

# Effects of maternal smoking during pregnancy on congenital anomalies: Results from the Japan Environment and Children's Study (JECS)

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## Research note

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# Abstract

Objective Tobacco smoke contains over 7,000 chemical compounds, tobacco smoking is a possible risk factor of congenital anomalies (CAs). Therefore, we investigated the relationship between maternal smoking during pregnancy and CAs in children. Drawing data from the Japan Environment and Children's Study (JECS), gathered between January 2011 and March 2014, 91,626 pregnant Japanese women were included. Results Of 91,626 subjects examined, 2.4% (2,183) of their infants had "any CAs." By smoking behavior; 1,256 (57.5%), 523 (23.9%), 271 (12.4%), and 136 (6.2%) subjects were in the "never smoked," "quit before pregnancy," "quit after pregnancy," and "still smoking" groups, respectively. The odds ratios (OR) for any CAs were not significant when "quit before pregnancy," or "quit after pregnancy," groups were compared to the "never smoked" group. However, upon comparing "never smoked" group with the "still smoking" group regarding "any CAs," the OR was significant (OR 1.38, 95% confidence interval, 1.13-1.69,  $p=0.002$ ). This study showed association between smoking continuation during pregnancy and an increased risk of CAs. This study results may be used as the basis for recommending anti-smoking education for pregnant women, and younger yet-to-become pregnant women.

## Introduction

According to the World Health Organization *Fact Sheet*, although approximately 50% of all congenital anomalies (CAs) cannot be associated with a specific cause, tobacco smoking is a possible risk factor of CAs and should be avoided by pregnant women [1].

The principal component of tobacco smoke (nicotine) is a nervous system teratogen [2], and carbon monoxide has also been indicated as a possible teratogen [3]. Furthermore, tobacco smoke contains over 7,000 chemical compounds, hundreds of which have harmful effects in humans [4]. Therefore, the possible associations between CAs and smoking during pregnancy and/or exposure to tobacco smoke must be investigated.

In a Danish register-based birth cohort study including 838,265 singleton liveborn babies, there was a significantly higher rate of CAs, including oral clefts and respiratory and cardiovascular abnormalities, in infants of women who had smoked while pregnant [5]. Moreover, among 1,413,811 infants registered at the Swedish Health Registries, there were significantly higher rates of "any malformations" among children of women who had smoked while pregnant [6]. However, no large-scale birth cohort study investigating the association between CAs and maternal smoking while pregnant has been conducted in Japan or in the general Asian region. In 2012, when the recruitment of the study subjects for the present study began, the average smoking rate among Japanese women in their twenties and thirties was 12.3% and 11.9%, respectively [7]. These were relatively high rates of smoking in women of reproductive age in Japan. The American Cancer Society revealed that the female smoking rate has not decreased as suggested by the global epidemic model [4].

In the present research, we investigated the associations between CAs and maternal smoking behavior in the early stages of pregnancy, using data that included approximately 100,000 pregnant women who participated in the nationwide birth cohort Japan Environment and Children's Study (JECS).

## Methods

### *Study design*

The JECS is a birth cohort study (conducted principally by the Ministry of the Environment) investigating the associations between environmental factors and childhood health and development. Recruitment for the study occurred across 15 regional centers within Japan from 2011 to 2014. Subject recruitment involved a face-to-face explanation of the survey to mothers, and self-administered informed consent was obtained. The details of the JECS design are well documented [8, 9].

The present research analyzed data from the "jecs-ag-2016042" and the "allbirth\_revice001\_ver001" datasets. Both datasets included 104,102 fetuses and their mothers. We included data on 91,626 subjects in our analysis, excluding the following: those with missing information about smoking during the early stages of pregnancy, 29 mothers who withdrew total consent, those with multiple consents for multiple participations (after the second instance), those with multiple births, or those with missing information transcribed from medical records at birth and at one-month-old (Fig 1).

#### **Fig 1. Flow diagram of the enrollment and exclusion process in this study.**

The JECS protocol received approval from the Ethics Committees of all participating institutions and the Ministry of the Environment.

