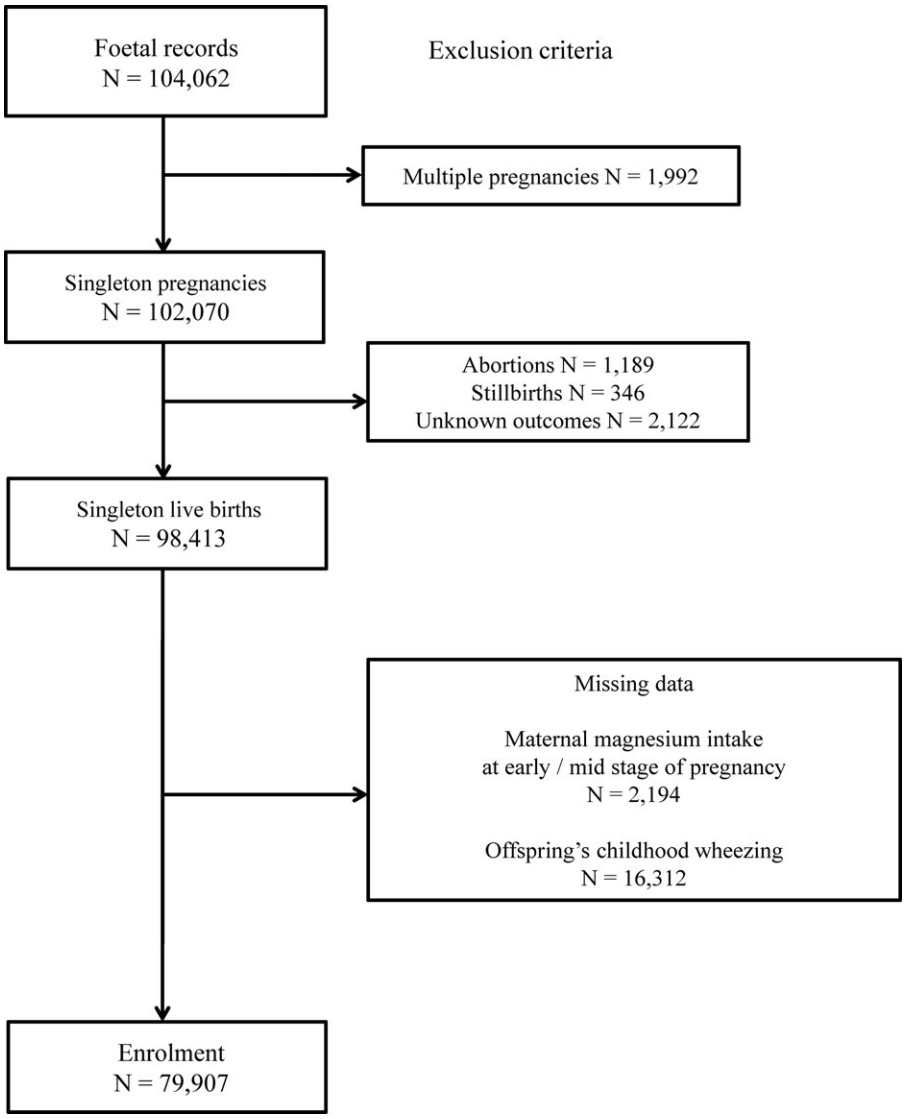

Fig. 1. Enrolment flow chart.

in the higher aMMI group showed a decreased trend; however, no significant difference was found in the aOR.

Table 4 summarises the cOR, aOR and 95 % CI for childhood wheezing in the offspring of participants in the above-ideal MMI group. The aOR for childhood wheezing in the offspring of participants in the above-ideal MMI groups was 1·04 (95 % CI, 0·98, 1·10), and there was no significant difference in aOR between the reference group and above-ideal MMI group.

Discussion

This study revealed a statistically significant but slight association between the highest levels of MMI during pregnancy and an increased incidence of childhood wheezing in offspring. However, there was no significant association between aMMI, above-ideal MMI levels and the incidence of childhood wheezing in the offspring. Contrary to our hypothesis, we conclude that higher MMI during pregnancy would not be useful for decreasing the incidence of childhood wheezing in offspring; a higher MMI during pregnancy, which reflects the real-world distribution of MMI across the nationwide population, is rather associated with a slightly elevated incidence of childhood wheezing in offspring.

