学位論文

Maternal exposure to smoking and infant's wheeze and asthma: Japan Environment and Children's Study

母体喫煙と乳児の喘鳴および喘息発症との関連：子どもの健康と環境に関する全国調査

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Abstract

Aim: When a woman smokes tobacco during her pregnancy, the fetus is put at risk of secondhand smoke exposure during the critical period of lung development. The developing lungs of the fetus are susceptible to tobacco compounds, and fetal secondhand smoke exposure may result in a low lung-function trajectory from birth to adulthood. A systematic review and meta-analysis of 79 prospective studies showed that exposure to prenatal maternal smoking increased the risk of developing wheeze and asthma in children up to the age of 2 years compared with unexposed children. However, evidence regarding independent effects of maternal smoking in different time frames of pregnancy and maternal exposure to secondhand smoke on the development of wheeze/asthma in her offspring is limited. I aimed to investigate the effect of maternal exposure to tobacco smoke on wheeze/asthma development at 1 year of age in her offspring using data from the nationwide birth cohort study in Japan.

Methods: Pregnant women who lived in the 15 designated regional centers throughout Japan were recruited. I obtained information about maternal smoking or secondhand smoke status during pregnancy, postnatal exposure of the infant to secondhand smoke, and wheeze/asthma development in the offspring from a self-administered questionnaire.

Results: I analyzed 90210 singleton births. Current maternal smoking during pregnancy increased the risks of wheeze/asthma in the offspring compared with no maternal smoking (wheeze: 1-10 cigarettes/day: adjusted odds ratio (aOR) 1.436, 95% CI 1.270-1.624; ≧ 11 cigarettes/day: aOR 1.669, 95% CI 1.341-2.078; asthma: 1-10 cigarettes/day: aOR 1.389, 95% CI 1.087-1.774; ≧11 cigarettes/day: aOR 1.565, 95% CI 1.045-2.344). Daily maternal exposure to secondhand smoke during pregnancy also increased the risks of wheeze/asthma in her offspring compared with no secondhand smoke exposure (wheeze:

aOR 1.166, 95% CI 1.083-1.256; asthma: aOR 1.258, 95% CI 1.075-1.473). The combination of current maternal smoking during pregnancy and maternal history of allergy increased the risks of wheeze/asthma in her offspring (wheeze: aOR 2.007, 95% CI 1.739-2.317; asthma: aOR 1.995, 95% CI 1.528-2.605).

Conclusions: I found that current maternal smoking and maternal secondhand smoke exposure during pregnancy increased the risks of wheeze and asthma in her offspring. I also found a positive additive effect of current maternal smoking and maternal history of allergy on the risks of wheeze and asthma in the offspring. These results provide clear evidence to support the importance of smoking cessation not only in pregnant mothers but also in all smokers in the homes of pregnant mothers in the prenatal and postnatal periods.

Abbreviations

aOR: adjusted odds ratio

JECS: Japan Environment and Children's Study

SHS: secondhand smoke

Introduction

The prevalence of allergic diseases has increased in recent decades[1-3]. The development of allergic disease is associated with genetic and environmental factors. However, the increased occurrence of allergic diseases during such a short period cannot be explained by only genetic factors and may be associated with changes in environmental factors.

The health and disease hypothesis proposes that development of the fetus is sensitive to various environmental factors to which pregnant women are exposed, and that fetal adaptations to these factors may lead to the development of non-communicable diseases[4, 5]. Based on this hypothesis, numerous studies have investigated the relationship between various environmental exposures and allergic diseases.

Prenatal exposure to tobacco smoke is preventable. In the nationwide survey on perinatal smoking behavior in Japan, the prevalence of maternal smoking before pregnancy and during pregnancy was 25.8% and 9.9%, respectively[6]. Worldwide, as many as 40% of children are regularly exposed to secondhand smoke (SHS) indoors[7]. When a woman smokes tobacco during her pregnancy, the fetus is put at risk of SHS exposure during the critical period of lung development. The developing lungs of the fetus are susceptible to tobacco compounds, and fetal SHS exposure may result in a low lung-function trajectory from birth to adulthood. Previous studies have reported poor alveolarization and

impairment of lung functions (functional residual capacity and tidal flow volume) in the offspring of women who smoked during pregnancy[8, 9].

A recent systematic review and meta-analysis of 79 prospective studies showed that exposure to prenatal or postnatal maternal smoking increased the risk of developing wheeze by 41% or 70%, respectively, in children up to the age of 2 years compared with unexposed children. Similar effects were observed on the relationship between prenatal maternal smoking and the prevalence of asthma in children up to the age of 2 years[10]. However, evidence regarding the independent effect of maternal active smoking and maternal exposure to SHS in different time frames of pregnancy on the development of wheeze and asthma in children is scarce.

