Association between maternal smoking history and congenital anomalies in children: Results from the Japan Environment and Children's Study

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Abstract
We investigated the relationship between maternal smoking history and congenital anomalies in children. Drawing on data from the Japan Environment and Children's Study collected between January 2011 and March 2014, the smoking habits of pregnant women were categorized as “never smoked,” “quit before pregnancy,” “quit after pregnancy,” and “full smoking.” Of the 91,626 participants examined, a total of 2199 (2.4%) infants were born with any congenital anomalies. Logistic regression analysis was used to determine the odds ratio for congenital anomalies in each group based on maternal smoking history. No significant difference was seen between the full-smoking and never smoked groups in the odds ratios for congenital anomalies of the nervous system; the eyes, ears, face, and neck; the cardiovascular system; or the musculoskeletal system. However, in the full-smoking group, the odds ratios for trisomy (adjusted odds ratio, 2.14; 95% confidence interval, 1.15-3.97) and any congenital anomalies (adjusted odds ratio, 1.35; 95% confidence interval, 1.09-1.67) were significantly higher compared with the never smoked group. Our results indicate that continuing to smoke during pregnancy is associated with increased risk of trisomy and any congenital anomalies in the general Japanese population.

KEYWORDS
birth cohort, birth defects, congenital malformation, tobacco smoke, trisomy

1 | INTRODUCTION

According to the World Health Organization, approximately 50% of all congenital anomalies (CAs) cannot be associated with a specific cause, but smoking tobacco during pregnancy is a possible risk factor for CAs and should be avoided by pregnant women.¹ Of the main components of tobacco smoke, nicotine has been identified as a nervous system teratogen² and carbon monoxide has been indicated as a possible teratogen.³ Tobacco smoke contains over 7000 chemical compounds, hundreds of which have harmful effects in humans.⁴ Therefore, it is important to investigate possible associations between CAs and smoking and/or exposure to tobacco smoke during pregnancy.

According to a meta-analysis⁵ of observational studies conducted between 1959 and 2010, high-incidence CAs correlated with maternal smoking during pregnancy. It was also noted that the risk of congenital anomalies increased with increasing smoke exposure. Therefore, the relationship between maternal smoking and congenital anomalies is of particular interest.
smoking during pregnancy include congenital heart defects, musculoskeletal system abnormalities, amelia, hyperdactyly, hypodactyly, clubfoot, craniostenosis, facial abnormalities, ocular abnormalities, cleft face, lip, and palate, gastrointestinal abnormalities, gastroschisis, anal atresia, hernias, and cryptorchidism. Other meta-analyses investigating the association between maternal smoking during pregnancy and CAs found a statistically significant association between maternal smoking and elevated risks for specific CAs, including cleft lip,8,9 congenital heart defects,8,9 cryptorchidism,10 and neural tube defects.11 Still other meta-analyses investigating the association between CAs and maternal exposure to second-hand smoke during pregnancy found elevated risks of cleft lip12 and neural tube defects.13 However, other meta-analyses examining a possible association between maternal smoking during pregnancy and Down syndrome found no apparent association.14

In a Danish register-based birth cohort study of 838,265 single-\footnote{To be continued}ton liveborn babies, there was a significantly higher rate of CAs, including oral clefts and respiratory and cardiovascular abnormalities, in children born to women who had smoked during pregnancy.15 Moreover, among 1,413,811 infants registered with the Swedish Health Registries, there were significantly higher rates of “any malformations” among children born to women who had smoked during pregnancy.16 However, no large-scale birth cohort study investigating the association between CAs and maternal smoking during pregnancy has been conducted in Japan or elsewhere in Asia. In 2012, the average smoking rate among Japanese women in their 20s and 30s was 12.3% and 11.9%, respectively.17 These are relatively high rates of smoking among women of reproductive age in Japan.

In this study, we examined data of approximately 100,000 pregnant women who participated in the Japan Environment and Children’s Study (JECS), a nationwide birth cohort study, to investigate the associations between CAs in infants and maternal smoking behavior in the early stages of pregnancy.

