Dose-dependent associations between prenatal caffeine consumption and small-for-gestational-age, preterm birth, and reduced birthweight in the Japan Environment and Children's Study

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Running head

Caffeine consumption and reduced birth weight

Synopsis

Study question

Does an association between prenatal caffeine intake and birth size show dose-dependency?

What's already known

Few previous studies have investigated the association between prenatal caffeine intake and birth size in Japan.

What this study adds

Continuous consumption of moderate or high levels of caffeine during pregnancy increased small-for-gestational-age risk and reduced birthweight Z-score, depending on the level of consumption. Prenatal caffeine consumption was associated with an increased risk of preterm birth at the 2nd trimester of gestation. However, as the association between prenatal caffeine consumption and birth size was likely confounded by unpredicted potential factors, our confidence in the true causality of the association is moderate.

Abstract

Background: Few previous studies have investigated the association between prenatal caffeine intake and birth size (small-for-gestational-age (SGA), preterm birth, and birthweight Z-score) in Japan.

Objectives: We examined the dose-dependency of this association (prenatal caffeine consumption and birth size) as part of the Japan Environment and Children's Study.

Methods: A prospective birth cohort included 94,876 fetuses in Japan. Participants were enrolled between January 2011 and March 2014. Adjusted multiple linear regression and Cox regression models were used to examine the association between prenatal caffeine levels and infant birth size.

Results: The median estimated caffeine consumption during pregnancy was 125.5 mg/day, as determined by self-administered questionnaires. There were 7,252 SGA infants (7.6%) and 4,281 preterm birth infants (4.5%). Compared with infants of mothers whose caffeine consumption during pregnancy was in the lowest quartile (4.2 to <86.4 mg/day), infants of mothers whose caffeine consumption was in the highest quartile 4 (205.5 to 5,080.0 mg/day) were at an increased risk of SGA (relative risk [RR]: 1.18; 95% confidence interval [CI]: 1.10, 1.27), and at an increased risk of preterm birth at the 2nd trimester of gestation (RR: 1.94; 95% CI: 1.12, 3.37), with a 0.32-day reduction in gestational age (95% CI: -0.52, -0.12) and with a 0.07 reduction in birthweight Z-score observed (95% CI: -0.09, -0.05).

Conclusions: Prenatal caffeine consumption was associated with birth size. However, as the association between prenatal caffeine consumption and birth size was likely

confounded by unpredicted potential factors, our confidence in the true causality of the association is moderate.

Keywords

Caffeine; Pregnancy; Birthweight; Small-for-gestational-age; Preterm birth; The Japan Environment and Children's Study

Word count: 3,389

Introduction

Small-for-gestational-age (SGA) is a predictor of inadequate fetal growth and is defined as birth weight below the 10th percentile. This condition is associated with an increased risk of perinatal morbidity and mortality,[1,2] adiposity, neurocognitive disorder, blood pressure, obesity, and cardiovascular disease during childhood and adulthood.[3-6] Preterm birth, which is defined as birth at 36 weeks of gestation or earlier, is also associated with an increased risk of mortality in young adulthood.[7] Therefore, it is important to note that predictors of birth outcomes, such as SGA and preterm birth, can be associated with lifelong adverse health problems.

One risk factor for both SGA and preterm birth is caffeine (1,3,7-trimethylxanthine) consumption during pregnancy. Caffeine, which is an alkaloid that is primarily found in tea, coffee, some soft drinks (including cola), and chocolate;[8] is known to cross the placenta via passive diffusion,[9] and stimulates the central nervous system by blocking the activity of adenosine as it acts as an antagonist for the adenosine A1 and A2A receptors.[9,10] Eighty percent of the caffeine we consume is metabolized to paraxanthine by cytochrome P450 (CYP) 1A2.[11,12] Our previous study out of the Japan Environment and Children's Study (JECS) revealed that infants of individuals with the maternal *CYP1A2* (C164A) genotype were susceptible to reduced birth weight as a consequence of prenatal caffeine intake during pregnancy.[13] In a previous meta-analysis that included 13 prospective studies consisting of approximately 100,000 participants from both Europe and North America, Chen et al.[14] reported that the risk of SGA increases in a dose-dependent manner with increasing caffeine intake during pregnancy,

and the risk is increased even at low exposure levels. However, previous studies of the association between prenatal caffeine intake and SGA, preterm birth and birthweight in Japan are limited.

The efficient clearance of maternal caffeine during pregnancy (10.5 h half-life),[15] means that a single measurement of maternal caffeine levels at a specific time point may not be suitable to evaluate chronic exposure. The food frequency questionnaire (FFQ) presents a better indication of chronic exposure, providing an accurate estimation of dietary intake among Japanese with a modern lifestyle, and it has been validated in Japanese populations.[16]

To date, the effects of chronic caffeine exposure during pregnancy remain unclear, and we predicted that a dose-dependent reduction in birth size and increased risk of both SGA and preterm birth would occur regardless of maternal genetic susceptibility. This hypothesis was tested using the FFQ in a prospective birth cohort of 94,876 fetal records of pregnant women in Japan.

Methods

Study design

JECS is an ongoing prospective birth cohort study in Japan. Details of the JECS project have been described elsewhere.[17,18] Briefly, pregnant women were recruited between January 2011 and March 2014. Eligibility criteria for participation included: residing in the study area at the time of recruitment, an expected delivery date after August 2011, comprehension of the Japanese language, and completing the self-administered questionnaire. Mothers residing outside the study area but attended cooperating health care providers within the study area were excluded. In total, 104,102 fetal records were included in the cohort, including multiple-births. The present study used the dataset jecs-ag-20160424 which was released in June 2016 and revised in October 2016.

Ethical statement

The JECS protocol was approved by the Ministry of the Environment's Institutional Review Board on Epidemiological Studies and by the Ethics Committees of each participating institution (Appendix 1). All participants provided informed, written consent in accordance with the Declaration of Helsinki.

Study participants

The flow diagram of participant enrollment is presented in Figure 1. Of the 104,102 fetal records included in the cohort, complete data for the maternal questionnaire during the first trimester (M-T1) and second and third trimesters (M-T2), medical record

transcription data during the first trimester (Dr-T1), and medical record transcription data at birth (Dr-0m) were available for 98,043 fetal records. Exclusion criteria included: stillbirth, natural abortion (miscarriage), induced abortion, and twin or multiple-birth gestation. In total, 2,068 fetal records were excluded based on this criteria. Data on caffeine consumption during pregnancy was absent for a further 1,099 fetal records. Finally, 94,876 fetal records were evaluated for associations between prenatal caffeine consumption and birth outcome.