The mechanism of a slightly but statistically significant increased incidence of childhood wheezing in offspring from mothers with the highest MMI is unknown. It is speculated that other maternal demographic, socio-economic, medical and other nutrient intake backgrounds would affect this association rather than MMI itself, despite adjusting these factors in multivariable logistic regression analyses. Meanwhile, there was a significant association between higher Mg levels in maternal urine samples collected before delivery and an increased incidence of offspring childhood asthma, although the underlying mechanism was unclear[33]. Another previous study reported that Mg intake in pre-school children might have contributed to

Table 1. Characteristics and outcomes of participants based on maternal magnesium intake in the second/third trimester status

	Q1		Q2		Q3		Q4		Q5	
	n 16 168		*n* 15 742		*n* 16 021		*n* 16 157		*n* 15 819	
	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*
MMI (mg/d)	<148·00		148·00–187·99		188·00–228·99		229·00–289·99		≥290·00	
Variable										
Maternal age										
<20 years	2·7	440	1·3	197	0·9	140	0·6	103	0·6	94
20–29 years	52·1	8426	45·3	7137	40·6	6510	37·8	6114	33·9	5358
30–39 years	43·3	7006	51·2	8053	55·9	8953	58·6	9473	61·9	9785
≥40 years	1·8	295	2·3	355	2·6	418	2·9	467	3·7	582
No answer	0·0	1	0·0	0	0·0	0	0·0	0	0·0	0
BMI before pregnancy										
<18·5 kg/m^2	17·0	2747	16·7	2622	16·1	2576	16·2	2625	14·8	2335
18·5–19·9 kg/m^2	24·3	3936	25·3	3976	25·9	4145	25·9	4182	24·9	3933
20·0–22·9 kg/m^2	36·2	5855	37·6	5921	38·3	6133	38·6	6235	39·8	6295
23·0–24·9 kg/m^2	10·5	1702	10·7	1679	10·3	1652	10·5	1691	10·7	1696
≥25·0 kg/m^2	11·9	1918	9·8	1539	9·4	1512	8·8	1416	9·8	1558
No answer	0·1	10	0·0	5	0·0	3	0·0	8	0·0	2
Parity										
Nulliparous	48·3	7810	43·0	6768	40·2	6434	37·5	6056	34·2	5409
Multiparous	48·8	7890	54·5	8574	57·5	9218	60·1	9716	63·9	10 106
No answer	2·9	468	2·5	400	2·3	369	2·4	385	1·9	304
Maternal smoking status										
No	94·3	15 239	95·8	15 079	96·1	15 398	96·4	15 573	95·5	15 103
Yes	5·1	817	3·6	561	3·3	525	2·9	473	3·9	624
No answer	0·7	112	0·6	102	0·6	98	0·7	111	0·6	92
Maternal educational status										
<10 years	6·0	978	3·7	588	3·1	491	2·9	463	3·1	497
10–12 years	37·0	5986	31·1	4888	28·1	4508	26·8	4323	27·0	4272
13–16 years	55·0	8890	63·4	9977	66·9	10 715	68·1	11 006	67·7	10 713
≥17 years	0·9	139	1·5	229	1·7	271	2·0	321	1·8	277
No answer	1·1	175	0·4	60	0·2	36	0·3	44	0·4	60
Annual household income										
<2 000 000 JPY	6·8	1100	4·4	697	4·0	633	3·8	621	4·2	671
2 000 000–5 999 999 JPY	64·5	10 430	64·4	10 142	63·2	10 129	62·1	10 031	61·6	9745
6 000 000–9 999 999 JPY	17·3	2792	21·3	3350	23·0	3692	23·7	3834	23·0	3641
≥10 000 000 JPY	2·8	450	3·7	578	4·3	688	4·7	762	5·1	807
No answer	8·6	1396	6·2	975	5·5	879	5·6	909	6·0	955
Maternal daily energy intake										
<1373 kcal/d	57·2	9248	32·2	5066	19·1	3062	10·5	1698	6·0	942
1373–1691 kcal/d	24·4	3948	35·1	5530	31·1	4979	22·3	3606	12·1	1917
1692–2104 kcal/d	12·0	1946	21·8	3436	31·3	5007	34·8	5616	25·1	3977
≥2105 kcal/d	6·3	1026	10·9	1710	18·6	2973	32·4	5237	56·8	8983
Caesarean section										
No	81·4	13 159	81·9	12 894	81·4	13 042	81·1	13 100	80·1	12 677
Yes	18·3	2951	17·8	2796	18·1	2907	18·5	2988	19·3	3057
No answer	0·4	58	0·3	52	0·4	72	0·4	69	0·5	85
Preterm birth										
No	86·6	14 005	86·5	13 612	86·2	13 816	86·0	13 893	85·1	13 455
Yes	13·3	2143	13·4	2106	13·6	2177	13·8	2233	14·7	2323
No answer	0·1	20	0·2	24	0·2	28	0·2	31	0·3	41
Low-birth-weight infant										
No	91·0	14 710	92·0	14 478	92·0	14 732	92·4	14 933	91·9	14 542
Yes	8·8	1429	7·8	1230	7·8	1251	7·3	1183	7·8	1233
No answer	0·2	29	0·2	34	0·2	38	0·3	41	0·3	44
Severe HDP										
No	98·9	15 987	99·0	15 586	98·9	15 849	98·9	15 979	98·8	15 623
Yes	1·0	161	0·8	132	0·9	144	0·9	147	1·0	155
No answer	0·1	20	0·2	24	0·2	28	0·2	31	0·3	41
Maternal asthma										
No	89·0	14 392	89·8	14 136	89·4	14 322	89·8	14 509	89·1	14 101
Yes	11·0	1776	10·2	1606	10·6	1699	10·2	1648	10·9	1718
Intra-uterine infection										
No	99·3	16 060	99·3	15 628	99·3	15 901	99·2	16 035	99·1	15 684
Yes	0·5	88	0·6	90	0·6	92	0·6	91	0·6	94
No answer	0·1	20	0·2	24	0·2	28	0·2	31	0·3	41