2 | MATERIALS AND METHODS

2.1 | Study design

The JECS is a birth cohort study (conducted principally by the Japanese Ministry of the Environment) investigating associations between environmental factors and childhood health and development. Recruitment for the study was carried out at 15 regional centers in Japan from 2011 to 2014. Participant recruitment involved a face-to-face explanation of the survey to pregnant women, after which self-administered informed consent was obtained. Further details of the JECS study design have been reported elsewhere.18,19
The present study analyzed data from the “jecs-ag-2016042” and “allbirth_revice001_ver001” datasets, both of which include data of 104 102 fetuses and their mothers. The final analysis included data on 91 626 participants after excluding those with missing data about smoking during the early stages of pregnancy, those who withdrew consent, those with multiple consents for multiplicate participation (after the second instance), those with multiple births, and those with missing data in transcripts of medical records at birth and at the 1-month follow-up (Figure 1).

The JECs protocol was reviewed and approved by the Ministry of the Environment’s Institutional Review Board on Epidemiological Studies and the Ethics Committees of all participating institutions.

2.1.1 | Questionnaires about Exposure to Tobacco Smoke

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

The questionnaire included the following item on the frequency of tobacco smoke exposure before pregnancy: “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?” Other items covered the smoking behavior of the child’s father, the number of smokers in the family, and the number of smokers around the mothers during the daytime.

2.1.2 | Main outcomes

Using hospital chart histories recorded during childbirth and at 1-month follow-up examinations, categorical data on 61 types of CAs were recorded in the questionnaires.

We selected the following 31 ailments that were easily identified at birth and necessitated clinical responses: anencephaly, encephalocele, hydrocephaly, holoprosencephaly, spina bifida, ablepharon, anophthalmos, congenital cataract, facial cleft, cleft palate, cleft lip, cleft lip and palate, esophageal atresia, intestinal atresia, duodenal atresia, anorectal atresia, cryptorchidism, hypospadias, polydactyly of fingers or toes, syndactyly of fingers or toes, cleft hand, cleft foot, diaphragmatic hernia, omphalocele, gastrochisis, trisomy 13, trisomy 18, and Down syndrome.

Data on outcomes were collected on two occasions: at birth and during the 1-month follow-up examination. In the event of a contradiction between the two time points, a CA was accepted as being present if the CA was indicated at either time point, except in the case of omphalocele. Omphalocele at the 1-month follow-up occurred 10 times more than expected. This might have resulted from the fact that the Japanese word for “omphalocele” is often confused with that for “umbilical hernia.” Therefore, we included omphalocele only when it was detected at birth. We determined the odds ratio (OR) to investigate the association of CA with smoking by using the main CA groups from the ICD-10 classification system of the genital organ CAs, cryptorchidism and hypospadias can occur in only male children, so the analysis of these conditions was performed for the 46 893 male children included in the study.

In addition, among the anomalies for which information was collected by the Japan Association of Obstetricians and Gynecologists (JAOG) survey, anomalies observed in more than 50 cases in this study were analyzed separately without grouping (Table 1). Although each disease included in the congenital heart disease category is a common congenital abnormality (eg, atrial septal defect, ventricular septal defect), we could not analyze individual diseases because the items on the transcription sheet in this study were for “congenital heart disease,” and were not listed by their individual disease names. The individual diseases analyzed in this study are as follows: hydrocephaly, cleft palate, cleft lip, cleft lip and palate, cryptorchidism, hypospadias, polydactyly of fingers, polydactyly of toes, syndactyly of toes, and Down syndrome.

2.1.3 | Statistical Analysis

Maternal age at delivery was categorized as <25, 25-29, 30-34, 35-39, and ≥40 years. Body mass index (BMI) before pregnancy was categorized as <18.5 kg/m², ≥18.5 to <25 kg/m², and ≥25 kg/m². Marital status was classified as “married” or, in the case of unmarried, divorced, or widowed mothers, “single.” Education history was categorized as <13 years, 13-14 years, and ≥15 years. Yearly income was categorized as ≤¥4 000 000, ¥4 000 000 to ¥6 000 000, and ≥¥6 000 000. Alcohol intake was categorized as “never drank,” “quit before pregnancy,” and “full drinking.” Based on the charts, we recorded “yes” for spontaneous pregnancy, “no” for “induction of ovulation,” and “artificial insemination by husband” for “in vitro fertilization,” “micro-fertilization,” “embryo transplantation,” “frozen embryo transplantation,” and “blastocyst implantation.” Folic acid intake was categorized as “yes” if the participant answered “once a month or more” on the early pregnancy questionnaire, and the response “don’t take it” was categorized as “no.”