Self-administered questionnaires including food frequency

Details of the self-administered FFQs in this study have been described previously.[17,19] Briefly, parity, maternal age, maternal height and weight before pregnancy, FFQ information[19] including consumption of caffeinated beverages (green tea, oolong tea, black tea and coffee), and alcohol during the year prior to pregnancy, and caffeine consumption during the year prior to pregnancy were obtained from M-T1; maternal smoking status during pregnancy, maternal education level, annual household income, and FFQ information during pregnancy[19] were obtained from M-T2; maternal height and weight before pregnancy were obtained from Dr-T1; and maternal age, infant sex, gestational age, single or multiple-birth gestation, maternal complications during pregnancy (hypertension and diabetes), pregnancy-induced complications (hypertension and gestational diabetes), live or stillbirth, and natural or induced abortion data were obtained from Dr-0m. Total energy intake (kcal) was calculated using FFQ information obtained from M-T2 according to the standard tables of food

composition in Japan (The 5th revised version).[20]

Calculations of daily caffeine consumption

Data concerning caffeinated beverage consumption during pregnancy (from M-T2) and the year prior to pregnancy (from M-T1) was collected using self-administered FFQs. To calculate the total amount (mg) of caffeine consumed per day, the following frequency scores were assigned: 0.14 (calculated by 1 divided by 7) for less than once per week, 0.21 (1.5 divided by 7) for one to two times per week, 0.50 (3.5 divided by 7) for three to four times per week, 0.79 (5.5 divided by 7) for five to six times per week, 1 for one cup per day, 2.5 (1 × 2.5) for two to three cups per day, 5 (1 × 5) for four to six cups per day, 8 (1 × 8) for seven to nine cups per day; 10 (1 × 10) for ten or more cups per day, and 0 for missing data. Beverages were classified as green tea (infusion), green tea (can/polyethylene terephthalate [PET] bottle), oolong tea (infusion), oolong tea (can/PET bottle), black tea (infusion), black tea (can/PET bottle), coffee (infusion), coffee (instant), and coffee (can/PET bottle). To calculate the total amount of caffeine consumed per day, one cup of green tea, oolong tea, black tea, coffee (infusion or can/PET bottle), or coffee (instant) was equivalent to 100, 30, 60, 50, and 60 mg of caffeine, respectively.[21] Generally, caffeine contents per 100 mL of black tea and coffee beverages are 30-53 mg and 40-100 mg, respectively, depending on the roasting method and type of tea. Caffeine contents of black tea and coffee beverages are therefore 45-80 mg and 60-150 mg, respectively, per 150 mL cup. Daily caffeine consumption (mg/day) was estimated by multiplying the total frequency score by the amount of caffeine in 1

cup of the appropriate beverage (green, oolong, and black teas and coffee). Increased, decreased, or no caffeine consumption during pregnancy was compared to caffeine consumption during the year prior to pregnancy by subtracting caffeine consumption during the year prior to pregnancy from consumption during pregnancy.

Outcome definitions

Birthweight was defined as the weight of each infant at birth. SGA was defined as a birth weight below the 10th percentile, accounting for infant sex, parity, and gestational age according to the Japan Pediatric Society.[22] Birthweight Z-score (standard deviation [SD] score) was defined as the SD of birthweight for gestational age in the normal distribution, accounting for infant sex, parity, and gestational age according to the Japan Pediatric Society.[22] Analyses of SGA and birthweight Z-score were carried out using Excel-based clinical tools for growth evaluation of children, based on the definition of percentiles from the Japan Pediatric Society, as defined by the Japanese Society for Pediatric Endocrinology.[23] Preterm birth, preterm birth at the 2nd trimester, and preterm birth at the 3rd trimester were defined as infants born at 28 to <37 weeks of gestation, infants born at 22 to <28 weeks of gestation, and infants born to 28 to <37 weeks of gestation, respectively.[24] Doctors used gestational age which is calculated from the last menstrual date or artificial insemination/*in-vitro* fertilization date. Gestational age was defined as the time from day zero of gestation to the date of birth. We used the gestational age data on the Dr-0m questionnaire.

Statistical analyses

Figure 2 illustrates the proportion (percentages) for all participants of estimated caffeine consumption during pregnancy. The association between estimated caffeine consumption during pregnancy (categorized into quartile 1 [4.2 to <86.4 mg/day], quartile 2 [86.4 to <125.5 mg/day], quartile 3 [125.5 to <205.5 mg/day], and quartile 4 [205.5 to 5,080.0 mg/day]) and SGA and the association between estimated caffeine consumption during pregnancy and preterm birth (at 22 to <37 weeks, at 22 to <28 weeks, and at 28 to <37 weeks of gestation) were analyzed using Cox regression models. In Cox regression models, the variable of survival time was defined as gestational age (days). The association between estimated caffeine consumption during pregnancy and gestational age, and the association between estimated caffeine consumption during pregnancy and birth size (birthweight Z-score) were analyzed using multiple linear regression models. These models were adjusted for maternal age (continuous), maternal body mass index (BMI) before pregnancy (continuous), maternal smoking during pregnancy (no/yes), maternal drinking during pregnancy (no/yes), maternal education level (<13 years/≥13 years), annual household income (<4 million Japanese yen/≥4 million Japanese yen), total energy intake (continuous), parity (primiparous/multiparous), infant sex (male/female), and gestational age (continuous). When SGA or birthweight Z-score was the dependent variable, defined by a combination of parity, infant sex, and gestational age, these were removed from the confounding factors. When gestational age was the dependent variable, maternal age, maternal BMI before pregnancy, parity, and infant sex were removed from the confounding factors. We

also examined the interaction of smoking during pregnancy (assigned as no = 0, and yes =1) and caffeine level (assigned as quartile 1 = 0, quartile 2 = 1, quartile 3 = 2, and quartile 4 = 3) using multiple linear regression and logistic regression models, as a high proportion of the participants who consumed caffeine were also smokers. We performed multiple imputation for missing data using Bayesian statistics[25,26] with Statistical Package for Social Sciences (SPSS) (SPSS Inc., Chicago, IL, USA). Minimum and maximum values were set for each variable. To create and analyze the 30 datasets, we imputed the missing values of: infant sex ($n_{missing}$ = 5 [0.0%]), infant birthweight ($n_{missing}$ = 59 [0.1%]), infant SGA ($n_{missing}$ = 361 [0.4%]), infant birthweight Z-score ($n_{missing}$ = 579 [0.6%]), gestational age ($n_{missing}$ = 0 [0.0%]), maternal age ($n_{missing}$ = 0 [0.0%]), BMI before pregnancy ($n_{missing}$ = 36 [0.0%]), total energy intake ($n_{missing}$ = 1 [0.0%]), parity ($n_{missing}$ = 298 [0.3%]), smoking during pregnancy ($n_{missing}$ = 569 [0.6%]), alcohol drinking during pregnancy ($n_{missing}$ = 406 [0.4%]), education level ($n_{missing}$ = 332 [0.4%]), annual household income ($n_{missing}$ = 6,390 [6.7%]), pregnancy-induced hypertension ($n_{missing}$ = 0 [0.0%]), and gestational diabetes ($n_{missing}$ = 0 [0.0%]) using the multiple imputation function of SPSS (SPSS Inc.). Analyses were performed using SPSS version 24 (SPSS Inc.). Data were considered statistically significant when $P < 0.05$.