I speculate that effects of offspring's exposure to smoking might appear differently depending on dose, duration, and timing of the exposure. To evaluate that, I examine the effects of maternal active smoking dose, frequency of maternal exposure to SHS during pregnancy, and postnatal exposure of the infant to SHS on the development of wheeze and asthma in the infant at 1 year of age using data from the Japan Environment and Children's Study (JECS). Furthermore, I assessed the combined role of maternal active smoking during pregnancy and maternal history of allergy on the development of wheeze and asthma in her offspring at 1 year of age.

This doctoral dissertation is based on the following paper: Wada T (2021), “Maternal exposure to smoking and infant's wheeze and asthma: Japan Environment and Children's Study.” Allergol Int 70:445-51 [11].

Methods

Study design and oversight

The JECS is a nationwide, government-funded birth cohort study. The aim of the JECS is to investigate the associations between the environment and children's health and development. The background and general procedure of the JECS have been described in previous articles[12, 13]. Pregnant women who live in the 15 designated study areas throughout Japan were recruited from January 2011 to March 2014. The participating children will be followed until they reach the age of 13 years.

The JECS was approved by the Ministry of the Environment's Institutional Review Board on Epidemiological Studies and by the Ethics Committees of all participating institutions. Written informed consent was obtained from all participants.

Study subjects

Eligibility criteria for participants in the JECS included the following: 1) the pregnant female resides in one of the study areas at the time of recruitment, 2) her expected delivery date is after August 1, 2011, and 3) the pregnant female is capable of comprehending the Japanese language and completing the self-administered questionnaires. I excluded from the JECS pregnant females who resided outside the study area but attended cooperating health care providers within the study area.

I enrolled 103,062 pregnancies in the JECS excluding mothers who withdrew consent. After excluding multiple conceptions, miscarriages, stillbirths, and subjects with missing information on maternal smoking status, I analyzed 90,210 singleton births in the present study (Fig.1). The present study is based on the jecs-an-20180131 dataset that was released in March 2018.

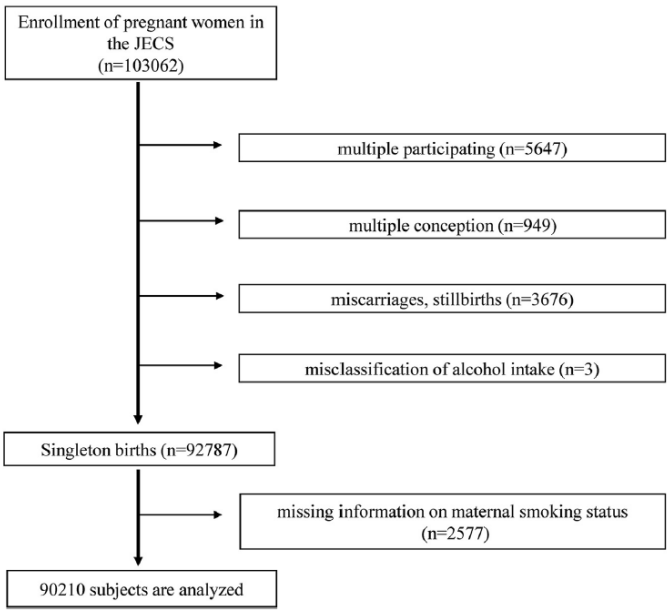

Fig. 1. Flowchart of the study participants. "Multiple participating" indicates already-enrolled mothers who became pregnant again during the study period. Subsequent children who were born to already-enrolled mothers were excluded from the present study.

Data collection

Self-administered questionnaires were given to mothers enrolled in the JECS at the first trimester and at the second/third trimester of pregnancy, and at 1 month, 6 months, and 1 year postpartum. A similar questionnaire was administered to their partners during the pregnancy. The questionnaire included questions about demographic factors, lifestyle, socioeconomic status, occupation, medical history, physical and mental health, environmental exposures at home and in the workplace, and housing conditions. Medical records such as perinatal information and infant physical examinations at birth and at 1 month of age were transcribed and obtained.

Assessment of smoking habits

Mothers were asked about their smoking status during pregnancy in the self-administered questionnaire that was given to the mothers at 1 month postpartum. Maternal smoking status was assessed with the following question: “Please choose an answer on your smoking status.” (never smoked, quit smoking before pregnancy, quit smoking during early pregnancy, smoked 1-10 cigarettes/day, smoked 11-20 cigarettes/day, smoked 21 or more cigarettes/day). To avoid small numbers of subjects, the data were recategorized into 1-10 and ≧11 cigarettes/day. The question about prenatal SHS exposure was asked in the questionnaire administered at the second/third trimester. Prenatal SHS exposure was assessed as exposure of the mother to other person’s smoking at home, in the workplace or in other indoor locations (frequency). Postnatal exposure of the infant to SHS was assessed with the question that asked if the infant was exposed to SHS at home at 1 month postpartum and, in that case, the location where the household member(s) smoked (none, outdoor, indoor).