British Journal of Nutrition

Table 1. (*Continued*)

	Q1		Q2		Q3		Q4		Q5	
	n 16 168		*n* 15 742		*n* 16 021		*n* 16 157		*n* 15 819	
	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*
MMI at the early stage of pregnancy										
<167·00 mg/d	63·4	10 243	32·8	5156	15·3	2455	6·9	1109	3·7	586
167·00–287·99 mg/d	32·3	5223	59·1	9300	68·7	11 003	59·8	9665	31·7	5015
≥288·00 mg/d	4·3	702	8·2	1286	16·0	2563	33·3	5383	64·6	10 218
Maternal Ca intake during pregnancy										
<320·00 mg/d	75·5	12 214	34·1	5365	12·0	1920	3·0	485	0·4	70
320·00–652·99 mg/d	24·0	3874	62·2	9789	76·2	12 202	64·0	10 343	23·6	3736
≥653·00 mg/d	0·5	80	3·7	588	11·9	1899	33·0	5329	75·9	12 013
Maternal Zn intake during pregnancy										
<5·40 mg/d	83·5	13 498	33·7	5298	8·8	1413	1·8	292	0·2	26
5·40–8·59 mg/d	16·3	2634	64·9	10 214	84·8	13 584	67·2	10 862	18·1	2858
≥8·60 mg/d	0·2	36	1·5	230	6·4	1024	31·0	5003	81·8	12 935
'Wheezing ever'										
Yes	29·2	4722	29·7	4671	30·2	4833	30·5	4927	32·4	5127
No	70·8	11 446	70·3	11 071	69·8	11 188	69·5	11 230	67·6	10 692

MMI, maternal magnesium intake; JPY, Japanese yen; HDP, hypertensive disorders of pregnancy.