Results

The FFQ data revealed the median estimated total caffeine consumption during pregnancy to be 125.5 mg/day which was lower than the estimated total caffeine consumption of 161.6 mg/day during the year prior to pregnancy (eTable 1). Green tea represented the highest contribution (median, 37.0%) to caffeine consumption during pregnancy among all participants (eTable 1).

The majority of pregnant women (37.8%) consumed an estimated 100 to <200 mg/day of caffeine (Figure 2 and eTable 2).

Compared with infants born to mothers whose estimated caffeine consumption during pregnancy was within quartile 1, those born to mothers whose estimated consumption was within quartile 4 showed increased SGA (8.1% versus 7.0%), increased preterm birth at the 3rd trimester (4.6% versus 4.5%), and lower mean birthweight Z-scores (0.03 versus 0.10) (Table 2). Compared with mothers whose estimated caffeine consumption during pregnancy was within quartile 1, those with estimated consumption levels in quartile 4 had a higher mean age (31.6 years versus 30.9 years), were more likely to be multiparous (66.1 % versus 47.5 %), and exhibited a higher smoking rate (21.0% versus 13.7%) (Table 2). Cessation of caffeine consumption during pregnancy compared with that in the year prior to pregnancy was not reported (eTable 3). In comparison with mothers whose estimated caffeine consumption during pregnancy was within quartile 1, mothers of the quartile 4 group were more likely to increase their total caffeine intake during pregnancy (60.1% versus 6.6%) (eTable 3).

The results of data without imputation revealed that compared to infants born to

mothers whose caffeine consumption was within quartile 1 during pregnancy, those born to mothers with estimated prenatal caffeine consumption in quartile 2 were at an increased risk of SGA (relative risk [RR]: 1.07; 95% confidence interval [CI]: 1.00, 1.15) (Table 2) and with a decrease of 0.02 in birthweight Z-score (95% CI: -0.04, 0.00) (Table 2). Infants born to mothers with prenatal levels of caffeine consumption within quartile 4 were also at an increased risk of SGA (RR: 1.18; 95% CI: 1.17, 1.19) and at an increased risk of preterm birth at the 2nd trimester (RR: 1.94; 95% CI: 1.12, 3.37), with a decrease of 0.32 days in gestational age (95% CI: -0.52, -0.12) and with a decrease of 0.07 in birthweight Z-score (95% CI: -0.09, -0.05)(Table 2). Caffeine intake of ≥86.4 mg/day during pregnancy resulted in a dose-dependent increase in the risks of SGA and reduced birthweight Z-score. The results of multiple linear and Cox regression models were similar for analyses with or without imputation for missing data (Table 2).

Comments

Principal Findings

The results presented here suggest that continuous consumption of moderate or high levels of caffeine during pregnancy increases SGA risk and reduced birthweight Z-score, depending on the level of consumption.

Interpretation

Of the participants who consumed caffeine many were also smokers. An interaction of smoking during pregnancy and prenatal caffeine consumption was observed for both SGA and birthweight Z-score (*P*-interaction <0.001 [for SGA] and <0.001 [for birthweight Z-score]). An interaction between smoking during pregnancy and prenatal caffeine consumption for the outcome of gestational age was also observed (*P*-interaction <0.001) using data without imputation. The interaction of smoking and caffeine consumption during pregnancy had a dramatic effect on both gestational age and birthweight (eTable 4); however, the non-linear association of birthweight with gestational age is well-known. Therefore, we propose that the relationships between caffeine, smoking, and gestational age with relation to both birth weight and SGA should be investigated in detail in further studies.

Among Japanese women, sources of caffeine intake have been reported to include Japanese/Chinese tea (such as green or oolong tea) (47.1%), coffee (46.7%), black tea (4.3%), sweets (0.5%), coffee-flavored beverages (0.2%), cocoa (0.2%), and soft drinks (0.1%).[27] Japanese/Chinese tea accounted for a similar percentage of caffeine intake as

coffee in the aforementioned study; however, the present study found both green and oolong teas to account for >10% more caffeine consumption than coffee.

The risk of SGA increases in a dose-dependent manner with increasing caffeine consumption during pregnancy, beginning even at low levels of caffeine exposure.[14] Dose-dependent reduction in birthweight with consumption of low levels of caffeine during pregnancy was reported in a study of 2,635 pregnant women in the United Kingdom.[28] This agrees with results of the present study; suggesting that the association between caffeine consumption during pregnancy and reduced birthweight Z-score and the increased risk of SGA starts at low caffeine levels, regardless of the caffeine source.

Although caffeine levels in biological samples such as blood, urine, and saliva reflect absolute caffeine amounts, caffeine levels calculated from the FFQ are relative levels. Hence, caffeine levels indicated from the FFQ in the present study may not be accurate. As maternal caffeine during pregnancy is cleared within one day,[16] measurement of maternal caffeine levels in biological samples at several specific points may be more suitable in evaluating chronic exposure. We did not measure the caffeine level in biological samples at this stage, therefore, analysis of the incomplete results of relative caffeine consumption during pregnancy is presented at this time.

The 4-8th month (the period between the last month of the 1st trimester and the first month of the 3rd trimester) of gestation represents the critical window of maternal exposure to chemicals leading to low birth weight.[29] Fetal growth is the most rapid from the 9th to the 10th month (the 3rd trimester) of gestation with an average increase of 240-g per week.[30] The critical window of maternal caffeine exposure may be the 2nd trimester

of gestation. Hence, we consider that our results showed an almost doubling of the risk of early preterm birth at the 2nd trimester of gestation in quartile 3 and 4 of prenatal caffeine level and no increased risk of late birth at the 3rd trimester of gestation for the exposure of prenatal caffeine level.

In the present study, among 7,252 SGA infants, those born in 22 to <28 weeks of gestation (preterm birth at the 2nd trimester) were 25 (0.3% out of all SGA infants and 18.4% out of 134 preterm birth infants at the 2nd trimester). SGA infants born in 28 to <37 weeks of gestation (preterm birth at the 3rd trimester) were 555 (7.7% out of all SGA infants and 13.4% of 4,147 preterm birth infants at the 3rd trimester). SGA infants of preterm birth were a minority among all preterm birth infants in the present study. Therefore, we consider that our results showed an almost two-fold increase in preterm birth at the 2nd trimester of gestation; however, up to 18% increased relative risk of SGA for prenatal caffeine level was noted.