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, history of diabetes mellitus, marital status, education history, annual household income, in vitro fertilization or artificial insemination, alcohol intake, frequency of tobacco smoke exposure, folic acid intake, antihypertensive intake, anti-convulsant intake, and retinoic acid intake during early pregnancy. All statistical analyses were performed using SAS version 9.4 software (SAS Institute Inc., Cary, NC).
Of the 91,626 participants included in our analysis, 2199 (2.4%) had CAs (any CAs).

Table 1 shows the number and frequency of CAs per 10,000 births according to maternal smoking behaviors during pregnancy. The most common CAs were cardiovascular anomalies, with 1058 cases (115.5 CAs per 10,000 births) recorded. Other CAs included...
| TABLE 2 Characteristics according to congenital anomalies (N = 91,626) |
|---------------------------------------------------------------|
| **Never smoked** | 53,356 | 58.2% | **Quit before pregnancy** | 21,406 | 23.4% | **Quit after pregnancy** | 12,437 | 13.6% | **Full smoking** | 4,427 | 4.8% |
| Age at delivery (years) | | | | | | | | | | | | |
| <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 |
| 35-39 | 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 |
| Body mass index | | | | | | | | | | | |
| <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 history | | | | | | | | | | | |
| Yes | 413 | 0.8 | 235 | 1.1 | 108 | 0.9 | 50 | 1.1 |
| Marital status | | | | | | | | | | | |
| 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 |
| Education history (years) | | | | | | | | | | | |
| <13 | 13,707 | 26.2 | 8,464 | 40.4 | 7,037 | 58.1 | 3,109 | 73.2 |
| 13-14 | 23,338 | 44.6 | 9,208 | 44.0 | 4,213 | 34.8 | 1,007 | 23.7 |
| ≥15 | 15,291 | 29.2 | 3,257 | 15.6 | 866 | 7.2 | 131 | 3.1 |
| Annual household income (yen) | | | | | | | | | | | |
| <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 |
| In vitro fertilization or artificial insemination | | | | | | | | | | | |
| Yes | 4,100 | 7.7 | 1,584 | 7.4 | 345 | 2.8 | 63 | 1.4 |
| Alcohol intake | | | | | | | | | | | |
| Never drank | 21,915 | 41.2 | 5,319 | 24.9 | 3,163 | 25.6 | 1,063 | 24.2 |
| Quit before pregnancy | 25,930 | 48.8 | 13,352 | 62.6 | 8,423 | 68.1 | 2,850 | 64.8 |
| Full drinking | 5,289 | 10.0 | 2,656 | 12.5 | 789 | 6.4 | 485 | 11.0 |
| Frequency of tobacco smoke exposure | | | | | | | | | | | |
| Never | 31,644 | 59.5 | 10,613 | 49.7 | 2,371 | 19.2 | 395 | 9.0 |
| 1 day a week | 7,151 | 13.5 | 2,899 | 13.6 | 1,011 | 8.2 | 179 | 4.1 |
| 2-3 days a week | 5,615 | 10.6 | 2,683 | 12.6 | 1,593 | 12.9 | 461 | 10.5 |
| 4-6 days a week | 3,732 | 7.0 | 1,816 | 8.5 | 1,703 | 13.8 | 519 | 11.8 |
| Everyday | 5,012 | 9.4 | 3,324 | 15.6 | 5,699 | 46.1 | 2,842 | 64.7 |
| Folic acid intake | | | | | | | | | | | |
| Yes | 27,245 | 51.2 | 10,858 | 50.9 | 5,383 | 43.4 | 1,463 | 33.2 |
| Anthypertensive intake | | | | | | | | | | | |
| Yes | 265 | 0.5 | 123 | 0.6 | 69 | 0.6 | 30 | 0.7 |
| Anti-convulsant intake | | | | | | | | | | | |