Outcome measures and covariates

The primary outcome was the incidence of development of wheeze and asthma in the offspring. The information on developing wheeze and asthma was assessed by the self-administered questionnaire given to the mothers when their offspring was 1 year of age. I defined current wheeze as a positive answer to the question, based on the criterion of

the International Study of Asthma and Allergies in Childhood: “Has your child ever had wheezing or whistling in the chest in the last 12 months?”[14]. I defined physician-diagnosed asthma as a positive answer to the question, “Has your child ever been diagnosed by a doctor as having asthma?”.

The covariates included in the analysis were maternal smoking status, frequency of prenatal maternal SHS exposure, location of postnatal infant’s exposure to SHS, maternal age at delivery, maternal body mass index before pregnancy, maternal physical activity, marital status, maternal employment status, maternal education level, maternal alcohol consumption, maternal history of allergy, infant's sex, gestational weeks at delivery, mode of delivery, birth weight, birth season, parity, infant's respiratory infection (upper, lower), infant anomaly, daycare attendance, pet rearing, and annual household income. Maternal history of allergy was assessed based on self-reported doctor’s diagnosis from the self-administered questionnaire. This study defined infant’s anomaly as one or more of the 31 congenital anomalies that are easily detected at delivery and that generally require prompt medical attention after delivery[15].

Statistical analysis

Maternal smoking status was classified into five groups for the statistical analysis (never, quit smoking before pregnancy, quit smoking during early pregnancy, current smoking 1-

10 cigarettes/day, current smoking ≧11 cigarettes/day). Analysis of variance and chi-square test were used to assess the significance of differences among the groups.

Multiple logistic regression analysis was conducted to identify the association between maternal exposure to tobacco smoke and development of wheeze and asthma in her child by 1 year of age. Analysis of prenatal SHS exposure was conducted among all subjects and among non-smoking mothers (never smoked, quit smoking before pregnancy, and quit smoking during early pregnancy). I evaluated the additive effect of maternal smoking and maternal history of allergy on wheeze/asthma in her offspring.

Results are presented as crude and adjusted odds ratios with 95% CI. Significance was set at $p<0.05$. I analyzed the data of mothers without missing values. Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Table 1 summarizes the characteristics of the participants. Of the 90210 mothers who reported smoking status during pregnancy, 52677 (58.4%), 20234 (22.4%), 13447 (14.9%), 3051 (3.4%) and 801 (0.9%) did not smoke, quit smoking before pregnancy, quit smoking during early pregnancy, currently smokes 1-10 cigarettes per day, or currently

smokes 11 or more cigarettes per day, respectively. There were significant differences in maternal age at delivery, maternal body mass index before pregnancy, maternal physical activity, marital status, maternal employment status, maternal education level, maternal alcohol consumption, maternal history of allergy, gestational weeks at delivery, birth weight, mode of delivery, parity, infant's respiratory infection (upper, lower), daycare attendance, pet rearing, and annual household income among the five groups that were categorized according to the maternal smoking status (Table 1). In contrast, infants' gender distribution, birth season, and the presence of anomaly in the infant were not significantly different among the five groups.

Table 1
Characteristics of the participants.