### *Questionnaires about exposure to tobacco smoke*

Self-administered smoking habits questionnaires were distributed to and collected from participants by the study research staff during the early pregnancy. Smoking habits were categorized into four possible responses as follows: "never smoked," "quit before pregnancy (QBP)," "quit after pregnancy (QAP)," and "still smoking." Those with a smoking history were asked about the age at which they started smoking and the approximate number of cigarettes they smoked per day on average, while those who had quit were asked when they quit. Based on these responses, the number of years smoked, and the packs-per-year were calculated.

The following questions on second-hand smoke exposure were asked: “What is the smoking behavior of the child’s father (the subject’s husband or partner)?,” “Before the present pregnancy, how many times per week did you encounter tobacco smoke from others, either within buildings outside the home, in the home, or at the workplace?.” “How many people in your family smoke?,” and “How many people smoke in your room at home?”

## ***Main outcomes***

Using hospital chart histories recorded during childbirth and at one-month follow-up examinations, categorical data on 61 types of CAs were recorded in the transcriptional sheets [10]. In the event of a contradiction between the two time points (at birth and one month later), a CA was accepted as being present if the CA had been indicated at either time point. We determined the odds ratio (OR), to investigate the association with smoking by using the main CA groups according to the ICD-10 classification system. Among genital organ CAs, since cryptorchidism and hypospadias afflicted only male children, the analysis was limited to the 46,893 male children included in the study.

## ***Statistical analysis***

To identify the association between CAs and maternal smoking, we performed a logistic regression analysis and determined the 95% confidence intervals (CI). In the multivariable logistic regression analysis, we adjusted for maternal age at delivery, pre-partum body mass index (BMI), diabetes mellitus, marital status, education history, annual household income, alcohol intake, folic acid intake, anticancer drug intake, antihypertensive intake, anti-convulsant intake, and retinoic acid intake during early pregnancy. We used SAS version 9.4 software (SAS Institute Inc., Cary, NC) for all statistical analyses.

## **Results**

Out of the 91,626 subjects included in our analysis, 2,186 (2.4%) had CAs (any CAs). Categorized by smoking behavior, “still smokers” had lower socioeconomic status indexes, such as education history and income, than the other groups (Table 1). An additional table file shows the number of CAs per 10,000 population according to maternal smoking behaviors during pregnancy in more detail [see Additional file 1].

**Table 1. Characteristics according to maternal smoking experience (n=91,626)**

	Never Smoked		Quit before pregnancy		Quit after pregnancy		Still smoking	
	n	%	n	%	n	%	n	%
53,356	58.2%	21,406	23.4%	12,437	13.6%	4,427	4.8%	
<b>Age at delivery (years)</b>								
<25	4,298	8.1	1,468	6.9	2,398	19.3	828	18.7
25-29	14,556	27.3	5,251	24.5	4,088	32.9	1,253	28.3
30-34	19,392	36.4	8,018	37.5	3,666	29.5	1,291	29.2
35-40	12,476	23.4	5,541	25.9	1,953	15.7	863	19.5
≥40	2,632	4.9	1,124	5.3	331	2.7	192	4.3
Mean (SD)	31.5	4.9	31.9	4.8	29.4	5.3	30.0	5.6
<b>Body mass index</b>								
<18.5	8,757	16.4	3,048	14.3	2,217	17.8	820	18.5
18.5-25	39,590	74.2	15,858	74.1	8,629	69.4	2,913	65.9
≥25	4,991	9.4	2,490	11.6	1,584	12.7	690	15.6
Diabetes mellitus	413	0.8	235	1.1	108	0.9	50	1.1
<b>Marital status</b>								
Married	51,570	97.0	20,678	96.9	11,085	89.8	3,738	85.8
Single	1,619	3.0	661	3.1	1,259	10.2	619	14.2
<b>Education history (years)</b>								
<12	13,707	26.2	8,464	40.4	7,037	58.1	3,109	73.2
12-13	23,338	44.6	9,208	44.0	4,213	34.8	1,007	23.7
>13	15,291	29.2	3,257	15.6	866	7.2	131	3.1
<b>Annual household income (yen)</b>								
<4 million	16,903	34.4	8,253	41.9	5,994	54.4	2,385	61.7
4-6 million	16,785	34.2	6,698	34.0	3,208	29.1	979	25.3
>6 million	15,463	31.5	4,727	24.0	1,813	16.5	500	12.9
Spontaneous pregnancy	49,043	92.3	19,717	92.6	12,024	97.2	4,347	98.6