Strengths and Limitations of the Study

The strength of this study was that it included data from 94,876 Japanese pregnant women to elucidate the association between prenatal caffeine consumption and both infant birthweight for gestational age and SGA risk. However, the study has some limitations. The data obtained for caffeine intake during pregnancy based on FFQ is less reliable than that based on chemical analysis. However, caffeine has a very short half-life and is difficult to determine using chemical analysis.[15] Furthermore, the results of FFQ may be inaccurate due to the lack of information regarding decaffeinated black tea and

coffee; caffeine consumption derived from energy drinks, medicinal, and over-the-counter drugs during pregnancy; and nausea and vomiting related changes in food preferences and diet during pregnancy, although we used the validated FFQ that has been documented in published studies.[17,19] The FFQ in the present study has not been validated for use with pregnant Japanese women. However, this FFQ was a modified questionnaire of the FFQ validated for use with pregnant Japanese women.[31] The National Health and Nutrition Survey in Japan in 2017 showed that the mean intake of tea in women aged 20-29 years and 30-39 years is 233.7 g/day and 180.1 g/day, respectively, and the mean intake of coffee and cocoa in women aged 20-29 years and 30-39 years is 64.8 g/day and 127.6 g/day, respectively.[32] Caffeine consumption per day changed from the above-mentioned data, using the Standard Tables of Food Composition in Japan,[20] which are higher than ours. This discrepancy may be derived from a kind of tea (e.g., high-quality green tea, middle-quality green tea, or roasted green tea) and the type of method used (food weighing method versus FFQ). The results of the present study must therefore be interpreted with care. Data for both confounding factors and birth outcome were missing for over 10,000 fetuses. Therefore, we analyzed the association between prenatal caffeine consumption and birth outcome using multiple imputation to account for the missing values. This confirmed that the original results were similar to those obtained using the imputed data.

Conclusion

Our findings demonstrate that prenatal caffeine levels are associated with an increased risk of SGA and preterm birth at the 2nd trimester of gestation and a reduced birthweight Z-score and gestational age. However, as the association between prenatal caffeine consumption and birth size was likely confounded by unpredicted potential factors, our confidence in the true causality of the association is moderate. Therefore, to verify our findings, it is essential to examine more well-designed studies in the future. Further studies on the interaction of smoking with caffeine consumption during pregnancy are also required to advance the results of this study.

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Appendix 1. Members of the Japan Environment and Children's Study (JECS) Group 2018

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Competing interests

None declared.

Figure legends

Figure 1. Flow diagram of participants enrolled in the Japan Environment and Children's Study.

Abbreviations: BMI: body mass index; Dr-0m, medical-record transcription data at birth; Dr-T1, medical-record transcription data during the first trimester; M-T1, maternal questionnaire during the first trimester; M-T2 maternal questionnaire during the second and third trimesters.

Figure 2. Histogram of estimated caffeine consumption during pregnancy (mg/day) for pregnant women enrolled in the Japan Environment and Children's Study.

Figure 1.

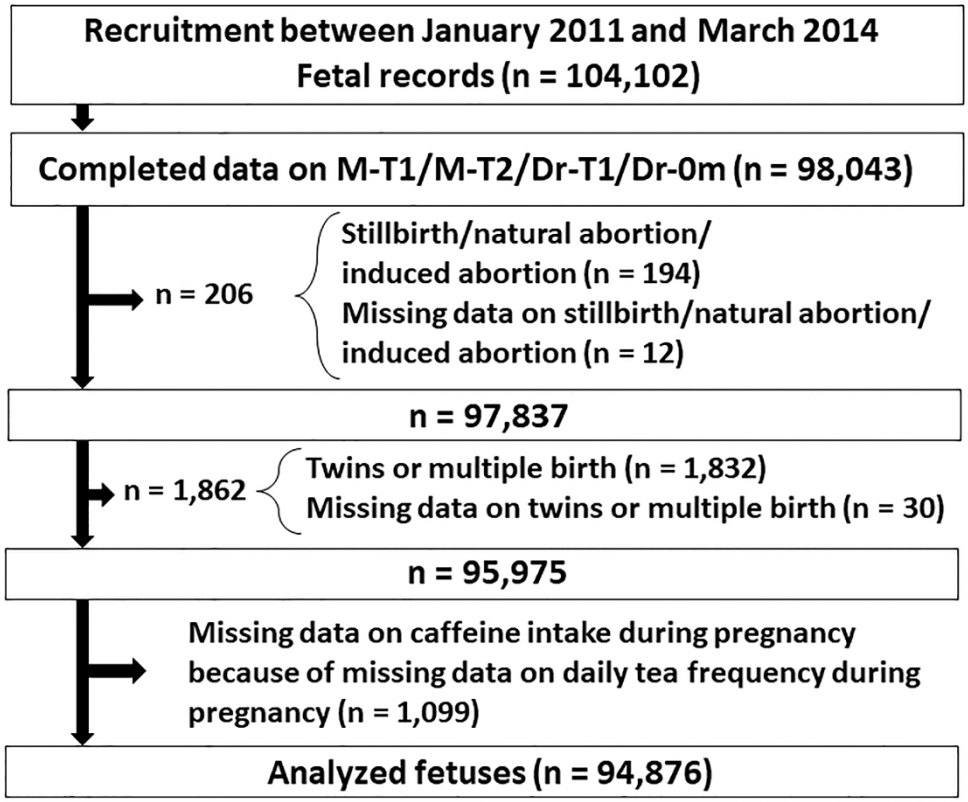
Recruitment between January 2011 and March 2014
Fetal records (n = 104,102)
Completed data on M-T1/M-T2/Dr-T1/Dr-0m (n = 98,043)
n = 206
Stillbirth/natural abortion/
induced abortion (n = 194)
Missing data on stillbirth/natural abortion/
induced abortion (n = 12)
n = 97,837
n = 1,862
Twins or multiple birth (n = 1,832)
Missing data on twins or multiple birth (n = 30)
n = 95,975
Missing data on caffeine intake during pregnancy
because of missing data on daily tea frequency during
pregnancy (n = 1,099)
Analyzed fetuses (n = 94,876)

Figure 2.