Table 2. Crude OR and adjusted OR for the incidence of 'wheezing ever' in women subdivided according to quintiles of maternal magnesium intake

	cOR		aOR	
Maternal magnesium intake	OR	95 % CI	OR	95 % CI
Q1 < 148·00 mg/d (*n* 16 168)	Ref	Ref	Ref	Ref
Q2 148·00–187·99 mg/d (*n* 15 742)	1·02	0·98, 1·07	1·04	0·98, 1·10
Q3 188·00–228·99 mg/d (*n* 16 021)	1·05	0·99, 1·10	1·06	0·98, 1·13
Q4 229·00–289·99 mg/d (*n* 16 157)	1·06	1·01, 1·12	1·05	0·98, 1·14
Q5 ≥ 290·00 mg/d (*n* 15 819)	1·16	1·11, 1·22	1·09	1·00, 1·20

cOR, crude OR; Ref, reference; aOR, adjusted OR.
Multivariable logistic regression analyses were adjusted for maternal age, BMI before pregnancy, parity, maternal smoking status, educational status, annual household income, maternal daily energy intake, mode of delivery, preterm birth, low birth weight, severe hypertensive disorders of pregnancy, maternal asthma, intra-uterine infection, maternal magnesium intake estimated at the early stage of pregnancy and maternal intake of Ca and Zn during pregnancy.

Table 3. Crude OR and adjusted OR for the incidence of 'wheezing ever' in women subdivided according to quintiles of adjusted maternal magnesium intake

	cOR		aOR	
Adjusted maternal magnesium intake	OR	95 % CI	OR	95 % CI
Q1 < 0·107 mg/kcal (*n* 15 531)	Ref	Ref	Ref	Ref
Q2 0·107–0·119 mg/kcal (*n* 15 838)	0·99	0·94, 1·03	1·00	0·95, 1·05
Q3 0·120–0·132 mg/kcal (*n* 16 752)	0·98	0·93, 1·03	0·99	0·94, 1·05
Q4 0·133–0·149 mg/kcal (*n* 15 683)	0·95	0·91, 1·00	0·97	0·92, 1·02
Q5 ≥ 0·150 mg/kcal (*n* 16 103)	0·96	0·92, 1·01	0·97	0·92, 1·03

cOR, crude OR; Ref, reference; aOR, adjusted OR.
Multivariable logistic regression analyses were adjusted for maternal age, BMI before pregnancy, parity, maternal smoking status, educational status, annual household income, mode of delivery, preterm birth, low birth weight, severe hypertensive disorders of pregnancy, maternal asthma, intra-uterine infection, maternal magnesium intake estimated at the early stage of pregnancy, and maternal intake of Ca and Zn during pregnancy.

Table 4. Crude OR and adjusted OR for the incidence of 'wheezing ever' in women in the above-ideal maternal magnesium intake group

	cOR		aOR	
Maternal magnesium intake	OR	95 % CI	OR	95 % CI
Reference group (*n* 67 519)	Ref	Ref	Ref	Ref
Above-ideal maternal magnesium intake group (*n* 12 388)	1·13	1·09, 1·18	1·04	0·98, 1·10

cOR, crude OR; Ref, reference; aOR, adjusted OR.
Multivariable logistic regression analyses were adjusted for maternal age, BMI before pregnancy, parity, maternal smoking status, educational status, annual household income, maternal daily energy intake, mode of delivery, preterm birth, low birth weight, severe hypertensive disorders of pregnancy, maternal asthma, intra-uterine infection, maternal magnesium intake estimated at the early stage of pregnancy, and maternal intake of Ca and Zn during pregnancy.

wheezing or asthma development in childhood, although the mechanism also remains to be elucidated[34]. To the best of our knowledge, this study is the first to clarify the association of MMI with the incidence of childhood wheezing in offspring using a nationwide cohort study with appropriate confounding factors, which might strengthen these previous results[33,34].