Alcohol intake								
Never drinker	21,915	41.2	5,319	24.9	3,163	25.6	1,063	24.2
Quit	25,930	48.8	13,352	62.6	8,423	68.1	2,850	64.8
Current drinker	5,289	10.0	2,656	12.5	789	6.4	485	11.0
Folic acid intake	27,245	51.2	10,858	50.9	5,383	43.4	1,463	33.2
Anticancer drug intake	39	0.1	25	0.1	7	0.1	4	0.1
Antihypertensive intake	265	0.5	123	0.6	69	0.6	30	0.7
Anti-convulsant intake	179	0.3	89	0.4	71	0.6	32	0.7
Retinoic acid intake	142	0.3	60	0.3	30	0.2	6	0.1

SD, standard deviation

Table 2 shows the OR from the logistic regression analysis of each smoking category, using never smokers as the reference, for the eight main CA groups, as well as the “any CAs” category. Compared to never smokers, the OR was significantly elevated in the QBP group for CAs related to the digestive system (adjusted OR 1.63, 95% CI, 1.01-2.62, p=0.04) and in still smoking group for trisomy (adjusted OR 2.24, 95% CI, 1.26-3.97, p=0.01) and “any CAs” (adjusted OR 1.38, 95% CI, 1.13-1.69, p=0.002). For “any CAs,” we further adjusted for history of diabetes and medication use and found that the results were similar; the ORs (95% CIs) were 1.06 (95% CI, 0.95-1.19), 0.94 (95% CI, 0.81-1.10), 1.38 (95% CI, 1.12-1.69) for the QBP, QAP, and still smoking groups, respectively. No significant elevation was found in the QBP, QAP, or still smoking groups for CAs related to the nervous system; eye, ear, face, and neck; cardiovascular system; genital organs; or musculoskeletal system.

Congenital anomalies	n	%	Crude		Adjusted	
			OR	95%CI	OR	95%CI
<b>Nervous system (Q00-07)</b>						
Never smoked	92	(0.18)	Reference		Reference	
Quit before pregnancy	39	(0.19)	1.06	( 0.73 – 1.54)	1.03	(0.66 – 1.59 )
Quit after pregnancy	16	(0.13)	0.75	(0.44 – 1.27)	0.74	(0.39 – 1.40)
Still smoking	11	(0.26)	1.44	(0.77 – 2.70)	1.34	(0.62 – 2.87)
<b>Eye, ear, face and neck (Q10-18)</b>						
Never smoked	38	(0.07)	Reference		Reference	
Quit before pregnancy	13	(0.06)	0.85	(0.45 – 1.60)	0.96	(0.49 – 1.89)
Quit after pregnancy	8*	(0.07)	-		-	
Still smoking	4*	(0.09)	-		-	
<b>Cardiovascular system (Q20-28)</b>						
Never smoked	616	(1.18)	Reference		Reference	
Quit before pregnancy	239	(1.14)	0.97	(0.83 – 1.12)	1.00	(0.85 – 1.17)
Quit after pregnancy	139	(1.14)	0.97	(0.80 – 1.16)	0.98	(0.98 – 1.21)
Still smoking	64	(1.49)	1.26	(0.97 – 1.63)	1.33	(1.33 – 1.77)
<b>Oral clefts (Q35-37)</b>						
Never smoked	128	(0.25)	Reference		Reference	
Quit before pregnancy	58	(0.28)	1.13	(0.83 – 1.54)	1.15	(0.81 – 1.62)
Quit after pregnancy	33	(0.27)	1.11	(0.75 – 1.62)	1.13	(0.73 – 1.74)
Still smoking	10	(0.23)	0.94	(0.49 – 1.79)	1.12	(0.57 – 2.20)
<b>Digestive system (Q38-45)</b>						
Never smoked	55	(0.11)	Reference		Reference	
Quit before pregnancy	31	(0.15)	1.41	(0.90 – 2.18)	1.63	(1.02 – 2.62)
Quit after pregnancy	2*	(0.02)	-		-	
Still smoking	3*	(0.07)	-		-	
<b>Genital organs (Q50-56)<sup>§</sup></b>						
Never smoked	190	(0.70)	Reference		Reference	