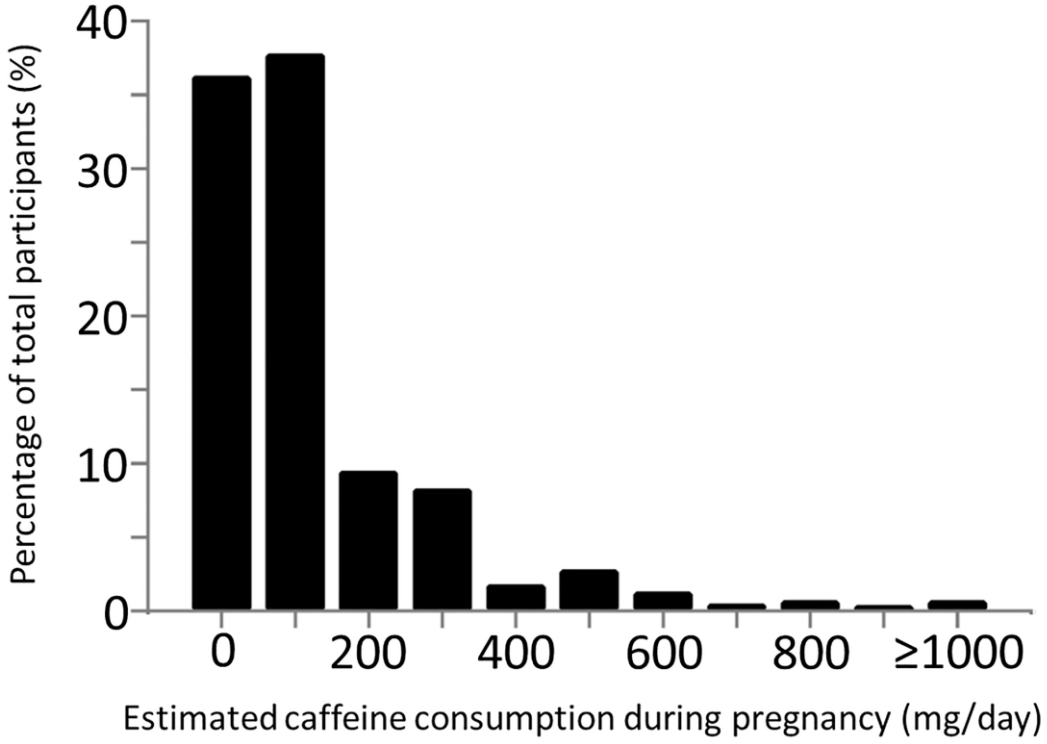
40
30
20
10
0
Percentage of total participants (%)
0
200
400
600
800
≥1000
Estimated caffeine consumption during pregnancy (mg/day)

Table 1. Characteristics of participants enrolled in the Japan Environment and Children's Study.

		Estimated caffeine consumption during pregnancy (mg/day)			
	All	Quartile 1	Quartile 2	Quartile 3	Quartile 4
		(4.2 to <86.4)	(86.4 to <125.5)	(125.5 to <205.5)	(205.5 to 5,080.0)
Characteristics	(n = 94,876)	(n = 23,816)	(n = 23,623)	(n = 23,720)	(n = 23,717)
Infants					
Sex					
Male	48,618 (51.2)	12,203 (51.2)	12,098 (51.2)	12,084 (50.9)	12,233 (51.6)
Female	46,253 (48.8)	11,612 (48.8)	11,524 (48.8)	11,634 (49.0)	11,483 (48.4)
Missing data	5 (0.0)	1 (0.0)	1 (0.0)	2 (0.0)	1 (0.0)
Birthweight (g)	3,026.5 (413.2)	3,026.8 (410.1)	3,035.3 (414.1)	3,024.9 (414.7)	3,019.1 (413.7)
SGA	7,252 (7.6)	1,671 (7.0)	1,763 (7.5)	1,896 (8.0)	1,922 (8.1)
Preterm birth	4,281 (4.5)	1,090 (4.6)	991 (4.2)	1,084 (4.6)	1,116 (4.7)
Preterm birth at the 2nd trimester	134 (0.1)	22 (0.1)	34 (0.1)	42 (0.2)	36 (0.2)
Preterm birth at the 3rd trimester	4,147 (4.4)	1,068 (4.5)	957 (4.1)	1,042 (4.4)	1,080 (4.6)
Birthweight Z-score	0.06 (0.98)	0.10 (0.99)	0.08 (0.98)	0.05 (0.97)	0.03 (0.97)
Gestational age (weeks)	38.8 (1.5)	38.9 (1.5)	38.9 (1.5)	38.8 (1.6)	38.8 (1.6)
Mothers					
Age (years)	31.2 (5.0)	30.9 (5.0)	30.9 (5.0)	31.4 (4.9)	31.6 (5.1)
BMI before pregnancy (kg/m^2)	21.2 (3.3)	21.1 (3.2)	21.2 (3.3)	21.2 (3.2)	21.3 (3.4)
Total energy intake (kcal)	1,746.6 (764.7)	1,580.7 (621.2)	1,670.6 (609.9)	1,792.8 (690.7)	1,942.7 (1,015.1)
Parity					
Primiparous	39,175 (41.3)	12,418 (52.1)	10,051 (42.5)	8,734 (36.8)	7,972 (33.6)
Multiparous	55,403 (58.4)	11,310 (47.5)	13,502 (57.2)	14,913 (62.9)	15,678 (66.1)
Missing data	298 (0.3)	88 (0.4)	70 (0.3)	73 (0.3)	67 (0.3)
Smoking during pregnancy					
No	77,111 (81.3)	20,427 (85.8)	19,164 (81.1)	18,932 (79.8)	18,588 (78.4)
Yes	17,196 (18.1)	3,272 (13.7)	4,316 (18.3)	4,635 (19.5)	4,973 (21.0)
Missing data	569 (0.6)	117 (0.5)	143 (0.6)	153 (0.6)	156 (0.7)
Drinking during pregnancy					
No	47,906 (50.5)	12,680 (53.2)	11,574 (49.0)	11,612 (49.0)	12040 (50.8)
Yes	46,504 (49.1)	11,034 (46.3)	11,938 (50.5)	12,001 (50.6)	11591 (48.9)
Missing data	406 (0.4)	102 (0.4)	111 (0.5)	107 (0.5)	86 (0.4)
Education levels (years)					
<13	34,201 (36.0)	8,324 (35.0)	8,635 (36.6)	8,489 (35.8)	8,753 (36.9)
≥13	60,333 (63.6)	15,399 (64.7)	14,915 (63.1)	15,136 (63.8)	14,883 (62.8)
Missing data	342 (0.4)	93 (0.4)	73 (0.3)	95 (0.4)	81 (0.3)
Annual household income (million JPY)					
<4	35,550 (37.5)	9,112 (38.3)	8,863 (37.5)	8,642 (36.4)	8,933 (37.7)
≥4	52,936 (55.8)	12,996 (54.6)	13,176 (55.8)	13,529 (57.0)	13,235 (55.8)
Missing data	6,390 (6.7)	1,708 (7.2)	1,584 (6.7)	1549 (6.5)	1,549 (6.5)
Pregnancy-induced hypertension	3,296 (3.5)	807 (3.4)	790 (3.3)	825 (3.5)	874 (3.7)
Gestational diabetes	2,979 (3.1)	741 (3.1)	662 (2.8)	748 (3.2)	828 (3.5)

Data is presented as n (%) or mean (standard deviation).