Analyses based on aMMI and ideal MMI showed no significant association between MMI and the incidence of childhood wheezing in offspring. According to our hypothesis, higher MMI may decrease inflammation and oxidative stress[13] and lead to hyperactivity of pulmonary functions in the offspring, stabilisation of T cells and inhibition of mast cell degranulation to reduce inflammatory mediators[35]. This was also supported by the study of non-pregnant adults who received oral Mg supplements[16]. Moreover, higher MMI would maintain pregnancy and prolong gestation because higher maternal serum Mg levels were associated with the activity of uterine smooth muscle (preterm birth group: 0·93 mmol/L *v.* control group: 1·12 mmol/L, $p < 0·01$)[11,12] and may be associated with a decreased incidence of childhood wheezing in offspring. These may have protected the offspring from childhood asthma and wheezing. The contrary results could have been caused by differences in the mechanisms affecting childhood health via inflammatory and oxidative pathways between MMI, maternal serum Mg levels and Mg supplementation. This study's incidence of preterm birth was relatively higher in the highest MMI group than in the other groups. The present study did not account for the effects of maternal serum Mg levels and maternal Mg supplementation; therefore, future prospective studies clarifying the impacts of MMI on childhood wheezing in offspring are warranted, considering the inflammatory and oxidative biomarkers and differences in MMI, maternal serum Mg levels, and Mg supplementation.

Overall, this study implies that MMI during pregnancy would not have significant clinical impact on the incidence of childhood wheezing in offspring. A previous study showed no association between MMI using FFQ collected during the 8th month of pregnancy and childhood asthma in offspring[15]. This previous study was a population-based prospective birth cohort study that analysed 2441 5-year-old offspring; the mean MMI from food in this population was 474 mg/d, which was significantly higher than that in this study. However, the present results were partly consistent with this previous one because no significant change was found in the OR for childhood wheezing in offspring of mothers with above-ideal MMI levels. Moreover, modifying MMI could not significantly improve the incidence of childhood wheezing in offspring, as well as in the previous study[15].

This study has some limitations. First, the incidence of offspring childhood wheezing might have been over- or under-reported; thus, the results should be interpreted with caution. However, the information on offspring childhood wheezing was based on the ISAAC questionnaire, and the parents' reports are expected to have good agreement with the physicians' diagnosis[36]. Second, there may be unmeasured potential confounding factors to be considered. Detailed data on the daily maternal use of supplementation and drugs, including magnesium oxidate, antiasthmatic medications, antioxidative supplements and antipyretic analgesics, were not included. Moreover, data on childhood exposure to Mg in the offspring are lacking. Finally, there is a concern regarding potential selection bias because several participants who had missing data and satisfied the exclusion criteria were excluded.

In conclusion, contrary to our hypothesis, the highest MMI group showed a slight association with increased childhood wheezing incidence in offspring. Regarding research implications of this study, further studies are needed to investigate the effects of MMI during pregnancy on childhood wheezing incidence in offspring considering the impact of other maternal diets and inflammatory and oxidative biomarkers and differences in MMI, maternal serum Mg levels, and Mg supplementation. However, this association was insignificant based on aMMI and the ideal MMI level. As a clinical implication, this study would imply that MMI during pregnancy would not have significant clinical impact on childhood wheezing incidence in offspring, and modifying MMI to the ideal amount for pregnant women may not significantly decrease the incidence. Therefore, further studies to clarify the association between other prenatal factors and childhood wheezing incidence in offspring are needed to decrease the incidence of childhood wheezing and asthma.

Acknowledgements

The authors are grateful to all participants in this study. The members of the JECS Group as of 2021 are as follows: 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), Hiroyasu Iso (Osaka University, Suita, Japan), Masayuki Shima (Hyogo College of Medicine, Nishinomiya, Japan), Hiroshige Nakamura (Tottori University, Yonago, Japan), Narufumi Suganuma (Kochi University, Nankoku, Japan), Koichi Kusuhara (University of Occupational and Environmental Health, Kitakyushu, Japan) and Takahiko Katoh (Kumamoto University, Kumamoto, Japan).

This work was funded by the Ministry of the Environment, Japan. The findings and conclusions of this article are solely the authors' responsibility and do not represent the official views of the Ministry of the Environment, Japan.

T. M., H. K., T. F., K. I., H. I., S. Y., A. Y., K. H., H. N., K. F., K. S., A. S. and Y. O.: substantial contributions to study conception and design, acquisition of data, and analysis and interpretation of data. T. M., M. H., S. Y., K. H., K. S., A. S., Y. O., H. N., K. F. and the JECS Group: drafting the article and revising it critically for important intellectual content.

There are no conflicts of interest.