| Yes | 179 | 0.3 | 89 | 0.4 | 71 | 0.6 | 32 | 0.7 |
| Retinoic acid intake | | | | | | | | | | | |
| Yes | 142 | 0.3 | 60 | 0.3 | 30 | 0.2 | 6 | 0.1 |
| ICD-10 code | n (%) | Crude OR (95% CI) | Adjusted<sup>a</sup> OR (95% CI) |
|-------------|-------|------------------|-------------------------------|
| **Nervous system (Q00-07)** | | | |
| Never smoked | 100 (0.19) | Reference | Reference |
| Quit before pregnancy | 43 (0.20) | 1.07 (0.75, 1.53) | 1.06 (0.70, 1.61) |
| Quit after pregnancy | 18 (0.14) | 0.77 (0.47, 1.28) | 0.76 (0.40, 1.43) |
| Full smoking | 12 (0.27) | 1.45 (0.80, 2.64) | 1.42 (0.66, 3.07) |
| **Eye, ear, face, and neck (Q10-18)** | | | |
| 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 (0.06) | 0.90 (0.42, 1.94) | 1.06 (0.45, 2.51) |
| Full smoking<sup>b</sup> | 4 (0.09) | – | – |
| **Cardiovascular system (Q20-28)** | | | |
| Never smoked | 616 (1.15) | Reference | Reference |
| Quit before pregnancy | 239 (1.12) | 0.97 (0.83, 1.12) | 1.00 (0.85, 1.17) |
| Quit after pregnancy | 139 (1.12) | 0.97 (0.80, 1.16) | 0.98 (0.79, 1.22) |
| Full smoking<sup>b</sup> | 64 (1.45) | 1.26 (0.97, 1.63) | 1.34 (0.99, 1.82) |
| **Oral clefts (Q35-37)** | | | |
| Never smoked | 128 (0.24) | Reference | Reference |
| Quit before pregnancy | 58 (0.27) | 1.13 (0.83, 1.54) | 1.16 (0.82, 1.64) |
| Quit after pregnancy | 33 (0.27) | 1.11 (0.76, 1.62) | 1.17 (0.74, 1.85) |
| Full smoking<sup>b</sup> | 10 (0.23) | 0.94 (0.49, 1.79) | 1.17 (0.58, 2.38) |
| **Digestive system (Q38-45)** | | | |
| Never smoked | 55 (0.10) | Reference | Reference |
| Quit before pregnancy | 31 (0.14) | 1.41 (0.91, 2.18) | 1.58 (0.98, 2.55) |
| Quit after pregnancy<sup>b</sup> | 2 (0.02) | – | – |
| Full smoking<sup>b</sup> | 3 (0.07) | – | – |
| **Genital organs (Q50-56)<sup>c</sup>** | | | |
| Never smoked | 190 (0.70) | Reference | Reference |
| Quit before pregnancy | 79 (0.72) | 1.04 (0.80, 1.35) | 0.99 (0.74, 1.32) |
| Quit after pregnancy | 38 (0.60) | 0.86 (0.61, 1.22) | 0.80 (0.53, 1.22) |
| Full smoking | 21 (0.92) | 1.33 (0.84, 2.08) | 1.22 (0.71, 2.11) |
| **Musculoskeletal system (Q65-79)** | | | |
| Never smoked | 185 (0.35) | Reference | Reference |
| Quit before pregnancy | 86 (0.40) | 1.16 (0.90, 1.50) | 1.18 (0.89, 1.57) |
| Quit after pregnancy | 38 (0.31) | 0.88 (0.62, 1.25) | 0.93 (0.62, 1.41) |
| Full smoking | 23 (0.52) | 1.50 (0.97, 2.32) | 1.40 (0.81, 2.43) |
| **Trisomy (Q90-91)** | | | |
| Never smoked | 110 (0.21) | Reference | Reference |
| Quit before pregnancy | 40 (0.19) | 0.91 (0.63, 1.30) | 0.75 (0.49, 1.15) |
| Quit after pregnancy | 14 (0.11) | 0.55 (0.31, 0.95) | 0.55 (0.28, 1.10) |
| Full smoking | 18 (0.41) | 1.98 (1.20, 3.26) | 2.14 (1.15, 3.97) |
| **Any congenital anomalies** | | | |
| Never smoked | 1263 (2.37) | Reference | Reference |
| Quit before pregnancy | 526 (2.46) | 1.04 (0.94, 1.15) | 1.06 (0.95, 1.19) |
| Quit after pregnancy | 273 (2.20) | 0.93 (0.81, 1.06) | 0.92 (0.79, 1.08) |
| Full smoking | 137 (3.09) | 1.32 (1.10, 1.58) | 1.35 (1.09, 1.67) |