Notes: Birthweight was defined as the weight of each infant at birth.

SGA was defined as a birth weight of less than the 10th percentile, combined infant sex, parity, and gestational age according to the Japan Pediatric Society.[22]

Preterm birth, preterm birth at the 2nd trimester, and preterm birth at the 3rd trimester were defined as infants born at 22 to <37 weeks of gestation, infants born at 22 to <28 weeks of gestation, and infants born at 28 to <37 weeks of gestation, respectively.[24]

Birthweight Z-score (SD-score) was defined as a standard deviation of birthweight for gestational age in the normal distribution, combined infant sex, parity, and gestational age according to the Japan Pediatric Society.[22]

Gestational age was defined as the period from the last menstrual first day to the birth day.

Data presented as n (%) or mean (SD).

Abbreviations: SGA: small-for-gestational-age; BMI, body mass index; JPY, Japanese yen; SD, standard deviation.

Table 2. Cox regression model and multiple linear regression model of estimated caffeine consumption during pregnancy based on food frequency questionnaires according to small-for-gestational-age, preterm birth, gestational age, and birthweight Z-score for pregnant women enrolled in the Japan Environment and Children's Study

	Estimated caffeine consumption during pregnancy (mg/day)	SGA (n_{case} = 7,252)	Preterm birth (22 to <37 weeks) (n_{case} = 4,281)	Preterm birth at the 2nd trimester (22 to <28 weeks) (n_{case} = 134)	Preterm birth at the 3rd trimester (28 to <37 weeks) (n_{case} = 4,147)	Gestational age (days)	Birthweight Z-score (SD-score)
		RR[a,b] (95% CI)	RR[a,c] (95% CI)	RR[a,c] (95% CI)	RR[a,c] (95% CI)	β[d,e] (95% CI)	β[d,f] (95% CI)
Original data	Quartile 1 (4.2 to <86.4)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	0.00 (Reference)	0.00 (Reference)
(Without imputation)	Quartile 2 (86.4 to <125.5)	1.07 (1.00, 1.15)	0.92 (0.84, 1.00)	1.58 (0.91, 2.76)	0.90 (0.82, 0.99)	0.14 (-0.06, 0.34)	-0.02 (-0.04, 0.00)
	Quartile 3 (125.5 to <205.5)	1.17 (1.09, 1.26)	0.98 (0.90, 1.07)	1.96 (1.14, 3.37)	0.96 (0.88, 1.05)	-0.12 (-0.32, 0.08)	-0.05 (-0.07, -0.04)
	Quartile 4 (205.5 to 5,080.0)	1.18 (1.10, 1.27)	0.99 (0.91, 1.09)	1.94 (1.12, 3.37)	0.97 (0.89, 1.07)	-0.32 (-0.52, -0.12)	-0.07 (-0.09, -0.05)
30 pooled data	Quartile 1 (4.2 to <86.4)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	0.00 (Reference)	0.00 (Reference)
(With imputation)	Quartile 2 (86.4 to <125.5)	1.07 (1.06, 1.08)	0.91 (0.90, 0.93)	1.63 (1.48, 1.80)	0.90 (0.88, 0.91)	0.13 (0.10, 0.17)	-0.02 (-0.04, 0.00)
	Quartile 3 (125.5 to <205.5)	1.16 (1.14, 1.17)	0.98 (0.97, 1.00)	2.06 (1.88, 2.26)	0.96 (0.95, 0.98)	-0.13 (-0.17, -0.09)	-0.05 (-0.07, -0.03)
	Quartile 4 (205.5 to 5,080.0)	1.18 (1.17, 1.19)	0.99 (0.98, 1.01)	1.79 (1.62, 1.97)	0.98 (0.96, 0.99)	-0.33 (-0.37, -0.29)	-0.07 (-0.09, -0.05)

Notes: SGA was defined as a birth weight of less than the 10th percentile, combined infant sex, parity, and gestational age according to the Japan Pediatric Society.[22]

Preterm birth, preterm birth at the 2nd trimester, and preterm birth at the 3rd trimester were defined as infants born at 22 to <37 weeks of gestation, infants born at 22 to <28 weeks of gestation, and infants born at 28 to <37 weeks of gestation, respectively.[24]

Gestational age was defined as the period from the last menstrual first day to the birth day.

Birthweight Z-score (SD-score) was defined as the standard deviation of birthweight for gestational age in the normal distribution, combined infant sex, parity, and gestational age according to the Japan Pediatric Society.[22]

Abbreviations: CI, confidence interval; RR, relative risk; SD, standard deviation; SGA, small-for-gestational-age.

[a] RR is the relative risk compared to that of infants of mothers with the quartile 1 (4.2 to <86.4 mg/day) of estimated caffeine consumption during pregnancy.

[b] β is the change in gestational age (days), birthweight Z-score or birthweight (g) compared to that of infants of mothers with the quartile 1 (4.2 to <86.4 mg/day) of estimated caffeine consumption during pregnancy.

[c] Cox regression models are adjusted for maternal age, maternal body mass index before pregnancy, smoking during pregnancy, drinking during pregnancy, maternal education level, annual household income, and total energy intake. The variable of survival time is defined as gestational age (days).

[d] Cox regression models are adjusted for maternal age, maternal body mass index before pregnancy, smoking during pregnancy, drinking during pregnancy, maternal education level, annual household income, total energy intake, parity, and infant sex. The variable of survival time is defined as gestational age (days).

[e] Multiple linear regression models are adjusted for smoking during pregnancy, drinking during pregnancy, maternal education level, annual household income, and total energy intake.