This study was conducted according to the guidelines of the Declaration of Helsinki, and all procedures involving human participants were approved by the Ministry of the Environment's Institutional Review Board on Epidemiological Studies (approval number: 100910001) and by the ethics committees of all participating institutions. Written informed consent was obtained from all participants.

References

1. Ebisawa M, Nishima S, Ohnishi H, *et al.* (2013) Pediatric allergy and immunology in Japan. *Pediatr Allergy Immunol* **24**, 704–714.
2. Morikawa E, Sasaki M, Yoshida K, *et al.* (2020) Nationwide survey of the prevalence of wheeze, rhino-conjunctivitis, and eczema among Japanese children in 2015. *Allergol Int* **69**, 98–103.
3. Yu B, Dai L, Chen J, *et al.* (2019) Prenatal and neonatal factors involved in the development of childhood allergic diseases in Guangzhou primary and middle school students. *BMC Pediatr* **19**, 479.
4. Furuhata M, Otsuka Y, Kaneita Y, *et al.* (2020) Factors associated with the development of childhood asthma in Japan: a nationwide longitudinal study. *Matern Child Health J* **24**, 911–922.
5. Owora AH & Zhang Y (2021) Childhood wheeze trajectory-specific risk factors: a systematic review and meta-analysis. *Pediatr Allergy Immunol* **32**, 34–50.
6. Takata N, Tanaka K, Nagata C, *et al.* (2019) Preterm birth is associated with higher prevalence of wheeze and asthma in a selected population of Japanese children aged three years. *Allergol Immunopathol* **47**, 425–430.
7. Thavagnanam S, Fleming J, Bromley A, *et al.* (2008) A meta-analysis of the association between caesarean section and childhood asthma. *Clin Exp Allergy* **38**, 629–633.
8. Ogawa K, Tanaka S, Limin Y, *et al.* (2017) Beta-2 receptor agonist exposure in the uterus associated with subsequent risk of childhood asthma. *Pediatr Allergy Immunol* **28**, 746–753.
9. Murata T, Kyozuka H, Yasuda S, *et al.* (2021) Association between maternal ritodrine hydrochloride administration during pregnancy and childhood wheezing up to three years of age: the Japan Environment and Children's Study. *Pediatr Allergy Immunol* **32**, 1455–1463.
10. Matsubara S, Takahashi H, Ohkuchi A, *et al.* (2018) Intrauterine ritodrine exposure and childhood asthma: is ritodrine a real culprit? *Pediatr Allergy Immunol* **29**, 332–333.
11. Dalton LM, Ní Fhloinn DM, Gaydadzhieva GT, *et al.* (2016) Magnesium in pregnancy. *Nutr Rev* **74**, 549–557.
12. Zhang Y, Xun P, Chen C, *et al.* (2021) Magnesium levels in relation to rates of preterm birth: a systematic review and meta-analysis of ecological, observational, and interventional studies. *Nutr Rev* **79**, 188–199.
13. Mousavi R, Alizadeh M, Asghari Jafarabadi M, *et al.* (2022) Effects of melatonin and/or magnesium supplementation on biomarkers of inflammation and oxidative stress in women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial. *Biol Trace Elem Res* **200**, 1010–1019.
14. Tsakiridis I, Kasapidou E, Dagklis T, *et al.* (2020) Nutrition in pregnancy: a comparative review of major guidelines. *Obstet Gynecol Surv* **75**, 692–702.
15. Nwaru BI, Erkkola M, Ahonen S, *et al.* (2011) Intake of antioxidants during pregnancy and the risk of allergies and asthma in the offspring. *Eur J Clin Nutr* **65**, 937–943.
16. Kazaks AG, Uriu-Adams JY, Albertson TE, *et al.* (2010) Effect of oral magnesium supplementation on measures of airway resistance and subjective assessment of asthma control and quality of life in men and women with mild to moderate asthma: a randomized placebo controlled trial. *J Asthma* **47**, 83–92.
17. Kawamoto T, Nitta H, Murata K, *et al.* (2014) Rationale and study design of the Japan environment and children's study (JECS). *BMC Public Health* **14**, 25.