Abbreviations: CI, confidence interval; OR, odds ratio.

<sup>a</sup>Adjusted for maternal age at delivery, body mass index, history of diabetes mellitus, marital status, education history, annual household income, in vitro fertilization or artificial insemination, alcohol intake, frequency of tobacco smoke exposure, folic acid intake, antihypertensive intake, anti-convulsant intake, and retinoic acid intake.

<sup>b</sup>We did not calculate the odds ratio because a number of cases were too small (<5 cases).

<sup>c</sup>Only boys were analyzed (n = 46 893).
Table 4: Association between maternal smoking history and frequent congenital anomalies in this study

| Anomalies                  | n (%)       | Crude OR (95% CI) | Adjusted* OR (95% CI) |
|---------------------------|-------------|-------------------|-----------------------|
| **Hydrocephaly**          |             |                   |                       |
| Never smoked              | 44 (0.08)   | Reference         | Reference             |
| Quit before pregnancy     | 19 (0.09)   | 1.08 (0.63, 1.84) | 1.22 (0.67, 2.22)     |
| Quit after pregnancy      | 10 (0.08)   | 0.98 (0.49, 1.94) | 1.13 (0.49, 2.62)     |
| Full smoking              | 8 (0.18)    | 2.19 (1.03, 4.66) | 2.55 (0.95, 6.86)     |
| **Cleft palate**          |             |                   |                       |
| Never smoked              | 34 (0.06)   | Reference         | Reference             |
| Quit before pregnancy     | 11 (0.05)   | 0.81 (0.41, 1.59) | 0.92 (0.45, 1.88)     |
| Quit after pregnancy      | 5 (0.04)    | 0.63 (0.25, 1.61) | 0.88 (0.31, 2.50)     |
| Full smoking              | 1 (0.02)    | –                 | –                     |
| **Cleft lip**             |             |                   |                       |
| Never smoked              | 38 (0.07)   | Reference         | Reference             |
| Quit before pregnancy     | 20 (0.09)   | 1.31 (0.76, 2.26) | 1.25 (0.66, 2.37)     |
| Quit after pregnancy      | 10 (0.08)   | 1.13 (0.56, 2.27) | 1.18 (0.50, 2.80)     |
| Full smoking              | 6 (0.14)    | 1.90 (0.81, 4.51) | 2.40 (0.87, 6.59)     |
| **Cleft lip and palate**  |             |                   |                       |
| Never smoked              | 63 (0.12)   | Reference         | Reference             |
| Quit before pregnancy     | 28 (0.13)   | 1.11 (0.71, 1.73) | 1.14 (0.70, 1.86)     |
| Quit after pregnancy      | 21 (0.17)   | 1.43 (0.87, 2.35) | 1.32 (0.72, 2.42)     |
| Full smoking              | 4 (0.09)    | –                 | –                     |
| **Cryptorchidism**        |             |                   |                       |
| Never smoked              | 161 (0.59)  | Reference         | Reference             |
| Quit before pregnancy     | 68 (0.62)   | 1.05 (0.79, 1.40) | 0.98 (0.72, 1.33)     |
| Quit after pregnancy      | 32 (0.51)   | 0.86 (0.59, 1.26) | 0.80 (0.51, 1.25)     |
| Full smoking              | 18 (0.79)   | 1.34 (0.82, 2.19) | 1.14 (0.63, 2.08)     |
| **Hypospadias**           |             |                   |                       |
| Never smoked              | 33 (0.12)   | Reference         | Reference             |
| Quit before pregnancy     | 15 (0.14)   | 1.13 (0.62, 2.09) | 1.27 (0.65, 2.47)     |
| Quit after pregnancy      | 7 (0.11)    | 0.92 (0.41, 2.07) | 0.91 (0.32, 2.57)     |
| Full smoking              | 3 (0.13)    | –                 | –                     |