	All %	Never-smokers	Quit smoking before pregnancy	Quit smoking during early pregnancy	Current smokers (cigarettes per day) during pregnancy		P-value
					1–10	≧11	
Participants, n (%)		52,677 (58.4)	20,234 (22.4)	13,447 (14.9)	3051 (3.4)	801 (0.9)	<0.0001*
Frequency of SHS exposure at second/third trimester, %							<0.0001*
Almost never	61.5	71.1	63.0	39.0	17.1	10.3	
≦ 1 day per week	11.9	11.5	13.5	13.2	6.7	5.2	
2–3 days per week	8.1	6.7	8.4	13.2	11.6	8.8	
4–6 days per week	4.8	3.9	4.8	7.9	9.2	8.3	
Every day	12.6	6.8	10.3	26.7	55.3	67.4	
Household smoking location at 1 month postpartum, %							<0.0001*
None	47.4	57.6	47.0	21.0	3.6	3.3	
Outdoor	50.0	41.0	50.7	74.4	87.9	78.0	
Indoor	2.4	1.4	2.3	4.6	8.4	18.8	
Maternal characteristics							
Maternal age, mean (SD)	31.0 (5.0)	31.3 (4.9)	31.7 (4.8)	29.1 (5.3)	29.8 (5.7)	29.7 (5.9)	<0.0001**
Maternal BMI before pregnancy, %							<0.0001*
<18.5 kg/m^2	16.1	16.4	14.0	17.6	19.4	15.9	
18.5–24.9 kg/m^2	73.3	74.3	74.7	70.0	66.2	63.3	
≧ 25 kg/m^2	10.5	9.3	11.3	12.4	14.4	20.9	
Physical activity during mid-late pregnancy, %							<0.0001**
Yes	75.0	75.6	77.0	75.3	75.4	73.7	
Marital status, %							<0.0001*
Married	94.5	97.0	97.1	89.8	87.3	84.0	
Single	3.6	2.6	2.2	8.2	8.2	10.0	
Widowed, divorced	0.8	0.3	0.7	1.9	4.5	6.1	
Maternal employment status, %							<0.0001*
Yes	44.9	43.7	49.0	47.1	50.5	55.9	
Maternal education, %							<0.0001*
<13 years	35.4	25.8	40.1	58.5	72.2	83.4	
13–15 years	41.7	44.9	44.2	34.5	24.8	15.0	
≧ 16 years	21.5	29.3	15.7	7.1	3.1	1.7	
Maternal alcohol consumption, %							<0.0001*
Never	32.9	39.9	24.1	24.9	23.5	23.0	
Quit before pregnancy	16.2	16.6	19.3	11.8	16.3	18.0	
Quit during early pregnancy	46.5	41.7	52.8	60.0	51.5	46.9	
Current drinkers	2.7	1.8	3.8	3.3	8.7	12.1	
Maternal history of allergy							<0.0001*
Yes	49.6	50.0	48.2	51.8	53.9	54.0	
Child's characteristics							
Male infants, %	51.3	51.3	51.2	51.4	51.1	52.4	0.9607*
Gestational weeks, mean (SD)	39.3 (1.5)	39.3 (1.5)	39.3 (1.5)	39.3 (1.6)	39.1 (1.6)	38.9 (1.8)	<0.0001**
Birth weight, mean (SD)	3026.6 (411.2)	3024.4 (408.6)	3050.1 (409.1)	3029.8 (420.3)	2925.6 (404.0)	2909.8 (431.7)	<0.0001**
Type of delivery, Caesarean, %							<0.0001*
Yes	18.7	18.2	19.6	18.8	20.4	20.5	
Birth season, %							0.0517*
March–May	23.3	23.3	23.3	23.6	22.2	21.1	
June–August	26.4	26.8	25.7	26.3	26.1	26.0	
September–November	27.6	27.4	27.8	27.7	28.5	27.2	
December–February	22.7	22.4	23.2	22.4	23.2	25.7	
Parity, %							<0.0001*
0	41.5	44.6	33.8	51.4	32.3	25.1	
≧1	56.0	55.4	66.1	48.6	67.7	74.9	
Upper respiratory infections at 1 year of age, %							<0.0001*
Yes	20.7	23.1	23.3	19.2	21.9	21.6	
Lower respiratory infections at 1 year of age, %							<0.0001*
Yes	5.5	5.6	6.7	6.1	8.4	10.0	
Infant anomaly, %							0.7005*
Yes	2.3	2.3	2.2	2.3	2.5	2.7	
Daycare attendance, %							<0.0001*
Yes	6.5	5.8	7.4	8.5	14.7	15.9	
Others							
Pet rearing, %							<0.0001*
Yes	23.4	21.5	26.4	33.0	33.9	64.5	
Household income, %							<0.0001*
<4 million yen/year	36.8	34.3	41.2	54.7	61.9	63.7	
4–5.9 million yen/year	30.5	34.1	34.7	28.7	25.1	25.1	
≧ 6 million yen/year	24.8	31.6	24.1	16.6	12.9	11.1	

SHS, secondhand smoke.
* P-value was calculated by chi-square test.
** P-value was calculated by analysis of variance.

The percentage of children who developed wheeze or asthma during the first year of life increased with the extent of maternal smoking during pregnancy. Table 2 shows

crude and adjusted odds ratios (aORs) with 95% CI of the association between maternal smoking or SHS status during pregnancy and current wheeze or physician-diagnosed asthma in the offspring. The prevalence of wheeze and asthma was 15.5% and 2.5%, respectively. In the crude model, all maternal smoking statuses during pregnancy were significantly associated with increased risks of wheeze and asthma in the offspring compared with no maternal smoking. After adjustment for the covariates, maternal smoking during pregnancy was significantly associated with an increased risk of wheeze in the offspring compared with no maternal smoking (1-10 cigarettes per day: aOR 1.436, 95% CI 1.270-1.624; ≧11 cigarettes per day: aOR 1.669, 95% CI 1.341-2.078). Moreover, even if mothers quit smoking early in pregnancy, there was a significantly increased risk of wheeze in the offspring (aOR 1.188, 95% CI 1.109-1.272). In addition, maternal smoking during pregnancy was significantly associated with an increased risk of asthma in the offspring (1-10 cigarettes per day: aOR 1.389, 95% CI 1.087-1.774; ≧ 11 cigarettes per day: aOR 1.565, 95% CI 1.045-2.344).