Quit before pregnancy	81	(0.74)	1.04	(0.80 – 1.35)	1.00	(0.75 – 1.32)
Quit after pregnancy	39	(0.62)	0.86	(0.61 – 1.22)	0.87	(0.59 – 1.29)
Still smoking	22	(0.96)	1.33	(1.33 – 2.08)	1.36	(0.81 – 2.26)
<b>Musculoskeletal system (Q65-79)</b>						
Never smoked	185	(0.36)	Reference		Reference	
Quit before pregnancy	86	(0.41)	1.16	(0.90 – 1.50)	1.21	(0.91 – 1.60)
Quit after pregnancy	38	(0.31)	0.88	(0.62 – 1.25)	0.99	(0.67 – 1.47)
Still smoking	23	(0.54)	1.50	(0.97 – 2.32)	1.53	(0.91 – 2.59)
<b>Trisomy (Q90-91)</b>						
Never smoked	110	(0.21)	Reference		Reference	
Quit before pregnancy	40	(0.19)	0.91	(0.63 – 1.30)	0.76	(0.50 – 1.17)
Quit after pregnancy	14	(0.12)	0.55	(0.55 – 0.95)	0.58	(0.30 – 1.13)
Still smoking	18	(0.42)	1.98	(1.20 – 3.26)	2.24	(1.26 – 3.97)
<b>Any congenital anomalies</b>						
Never smoked	1,256	(2.41)	Reference		Reference	
Quit before pregnancy	523	(2.50)	1.04	(0.94 – 1.15)	1.07	(0.95 – 1.19)
Quit after pregnancy	271	(2.23)	0.92	(0.81 – 1.06)	0.94	(0.81 – 1.10)
Still smoking	136	(3.17)	1.32	(1.10 – 1.57)	1.38	(1.13 – 1.69)

**Table 2. Association between maternal smoking experience and congenital anomalies**

†Adjusted for maternal age at delivery, body mass index, diabetes mellitus, marital status, education, annual household income, spontaneous pregnancy, alcohol intake, folic acid intake, anticancer drug intake, antihypertensive intake, anti-convulsant intake, and retinoic acid intake

\* We did not calculate the odds ratio for cases less than 10.

- Only data on boys were analyzed (n=46,893) OR, odds ratio; CI, confidence interval

## Discussion

The still smoking group had a significantly elevated OR for “any CAs” compared to the never smoked group (1.38, 95%CI, 1.12-1.68, p=0.003). For CAs related to the nervous system; eye, ear, face, and neck;



cardiovascular system; oral clefts; genital organs; and the musculoskeletal system, there were no significant associations with the still smoking group. However, stronger ORs occurred between any CAs and the still smoking group for the cardiovascular system, musculoskeletal system, and genital organs compared to the ORs for QBP or QAP groups. Since many subcategories were included in the any CAs category, the abnormalities might have occurred at various stages of embryological development. In general, most CAs occur during organ formation (between the fourth and seventh week of pregnancy) [11]. While some mothers notice their pregnancy during this early stage, many do not, hence, it is uncertain why the findings could be so different for the QAP group (those who quit smoking only after realizing they were pregnant). Even after pregnancy, quitting smoking might be preventive against the occurrence of CAs in infants. However, the characteristics of subjects with other tobacco smoke exposures were much worse in the still smoking group compared to the other groups, an additional table file shows this in more detail [see Additional file 2].

On the other hand, we could not show the risk of CAs for each organ category unlike in a previous research, the Danish register-based cohort study [5]. It is also possible, despite the large sample size of 91,626 subjects in this study, this may not have been sufficient to give interpretive weight to an investigation on an ailment like CAs, which has a relatively low incidence rate. Therefore, a study with a larger cohort might be necessary.