(Continues)

Table 4 (Continued)

| Anomalies                  | n (%)       | Crude OR (95% CI) | Adjusted* OR (95% CI) |
|---------------------------|-------------|-------------------|-----------------------|
| **Polydactyly of fingers**|             |                   |                       |
| Never smoked              | 57 (0.11)   | Reference         | Reference             |

Abbreviations: CI, confidence interval; OR, odds ratio.
*Adjusted for maternal age at delivery, body mass index, history of diabetes mellitus, marital status, education history, annual household income, in vitro fertilization or artificial insemination, alcohol intake, frequency of tobacco smoke exposure, folic acid intake, antihypertensive intake, anti-convulsant intake, and retinoic acid intake.
*We did not calculate the odds ratio because the number of cases was too small (<5 cases).
*Only boys were analyzed (n = 46 893).

328 genital organ CAs (69.9 per 10 000 male births), 332 musculoskeletal CAs (36.2 per 10 000 births), 229 oral clefts (25.0 per 10 000 births), 182 trisomy (19.9 per 10 000 births), 173 CAs related to the nervous system (18.9 per 10 000 births), and < 100 CAs related to the digestive system and the eyes, ears, face, and neck (9.9 and 6.9 per 10 000 births, respectively).

Categorized by smoking habit, “full smoking” was associated with indices of lower socioeconomic status (e.g., BMI, marital status, education history, and annual household income) compared with the other groups (Table 2).
Table 3 shows the ORs from the logistic regression analysis of each smoking category (using “never smoked” as the reference) for the eight main CA groups as well as the “any CAs” category. Compared with never-smokers, the OR was significantly elevated in the full-smoking group for trisomy (adjusted OR, 2.14; 95% CI, 1.15-3.97) and “any CAs” (adjusted OR, 1.35; 95% CI, 1.09-1.67). No significant elevation was found in the QBP, QAP, or full-smoking groups for CAs related to the nervous system; eyes, ears, face, and neck; cardiovascular system; oral clefts; digestive system; genital organs; or musculoskeletal system.

Table 4 shows the ORs from the logistic regression analysis of each smoking category for the 10 anomalies. Compared with never-smokers, the OR in the full-smoking group was significantly elevated for only Down syndrome (adjusted OR, 2.01; 95% CI, 1.01-4.25).

4 | DISCUSSION

In this study, we showed that the risk of any CAs and trisomy was significantly increased in the full-smoking during pregnancy group compared with the never smoked group. We recruited pregnant women who visited general obstetric clinics, which covered nearly 50% of all births in the 15 different regions throughout Japan. Data on CAs were collected by transcribing information from medical records at two time points: at birth and at 1 month postpartum. We collected records on abortion and stillborn infants as well as live infants. In addition, we found that several indicators are similar to those of the 2013 National Vital Statistics Survey and we therefore believe that our results are representative of the general population in Japan. To our knowledge, the present study is the first to report on the association of maternal smoking history and CA risk in a Japan-wide birth cohort.

On the other hand, except for trisomy, there were no significant associations between the full-smoking group and CAs related to the nervous system; eyes, ears, face, and neck; cardiovascular system; oral clefts; genital organs; and the musculoskeletal system. For CAs of the cardiovascular system, the OR was higher in the full-smoking group, but not significantly (1.34; 95% CI, 0.99-1.82). A systematic review that analyzed 43 studies reported that smoking during pregnancy increases the risk of congenital heart disease (CHD). The association between the effect of tobacco smoke exposure during pregnancy and CHD has not been fully elucidated, but there are reports of genetic polymorphisms that increase the risk of CHD in children whose mothers were exposed to tobacco smoke. Although our results on CHD were not statistically significant, we believe that maternal smoking increases the risk of CHD. Half of the CAs assessed in this study were CHD, which might have had a major impact on the overall results.