Maternal SHS exposure in the second/third trimester was significantly associated with the development of wheeze in the offspring compared with no SHS exposure (Table 2). This risk increased in association with increasing frequency of SHS exposure (≦ 1 day per week: aOR 1.124, 95% CI 1.051-1.203; 2-3 days per week: aOR 1.115, 95% CI

1.028-1.209; 4-6 days per week: aOR 1.175, 95% CI 1.064-1.298; every day: aOR 1.166, 95% CI 1.083-1.256). Similarly, only daily maternal exposure to SHS in the second/third trimester was significantly associated with the development of asthma in the offspring compared with no SHS exposure (every day: aOR 1.258, 95% CI 1.075-1.473). Similar results were obtained when the analysis was performed only among non-smoking mothers (wheeze: ≦ 1 day per week: aOR 1.150, 95% CI 1.051-1.259; 2-3 days per week: aOR 1.135, 95% CI 1.011-1.275; 4-6 days per week: aOR 1.238, 95% CI 1.071-1.430; every day: aOR 1.300, 95% CI 1.162-1.455; asthma: every day: aOR 1.386, 95% CI 1.088-1.765) (data not shown).

Infants who were exposed to tobacco smoke outdoors or indoors at 1 month postpartum had a significantly increased risk of wheeze compared with infants who were not exposed to tobacco smoke (outdoors: aOR 1.105, 95% CI 1.052–1.160, indoors: aOR 1.196, 95% CI 1.040–1.375). However, none of the groups of infants who were exposed to SHS had a significantly increased risk for the development of asthma.

Table 2
Associations between maternal smoking during pregnancy or SHS status and wheeze or asthma development at 1 year of age.

	Cases, n	Subtotal, n	Prevalence, %	Crude OR	(95% CI)	Adjusted OR[†]	(95% CI)
Current wheeze	12,804	82,635	15.5				
Maternal smoking status							
Never-smokers	6738	49,272	13.68	1.000		1.000	
Quit smoking before pregnancy	3177	18,679	17.01	1.294	(1.236, 1.355)	1.119	(1.060, 1.181)
Quit smoking early in pregnancy	2085	11,641	17.91	1.377	(1.305, 1.454)	1.188	(1.109, 1.272)
Current smokers during pregnancy							
1−10 cigarettes per day	621	2435	25.50	2.161	(1.966, 2.376)	1.436	(1.270, 1.624)
≧11 cigarettes per day	183	608	30.10	2.718	(2.281, 3.239)	1.669	(1.341, 2.078)
P for trend				<0.0001		<0.0001	
Frequency of maternal SHS exposure at second/third trimester							
Almost never	7119	51,796	13.74	1.000		1.000	
≦ 1 day per week	1616	9824	16.45	1.236	(1.165, 1.311)	1.124	(1.051, 1.203)
2−3 days per week	1179	6583	17.91	1.369	(1.279, 1.465)	1.115	(1.028, 1.209)
4−6 days per week	739	3953	18.69	1.443	(1.327, 1.569)	1.175	(1.064, 1.298)
Everyday	2016	9810	20.55	1.623	(1.536, 1.715)	1.166	(1.083, 1.256)
P for trend				<0.0001		<0.0001	
Household smoking location at 1 month postpartum							
None	5429	40,112	13.53	1.000		1.000	
Outdoor	6933	40,499	17.12	1.320	(1.270, 1.371)	1.105	(1.052, 1.160)
Indoor	417	1892	22.04	1.806	(1.614, 2.021)	1.196	(1.040, 1.375)
P for trend				<0.0001		<0.0001	
Physician-diagnosed asthma	2045	82,891	2.5				
Maternal smoking status							
Never-smokers	1011	49,409	2.05	1.000		1.000	
Quit smoking before pregnancy	491	18,733	2.62	1.289	(1.155, 1.437)	1.026	(0.906, 1.161)
Quit smoking early in pregnancy	367	11,694	3.14	1.551	(1.374, 1.751)	1.190	(1.023, 1.384)
Current smokers during pregnancy							
1−10 cigarettes per day	133	2443	5.44	2.756	(2.289, 3.318)	1.389	(1.087, 1.774)
≧11 cigarettes per day	43	612	7.03	3.618	(2.637, 4.963)	1.565	(1.045, 2.344)
P for trend				<0.0001		0.0005	
Frequency of maternal SHS exposure at second/third trimester							
Almost never	1076	51,943	2.07	1.000		1.000	
≦ 1 day per week	228	9857	2.31	1.119	(0.969, 1.293)	1.029	(0.877, 1.208)
2−3 days per week	196	6611	2.96	1.444	(1.238, 1.686)	1.073	(0.894, 1.286)
4−6 days per week	116	3963	2.93	1.425	(1.174, 1.731)	1.075	(0.861, 1.343)
Everyday	410	9845	4.16	2.054	(1.830, 2.307)	1.258	(1.075, 1.473)
P for trend				<0.0001		0.0016	
Household smoking location at 1 month postpartum							
None	818	40,231	2.03	1.000		1.000	
Outdoor	1143	40,620	2.81	1.395	(1.274, 1.528)	1.048	(0.936, 1.173)
Indoor	83	1905	4.36	2.195	(1.743, 2.765)	1.161	(0.873, 1.544)
P for trend				<0.0001		0.2829	

SHS, secondhand smoke.
[†] Adjusted for maternal smoking status, frequency of prenatal maternal SHS exposure, location of postnatal infant's exposure to SHS, maternal age at delivery, maternal body mass index before pregnancy, maternal physical activity, marital status, maternal employment status, maternal education level, maternal alcohol consumption, maternal history of allergy, infant's sex, gestational weeks at delivery, mode of delivery, birth weight, birth season, parity, infant's respiratory infection (upper, lower), infant anomaly, daycare attendance, pet rearing, and annual household income.