[f] Multiple linear regression models are adjusted for maternal age, maternal body mass index before pregnancy, smoking during pregnancy, drinking during pregnancy, maternal education level, annual household income, and total energy intake.

eTable 1. Distribution of estimated caffeine consumption during pregnancy and the year prior to pregnancy based on food frequency questionnaires for pregnant women enrolled in the Japan Environment and Children's Study

		Estimated caffeine consumption (mg/day)					
	Median (Inter-quartile range)	Mean	Minimum	25th percentiles	Median	75th percentiles	Maximum
During pregnancy (mg/day)							
Total caffeine intake	100.0 %	185.8	4.2	86.4	125.5	205.5	5,080.0
From green tea	37.0 (32.0, 56.1) %	101.8	0.0	28.0	35.0	100.0	2,000.0
From oolong tea	8.6 (5.2, 11.1) %	15.7	0.0	8.4	8.4	10.5	600.0
From black tea	17.6 (10.4, 22.2) %	24.9	0.0	16.8	16.8	21.0	1,200.0
From coffee	28.1 (17.6, 33.3) %	43.4	0.0	22.4	25.9	47.5	1,600.0
Year prior to pregnancy (mg/day)							
Total caffeine intake	100.0 %	226.8	0.0	106.4	161.6	276.0	4,900.0
From green tea	40.4 (29.9, 59.9) %	123.9	0.0	35.0	64.0	121.0	2,000.0
From oolong tea	7.3 (4.1, 11.1) %	19.1	0.0	8.4	8.4	12.6	600.0
From black tea	14.5 (8.4, 21.9) %	28.4	0.0	16.8	21.0	25.2	1,200.0
From coffee	26.5 (15.3, 36.7) %	55.4	0.0	22.4	30.1	65.4	1,600.0

eTable 2. Estimated caffeine consumption during pregnancy based on food frequency questionnaires, small-for-gestational-age, and preterm birth for pregnant women enrolled in Japan Environment and Children's Study

Estimated caffeine consumption during pregnancy (mg/day)	All (n = 94,876)	SGA (n = 7,252)	Preterm birth (22 to <37 weeks) (n = 4,281)	Preterm birth at the 2nd trimester (22 to <28 weeks) (n = 134)	Preterm birth at the 3rd trimester (28 to <37 weeks) (n = 4,147)
	n (%)	n (%)	n (%)	n (%)	n (%)
0 to <100	34,468 (36.3)	2,433 (7.1)	1,552 (4.5)	38 (0.1)	1,514 (4.4)
100 to <200	35,837 (37.8)	2,828 (7.9)	1,579 (4.4)	59 (0.2)	1,520 (4.2)
200 to <300	8,993 (9.5)	705 (7.8)	410 (4.6)	14 (0.2)	396 (4.4)
300 to <400	7,903 (8.3)	628 (7.9)	359 (4.5)	12 (0.2)	347 (4.4)
400 to <500	1,691 (1.8)	162 (9.6)	90 (5.3)	4 (0.2)	86 (5.1)
500 to <600	2,703 (2.8)	220 (8.1)	143 (5.3)	4 (0.1)	139 (5.1)
600 to <700	1,247 (1.3)	107 (8.6)	60 (4.8)	1 (0.1)	59 (4.7)
700 to <800	452 (0.5)	46 (10.2)	13 (2.9)	0 (0.0)	13 (2.9)
800 to <900	629 (0.7)	41 (6.5)	32 (5.1)	0 (0.0)	32 (5.1)
900 to <1,000	246 (0.3)	20 (8.1)	10 (4.1)	1 (0.4)	9 (3.7)
≥1,000	707 (0.7)	62 (8.8)	33 (4.7)	1 (0.1)	32 (4.5)

Abbreviations: SGA, small-for-gestational-age.

eTable 3. Distribution of estimated caffeine consumption during pregnancy and the year prior to pregnancy based on food frequency questionnaires for pregnant women enrolled in the Japan Environment and Children's Study.

		Estimated caffeine consumption during pregnancy (mg/day)			
	All	Quartile 1 (4.2 to <86.4)	Quartile 2 (86.4 to <125.5)	Quartile 3 (125.5 to <205.5)	Quartile 4 (205.5 to 5,080.0)
	(n = 94,876)	(n = 23,816)	(n = 23,623)	(n = 23,720)	(n = 23,717)
Caffeine during pregnancy in comparison with the year before pregnancy					
Total caffeine intake					
Increased	30,281 (31.9)	1,567 (6.6)	5,582 (23.6)	8,881 (37.4)	14,251 (60.1)
No change	6,222 (6.6)	3,176 (13.3)	986 (4.2)	938 (4.0)	1,122 (4.7)
Decreased	57,753 (60.9)	18,895 (79.3)	16,933 (71.7)	13,750 (58.0)	8,175 (34.5)
Stopped	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing data[a]	620 (0.7)	178 (0.7)	122 (0.5)	151 (0.6)	169 (0.7)
Green tea					
Increased	23,020 (24.3)	771 (3.2)	3,741 (15.8)	6,981 (29.4)	11,527 (48.6)
No change	27,503 (29.0)	9,235 (38.8)	7,247 (30.7)	5,852 (24.7)	5,169 (21.8)
Decreased	43,555 (45.9)	13,498 (56.7)	12,500 (52.9)	10,717 (45.2)	6,840 (28.8)
Stopped	178 (0.2)	134 (0.6)	13 (0.1)	19 (0.1)	12 (0.1)
Missing data[a]	620 (0.7)	178 (0.7)	122 (0.5)	151 (0.6)	169 (0.7)
Oolong tea					
Increased	14,110 (14.9)	1,193 (5.0)	3,334 (14.1)	4,585 (19.3)	4,998 (21.1)
No change	50,853 (53.6)	13,996 (58.8)	12,494 (52.9)	12,111 (51.1)	12,252 (51.7)
Decreased	28,921 (30.5)	8,282 (34.8)	7,621 (32.3)	6,826 (28.8)	6,192 (26.1)
Stopped	372 (0.4)	167 (0.7)	52 (0.2)	47 (0.2)	106 (0.4)
Missing data[a]	620 (0.7)	178 (0.7)	122 (0.5)	151 (0.6)	169 (0.7)
Black tea					
Increased	17,545 (18.5)	1,298 (5.5)	4,686 (19.8)	5,550 (23.4)	6,011 (25.3)
No change	45,799 (48.3)	13,234 (55.6)	10,869 (46.0)	10,770 (45.4)	10,926 (46.1)
Decreased	30,599 (32.3)	8,951 (37.6)	7,910 (33.5)	7,213 (30.4)	6,525 (27.5)
Stopped	313 (0.3)	155 (0.7)	36 (0.2)	36 (0.2)	86 (0.4)
Missing data[a]	620 (0.7)	178 (0.7)	122 (0.5)	151 (0.6)	169 (0.7)
Coffee					
Increased	20,554 (21.7)	1,405 (5.9)	5,174 (21.9)	6,740 (28.4)	7,235 (30.5)

No change	35,351 (37.3)	11,901 (50.0)	7,851 (33.2)	7,420 (31.3)	8,179 (34.5)
Decreased	38,040 (40.1)	10,162 (42.7)	10,448 (44.2)	9,380 (39.5)	8,050 (33.9)
Stopped	311 (0.3)	170 (0.7)	28 (0.1)	29 (0.1)	84 (0.4)
Missing data[a]	620 (0.7)	178 (0.7)	122 (0.5)	151 (0.6)	169 (0.7)

Notes: Data are presented as n (%).