Given that many subcategories were included in the “any CAs” category, these abnormalities might have occurred at various stages of embryological development. In general, most CAs occur during organ formation (between the 4th and 7th week of pregnancy). Although 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 (i.e., those who quit smoking only after realizing they were pregnant). However, even after becoming pregnant, quitting smoking might be preventive against the occurrence of CAs in fetuses. In two birth cohort studies, smoking during pregnancy was found to increase the incidence of any CAs. To trace associations between these previous studies and the present study, we examined the risk of CAs in the combined QAP and full-smoking groups as a single “smoking during conception” group, but found no significant associations for any categories of anomalies (Table S1) or frequent congenital anomalies (Table S2). This finding might indicate the possibility of low tobacco exposure in the QAP group; indeed, none of the CAs observed in the QAP group showed a significant association. The frequency of maternal smoking during pregnancy in the Danish register-based cohort study was 18.6%, which is nearly the same as the rate of 18.4% in the combined QAP and full-smoking groups in the JECS; however, in the Danish study, only 11.5% of mothers who smoked quit during pregnancy compared with 73.7% in the JECS. This also suggests that the QAP group in the JECS might have been less dependent on tobacco; hence, the exposure might have been weaker for the same reason. Therefore, it is not possible to determine from our study whether quitting smoking after pregnancy is preventive. We hope that this will be verified in future trials of smoking cessation interventions for pregnant women.

For trisomy, our results showed increased risk in the full-smoking group, but some previous studies have shown no significant associations between maternal smoking and trisomy or have shown low ORs for trisomy in children of smokers. Therefore, the results of the present study need to be interpreted carefully. Trisomy zygotes are primarily a result of maternal meiotic I errors, and the risk of oocyte aneuploidy increases with age. The mechanism that gives rise to oocyte aneuploidy with aging has not yet been elucidated, but some of the molecular pathways are becoming clearer and age-related degradation of cohesin has been suggested as a possible mechanism. Along with aging, long-term exposure to tobacco smoke might be related to a molecular mechanism such as degradation of cohesin in the full-smoking group. In addition, compared with the other groups, the full-smoking group might be more susceptible to oocyte degradation because they had more tobacco smoke exposure as a result of their partner’s or the other family member’s smoking habit (Table S3). Thus, further research is needed to elucidate whether long-term exposure to tobacco smoke might be related to oocyte degradation. However, we cannot deny the possibility of bias induced by artificial abortion as a result of prenatal diagnosis of trisomy. Compared with the full-smoking group, it seems that it is easier to approach the non-smoking group in order to investigate trisomy-specific abortions because the women in this group have higher income and higher frequency of using assisted reproductive technologies (in vitro fertilization and/or artificial insemination). Although our analysis included cases of abortion, some women might have withdrawn from the study after an abortion and their records would be unavailable for analysis.

In addition to the aforementioned limitation, there are some further limitations in this study. First, the data we collected related to smoking histories and quantity were self-reported and therefore could not be analyzed as objective measures. In previous studies based on cotinine concentrations detected in blood, some mothers who self-
reported that they had “never smoked” were evidently “full smoking.” In the present study, the never smoked and QBP groups might have included participants who gave false or mistaken answers. Second, this study used the 31 ailments and abnormalities defined by the JECS, and thus the analysis was conducted based on these categories. The strength of this study is that it is based on a nationwide survey conducted in Japan with a very high response rate from the start of the study (during pregnancy) to the time of delivery. Many responses related to smoking behaviors were obtained. Multiple covariates (confounding factors) regarded as optimal for analysis were available in the study, thereby enabling many different effects to be considered and discarded.

5 | CONCLUSIONS

This study showed that children born to women who continue to smoke during pregnancy have increased risk of trisomy and CAs. We eagerly await further studies that will clarify the etiology and underlying mechanisms that induce CAs due to maternal smoking.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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**APPENDIX A.**

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