The present study's strength is that it is based on a nationwide survey of Japan with a very high response rate from the start of the study (during pregnancy) to the time of delivery. Many responses relating to smoking behaviors were obtained. Multiple covariates (confounding factors), thought to be optimal for analysis, were available in the study, enabling many different effects to be considered and discarded.

In summary, this study showed that smoking continuation during pregnancy was associated with an increased risk of CAs. Therefore, this study may serve as justification for anti-smoking education for pregnant women and younger women who are yet to be pregnant.

## Limitations

A limitation of the present study, therefore, is that the data relating to smoking behaviors and quantity are self-reported, and therefore could not be analyzed objectively. Further, the present study used the 30 ailments and abnormalities defined by the JECS and, therefore, conducted its analysis based on these categories. Moreover, due to small numbers, further statistical analysis of the QAP or the still smoking groups could not be performed.

## Abbreviations

BMI, body mass index

CA, congenital anomalies

CI, confidence interval

JECS, Japan Environment and Children's Study

OR, odds ratio

QAP, quit after pregnancy

QBP, quit before pregnancy

SD, standard deviation

## **Declarations**

### **Consent for publication**

Not applicable.

## **Ethics approval and consent to participate**

The JECS protocol was approved by the Review Board of the Ministry of the Environment for epidemiological studies, and by the Ethics Committees of all participating institutions. The JECS is conducted in accordance with the Declaration of Helsinki and other nationally valid regulations, and written informed consent was obtained from all participants.

## **Availability of data and materials**

The data used to derive our conclusions are unsuitable for public deposition due to ethical restrictions and specific legal framework in Japan. The Ethical Guidelines for Epidemiological Research enforced by the Japan Ministry of Education, Culture, Sports, Science, and Technology; and the Ministry of Health, Labor, and Welfare also restricts the open sharing of epidemiological data.

# Competing interests

The authors declare that they have no competing interests.

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## Authors' contributions

AT, KH, and HI designed the study. AT, KH, and HI analyzed and interpreted the data. AT and HI wrote the manuscript. All authors contributed to the critical revision of the manuscript. All authors read and approved the final manuscript.

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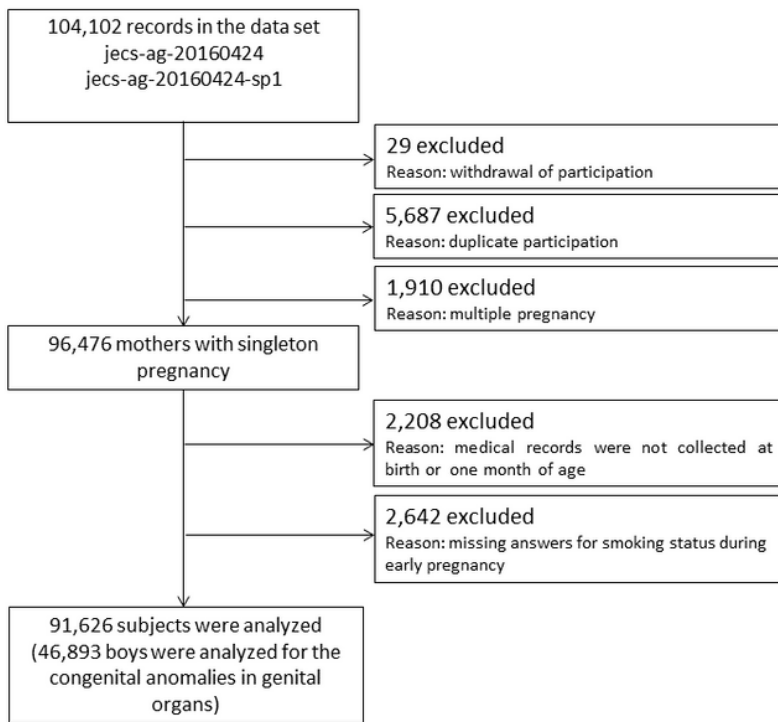
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## Figures



**Figure 1**

Flow diagram of the enrollment and exclusion process in this study.

## Supplementary Files

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