[a] Missing data due to the lack of data of caffeine consumption during the year before pregnancy.

eTable 4. Cox regression model and multiple linear regression model of estimated caffeine consumption during pregnancy based on food frequency questionnaires according to small-for-gestational-age, preterm birth, gestational age, and birthweight Z-score for pregnant smokers and non-smokers enrolled in the Japan Environment and Children's Study

Smoking status during pregnancy	Data	Estimated caffeine consumption during pregnancy (mg/day)	SGA	Preterm birth (22 to <37 weeks)	Preterm birth at the 2nd trimester (22 to <28 weeks)	Preterm birth at the 3rd trimester (28 to <37 weeks)	Gestational age (days)	Birthweight Z-score (SD-score)
			RR[a,c] (95% CI)	RR[a,d] (95% CI)	RR[a,d] (95% CI)	RR[a,d] (95% CI)	β[b,e] (95% CI)	β[b,f] (95% CI)
Non-smokers	Original data (Without imputation)	Quartile 1 (4.2 to <86.4)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	0.00 (Reference)	0.00 (Reference)
		Quartile 2 (86.4 to <125.5)	1.04 (0.96, 1.12)	0.92 (0.83, 1.01)	1.54 (0.85, 2.78)	0.90 (0.82, 1.00)	0.16 (-0.06, 0.38)	-0.02 (-0.04, 0.00)
		Quartile 3 (125.5 to <205.5)	1.13 (1.05, 1.22)	0.97 (0.88, 1.07)	1.87 (1.04, 3.35)	0.95 (0.86, 1.05)	-0.11 (-0.33, 0.11)	-0.05 (-0.07, -0.03)
		Quartile 4 (205.5 to 5,080.0)	1.10 (1.02, 1.19)	0.94 (0.86, 1.04)	1.87 (1.04, 3.38)	0.93 (0.84, 1.02)	-0.20 (-0.42, 0.02)	-0.06 (-0.08, -0.04)
	30 pooled data (With imputation)	Quartile 1 (4.2 to <86.4)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	0.00 (Reference)	0.00 (Reference)
		Quartile 2 (86.4 to <125.5)	1.04 (1.03, 1.06)	0.90 (0.89, 0.92)	1.52 (1.37, 1.68)	0.89 (0.88, 0.91)	0.16 (0.12, 0.20)	-0.02 (-0.02, -0.02)
		Quartile 3 (125.5 to <205.5)	1.12 (1.11, 1.14)	0.96 (0.94, 0.98)	1.92 (1.74, 2.13)	0.94 (0.93, 0.96)	-0.11 (-0.15, -0.07)	-0.05 (-0.05, -0.04)
		Quartile 4 (205.5 to 5,080.0)	1.11 (1.09, 1.12)	0.94 (0.92, 0.95)	1.74 (1.57, 1.93)	0.92 (0.91, 0.94)	-0.20 (-0.24, -0.16)	-0.06 (-0.07, -0.06)
Smokers	Original data (Without imputation)	Quartile 1 (4.2 to <86.4)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	0.00 (Reference)	0.00 (Reference)
		Quartile 2 (86.4 to <125.5)	1.29 (1.08, 1.55)	0.97 (0.77, 1.23)	1.97 (0.38, 10.2)	0.95 (0.75, 1.21)	0.03 (-0.51, 0.56)	-0.07 (-0.12, -0.03)
		Quartile 3 (125.5 to <205.5)	1.44 (1.21, 1.72)	1.11 (0.88, 1.39)	2.65 (0.54, 12.9)	1.08 (0.86, 1.36)	-0.23 (-0.76, 0.29)	-0.14 (-0.19, -0.09)
		Quartile 4 (205.5 to 5,080.0)	1.63 (1.38, 1.93)	1.25 (1.01, 1.56)	2.48 (0.50, 12.3)	1.24 (0.99, 1.54)	-0.86 (-1.39, -0.34)	-0.17 (-0.22, -0.13)
	30 pooled data (With imputation)	Quartile 1 (4.2 to <86.4)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	0.00 (Reference)	0.00 (Reference)
		Quartile 2 (86.4 to <125.5)	1.27 (1.23, 1.31)	1.01 (0.97, 1.05)	2.61 (1.97, 3.45)	0.99 (0.95, 1.03)	-0.01 (-0.10, 0.09)	-0.06 (-0.07, -0.06)
		Quartile 3 (125.5 to <205.5)	1.40 (1.36, 1.44)	1.15 (1.11, 1.20)	3.20 (2.44, 4.21)	1.12 (1.08, 1.16)	-0.27 (-0.36, -0.17)	-0.13 (-0.14, -0.13)
		Quartile 4 (205.5 to 5,080.0)	1.56 (1.52, 1.61)	1.30 (1.25, 1.35)	2.38 (1.80, 3.16)	1.28 (1.23, 1.33)	-0.89 (-0.99, -0.80)	-0.16 (-0.17, -0.15)

Notes: SGA was defined as a birth weight of less than the 10th percentile, combined infant sex, parity, and gestational age according to the Japan Pediatric Society.[22]
Preterm birth, preterm birth at the 2nd trimester, and preterm birth at the 3rd trimester were defined as infants born at 22 to <37 weeks of gestation, infants born at 22 to <28 weeks of gestation, and infants born at 28 to <37 weeks of gestation, respectively.[24]
Gestational age was defined as the period from the last menstrual first day to the birth day.
Birthweight Z-score (SD-score) was defined as the standard deviation of birthweight for gestational age in the normal distribution, combined infant sex, parity, and gestational age according to the Japan Pediatric Society.[22]
Abbreviations: CI, confidence interval; RR, relative risk; SD, standard deviation; SGA, small-for-gestational-age.
[a] RR is the relative risk compared to that of infants of mothers with the quartile 1 (4.2 to <86.4 mg/day) of estimated caffeine consumption during pregnancy.
[b] β is the change in gestational age (days), birthweight Z-score or birthweight (g) compared to that of infants of mothers with the quartile 1 (4.2 to <86.4 mg/day) of estimated caffeine consumption during pregnancy.
[c] Cox regression models are adjusted for maternal age, maternal body mass index before pregnancy, drinking during pregnancy, maternal education level, annual household income, and total energy intake. The variable of survival time is defined as gestational age (days).
[d] Cox regression models are adjusted for maternal age, maternal body mass index before pregnancy, drinking during pregnancy, maternal education level, annual household income, total energy intake, parity, and infant sex. The variable of survival time is defined as gestational age (days).
[e] Multiple linear regression models are adjusted for drinking during pregnancy, maternal education level, annual household income, and total energy intake.
[f] Multiple linear regression models are adjusted for maternal age, maternal body mass index before pregnancy, drinking during pregnancy, maternal education level, annual household income, and total energy intake.