Table 3 shows additive effects of maternal smoking during pregnancy and maternal history of allergy on current wheeze and physician-diagnosed asthma in the offspring. Maternal lifetime prevalence of asthma, atopic dermatitis, allergic rhinitis, allergic conjunctivitis, or food allergy was 50.0%. The combination of current maternal smoking and maternal history of allergy was significantly associated with an increased risk of wheeze and asthma in her offspring (wheeze: aOR 2.007, 95% CI 1.739-2.317; asthma: aOR 1.995, 95% CI 1.528-2.605).

Table 3
Additive effects of maternal smoking during pregnancy and maternal history of allergy on wheeze and asthma development at 1 year of age.

Maternal smoking (current smokers during pregnancy)	Maternal history of allergy	Cases, n	Subtotal, n	Prevalence, %	Crude OR (95% CI)	P-value	Adjusted OR† (95% CI)	P-value
Current wheeze								
No	No	5248	39,313	13.35	1.000		1.000	
No	Yes	6690	39,866	16.78	1.309 (1.259, 1.361)	<0.0001	1.301 (1.245, 1.361)	<0.0001
Yes	No	354	1616	21.91	1.821 (1.613, 2.056)	<0.0001	1.228 (1.055, 1.429)	0.0081
Yes	Yes	444	1410	31.49	2.984 (2.657, 3.351)	<0.0001	2.007 (1.739, 2.317)	<0.0001
Physician-diagnosed asthma								
No	No	752	39,453	1.91	1.000			
No	Yes	1107	39,968	2.77	1.466 (1.335, 1.610)	<0.0001	1.436 (1.295, 1.593)	<0.0001
Yes	No	65	1622	4.01	2.148 (1.659, 2.782)	<0.0001	1.295 (0.948, 1.769)	0.1042
Yes	Yes	109	1416	7.70	4.293 (3.486, 5.288)	<0.0001	1.995 (1.528, 2.605)	<0.0001

† Adjusted for maternal smoking status, frequency of prenatal maternal SHS exposure, location of postnatal infant's exposure to SHS, maternal age at delivery, maternal body mass index before pregnancy, maternal physical activity, marital status, maternal employment status, maternal education level, maternal alcohol consumption, maternal history of allergy, infant's sex, gestational weeks at delivery, mode of delivery, birth weight, birth season, parity, infant's respiratory infection (upper, lower), infant anomaly, daycare attendance, pet rearing, and annual household income.

Discussion

In Japan, the rate of current active smoking has decreased from 24.2% in 2005 to 18.2% of adults (30.1% men, 7.9% women) in 2015[16, 17]. Meanwhile, the lack of strong smoke-free laws in Japan has led to extremely high rates of exposure to SHS in public places (49% of workplaces, 55% of restaurants, and 83% of bars)[18].

In this large nationwide birth cohort study, I found that maternal smoking during pregnancy increased the risks of wheeze and asthma in the offspring in a dose-dependent manner. Consistent with my results, a recent systematic review and meta-analysis has shown that prenatal maternal smoking was associated with the development of childhood asthma and wheeze[19]. A few studies showed a dose-response relationship between the number of cigarettes smoked by the mother during pregnancy and wheeze in adolescents or asthma in schoolchildren[20, 21].

Not only smoking dose but also the time window of exposure to smoke during pregnancy might be critical for the development of wheeze and asthma in the offspring. In a prospective birth cohort study, maternal smoking throughout pregnancy was a significant risk factor for wheeze in children, although there were no associations between maternal smoking in the first trimester only or in the second and/or third trimesters and the development of wheeze compared with no maternal smoking during pregnancy[22]. Another population-based prospective cohort study in the Netherlands showed no association between maternal smoking during the first trimester and wheeze in preschool children[23, 24]. Contrary to these studies, the present study showed that even if mothers quit smoking early in pregnancy, there were significantly increased risks of wheeze and asthma in the offspring. Further studies are warranted to clarify the critical time window of exposure to tobacco smoke in utero for the development of wheeze and asthma in the offspring.