18. Michikawa T, Nitta H, Nakayama SF, *et al.* (2018) Baseline profile of participants in the Japan Environment and Children's Study (JECS). *J Epidemiol* **28**, 99–104.
19. Yokoyama Y, Takachi R, Ishihara J, *et al.* (2016) Validity of short and long self-administered food frequency questionnaires in ranking dietary intake in middle-aged and elderly Japanese in the Japan Public Health Center-Based Prospective Study for the Next Generation (JPHC-NEXT) protocol area. *J Epidemiol* **26**, 420–432.
20. Miura K, Takamori A, Hamazaki K, *et al.* (2020) Dietary patterns during pregnancy and health-related quality of life: the Japan Environment and Children's Study. *PLoS One* **15**, e0236330.
21. Eshak ES, Okada C, Baba S, *et al.* (2020) Maternal total energy, macronutrient and vitamin intakes during pregnancy associated with the offspring's birth size in the Japan Environment and Children's Study. *Br J Nutr* **124**, 558–566.
22. Ogawa K, Jwa SC, Kobayashi M, *et al.* (2017) Validation of a food frequency questionnaire for Japanese pregnant women with and without nausea and vomiting in early pregnancy. *J Epidemiol* **27**, 201–208.
23. Tomova GD, Arnold KF, Gilthorpe MS, *et al.* (2022) Adjustment for energy intake in nutritional research: a causal inference perspective. *Am J Clin Nutr* **115**, 189–198.
24. Asher MI, Keil U, Anderson HR, *et al.* (1995) International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J* **8**, 483–491.
25. Weiland SK, Björkstén B, Brunekreef B, *et al.* (2004) Phase II of the International Study of Asthma and Allergies in Childhood (ISAAC II): rationale and methods. *Eur Respir J* **24**, 406–412.
26. Ellwood P, Asher MI, Beasley R, *et al.* (2005) The International Study of Asthma and Allergies in Childhood (ISAAC): phase three rationale and methods. *Int J Tuberc Lung Dis* **9**, 10–16.
27. Kotani M, Kim KH, Ishizaki N, *et al.* (2013) Magnesium and calcium deficiencies additively increase zinc concentrations and metallothionein expression in the rat liver. *Br J Nutr* **109**, 425–432.
28. Miyake Y, Sasaki S, Tanaka K, *et al.* (2010) Dairy food, calcium and vitamin D intake in pregnancy, and wheeze and eczema in infants. *Eur Respir J* **35**, 1228–1234.
29. Adams JB, Sorenson JC, Pollard EL, *et al.* (2021) Evidence-based recommendations for an optimal prenatal supplement for women in the U.S., part two: minerals. *Nutrients* **13**, 1849.
30. Litonjua AA, Rifas-Shiman SL, Ly NP, *et al.* (2006) Maternal antioxidant intake in pregnancy and wheezing illnesses in children at 2 years of age. *Am J Clin Nutr* **84**, 903–911.
31. Murata T, Kyozuka H, Yamaguchi A, *et al.* (2021) Maternal pre-pregnancy body mass index and foetal acidosis in vaginal and caesarean deliveries: the Japan Environment and Children's Study. *Sci Rep* **11**, 4350.
32. Brown MA, Magee LA, Kenny LC, *et al.* (2018) Hypertensive disorders of pregnancy: ISSHP classification, diagnosis, and management recommendations for international practice. *Hypertens* **72**, 24–43.

33. Karakis I, Landau D, Gat R, *et al.* (2021) Maternal metal concentration during gestation and pediatric morbidity in children: an exploratory analysis. *Environ Health Prev Med* **26**, 40.
34. Emmanouil E, Manios Y, Grammatikaki E, *et al.* (2010) Association of nutrient intake and wheeze or asthma in a Greek pre-school population. *Pediatr Allergy Immunol* **21**, 90–95.
35. Davalos Bichara M & Goldman RD (2009) Magnesium for treatment of asthma in children. *Can Fam Physician* **55**, 887–889.
36. Roy A, Kocak M, Hartman TJ, *et al.* (2018) Association of prenatal folate status with early childhood wheeze and atopic dermatitis. *Pediatr Allergy Immunol* **29**, 144–150.

British Journal of Nutrition