Maternal SHS exposure during pregnancy might also be associated with the risk of wheeze and asthma development in the offspring. In this study, there were significant associations between the frequency of maternal SHS exposure and the development of wheeze and asthma in her offspring. Fifteen European Union birth cohort studies were combined in pooled analysis, which showed that maternal SHS exposure during

pregnancy increased the risk of development of wheeze in children up to the age of 2 years[22, 25]. Similarly, a population-based cohort study in Canada reported that maternal SHS exposure during pregnancy was associated with the development of asthma in the offspring, even if the mother did not smoke actively during pregnancy[26]. The finding that maternal SHS exposure during pregnancy is an independent risk factor for wheeze and asthma in the offspring deserves more attention. Furthermore, Carlsten et al. showed that both the presence of a family member who smoked during the third trimester and an elevated cotinine level in cord blood were associated with a significantly increased risk for recurrent wheeze at 2 years of age[27]. It can be presumed that frequent prenatal exposure to SHS is responsible for the development of wheeze or asthma in the infant.

My study found that infants who were exposed to tobacco smoke outdoors or indoors had a significantly increased risk of wheeze compared with unexposed infants, although the exposed infants did not have a significantly increased risk for the development of asthma. Consistent with my results, in a recent systematic review and meta-analysis, postnatal exposure of infants to SHS (maternal or household) was associated with the development of wheeze in infants up to the age of 2 years, but was not associated with the development of asthma[10].

I found an additive effect of current maternal smoking and maternal history of allergy on

the development of wheeze and asthma in the offspring. In pooled analysis of 15 European Union birth cohort studies, it was found that maternal active smoking during pregnancy increased the risk of development of wheeze in their children among those with a family history of allergy compared to those without[25]. Additionally, household smoking with a positive parental allergic history was significantly associated with the development of wheeze and asthma in Japanese schoolchildren[28]. There is a possibility that the association between maternal smoking and wheeze in her offspring differs depending on the presence or absence of a familial history of allergy[29-31].

Strength of my study is that this is the first nationwide birth cohort study to evaluate effects of maternal exposure to smoking on the infants' wheeze in Japan. Furthermore, I have assessed prenatal maternal active smoking in different time frames of pregnancy, frequency of maternal exposure to SHS during pregnancy, and postnatal exposure of the infant to SHS, separately. In addition, many potential covariates such as lifestyle, physical factors, and social factors were controlled for in the analysis.

There are several limitations to this study. First, I evaluated prenatal and postnatal smoking status using self-administered questionnaires, which may be subject to underreporting and recall bias. Second, although I defined wheeze based on the criteria of the International Study of Asthma and Allergies in Childhood, this may have led to

misclassification. Third, wheezing episodes in one-year-old infants may be associated with health conditions other than asthma. Follow-up studies are required. Despite these limitations, this study is worthy of note as nationwide research using multivariate analysis. My results provide clear evidence to support the importance of smoking cessation not only in pregnant mothers but also in all smokers in the homes of pregnant mothers in the prenatal and postnatal periods. In addition, all co-workers of pregnant women should be careful not to expose pregnant women to SHS.

In conclusion, my findings indicated that current maternal smoking and frequency of maternal SHS exposure during pregnancy increased the risks of wheeze and asthma in their offspring. I also found a positive additive effect of current maternal smoking and maternal history of allergy on the risks of wheeze and asthma in the offspring. Further research is needed to determine whether these maternal exposures affect the long-term respiratory health of their offspring in a Japanese population

References

1. Wong GW, Leung TF, Ko FW. Changing prevalence of allergic diseases in the Asia-pacific region. *Allergy Asthma Immunol Res* 2013;**5**:251-7.
2. Chinn S, Jarvis D, Burney P, Luczynska C, Ackermann-Liebrich U, Anto JM, et al. Increase in diagnosed asthma but not in symptoms in the European Community Respiratory Health Survey. *Thorax* 2004;**59**:646-51.
3. von Mutius E. The rising trends in asthma and allergic disease. *Clin Exp Allergy* 1998;**28 Suppl 5**:45-9; discussion 50-1.
4. MacGillivray DM, Kollmann TR. The role of environmental factors in modulating immune responses in early life. *Front Immunol* 2014;**5**:434.
5. Barouki R, Gluckman PD, Grandjean P, Hanson M, Heindel JJ. Developmental origins of non-communicable disease: implications for research and public health. *Environ Health* 2012;**11**:42.
6. Kaneita Y, Tomofumi S, Takemura S, Suzuki K, Yokoyama E, Miyake T, et al. Prevalence of smoking and associated factors among pregnant women in Japan. *Prev Med* 2007;**45**:15-20.
7. Oberg M, Jaakkola MS, Woodward A, Peruga A, Pruss-Ustun A. Worldwide burden of disease from exposure to second-hand smoke: a retrospective analysis of data from 192 countries. *Lancet* 2011;**377**:139-46.
8. McEvoy CT, Spindel ER. Pulmonary Effects of Maternal Smoking on the Fetus and Child: Effects on Lung Development, Respiratory Morbidities, and Life Long Lung Health. *Paediatr Respir Rev* 2017;**21**:27-33.
9. Rehan VK, Asotra K, Torday JS. The effects of smoking on the developing lung: insights from a biologic model for lung development, homeostasis, and repair. *Lung* 2009;**187**:281-9.
10. Burke H, Leonardi-Bee J, Hashim A, Pine-Abata H, Chen Y, Cook DG, et al. Prenatal and passive smoke exposure and incidence of asthma and wheeze: systematic review and meta-analysis. *Pediatrics* 2012;**129**:735-44.
11. Wada T, Adachi Y, Murakami S, Ito Y, Itazawa T, Tsuchida A, et al. Maternal exposure to smoking and infant's wheeze and asthma: Japan Environment and Children's Study. *Allergol Int* 2021;**70**:445-51.
12. Kawamoto T, Nitta H, Murata K, Toda E, Tsukamoto N, Hasegawa M, et al. Rationale and study design of the Japan environment and children's study (JECS). *BMC Public Health* 2014;**14**:25.
13. Michikawa T, Nitta H, Nakayama SF, Yamazaki S, Isobe T, Tamura K, et al. Baseline Profile of Participants in the Japan Environment and Children's Study (JECS). *J Epidemiol* 2018;**28**:99-104.
14. Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J* 1995;**8**:483-91.
15. Mezawa H, Tomotaki A, Yamamoto-Hanada K, Ishitsuka K, Ayabe T, Konishi M, et al. Prevalence of Congenital Anomalies in the Japan Environment and Children's Study. *J*

Epidemiol 2019;**29**:247-56.
16. *WHO report on the global tobacco epidemic 2017*. 2017.
17. . <The National Health and Nutrition Survey (NHNS) Japan, 2014.pdf> 2014DOI.
18. Sansone G, Fong GT, Meng G, Craig LV, Xu SS, Quah ACK, et al. Secondhand Smoke Exposure in Public Places and Support for Smoke-Free Laws in Japan: Findings from the 2018 ITC Japan Survey. *Int J Environ Res Public Health* 2020;**17**.
19. He Z, Wu H, Zhang S, Lin Y, Li R, Xie L, et al. The association between secondhand smoke and childhood asthma: A systematic review and meta-analysis. *Pediatr Pulmonol* 2020;**55**:2518-31.
20. Lewis SA, Britton JR. Consistent effects of high socioeconomic status and low birth order, and the modifying effect of maternal smoking on the risk of allergic disease during childhood. *Respir Med* 1998;**92**:1237-44.
21. Jaakkola JJ, Gissler M. Maternal smoking in pregnancy, fetal development, and childhood asthma. *Am J Public Health* 2004;**94**:136-40.
22. Tanaka K, Miyake Y, Furukawa S, Arakawa M. Secondhand smoke exposure and risk of wheeze in early childhood: a prospective pregnancy birth cohort study. *Tob Induc Dis* 2017;**15**:30.
23. Duijts L, Jaddoe VWV, van der Valk RJP, Henderson JA, Hofman A, Raat H, et al. Fetal exposure to maternal and paternal smoking and the risks of wheezing in preschool children: the Generation R Study. *Chest* 2012;**141**:876-85.
24. den Dekker HT, Voort A, de Jongste JC, Reiss IK, Hofman A, Jaddoe VWV, et al. Tobacco Smoke Exposure, Airway Resistance, and Asthma in School-age Children: The Generation R Study. *Chest* 2015;**148**:607-17.
25. Vardavas CI, Hohmann C, Patelarou E, Martinez D, Henderson AJ, Granell R, et al. The independent role of prenatal and postnatal exposure to active and passive smoking on the development of early wheeze in children. *Eur Respir J* 2016;**48**:115-24.
26. Simons E, To T, Moineddin R, Stieb D, Dell SD. Maternal second-hand smoke exposure in pregnancy is associated with childhood asthma development. *J Allergy Clin Immunol Pract* 2014;**2**:201-7.
27. Carlsten C, Dimich-Ward H, DyBuncio A, Becker AB, Chan-Yeung M. Cotinine versus questionnaire: early-life environmental tobacco smoke exposure and incident asthma. *BMC Pediatr* 2012;**12**:187.
28. Tanaka K, Miyake Y, Arakawa M, Sasaki S, Ohya Y. Prevalence of asthma and wheeze in relation to passive smoking in Japanese children. *Ann Epidemiol* 2007;**17**:1004-10.
29. Henderson AJ, Sherriff A, Northstone K, Kukla L, Hruba D. Pre- and postnatal parental smoking and wheeze in infancy: cross cultural differences. Avon Study of Parents and Children (ALSPAC) Study Team, European Longitudinal Study of Pregnancy and Childhood (ELSPAC) Co-ordinating Centre. *Eur Respir J* 2001;**18**:323-9.
30. Gilliland FD, Li YF, Peters JM. Effects of maternal smoking during pregnancy and environmental tobacco smoke on asthma and wheezing in children. *Am J Respir Crit Care Med* 2001;**163**:429-36.

31. Haberg SE, Stigum H, Nystad W, Nafstad P. Effects of pre- and postnatal exposure to parental smoking on early childhood respiratory health. *Am J Epidemiol* 2007;**166**:679-86.