

Dose–response association between maternal smoking during pregnancy and the risk of infant death: a nationwide, population-based, retrospective cohort study



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Summary

Background Association of timing and intensity of maternal smoking during pregnancy with all-cause and cause-specific infant death remains inconclusive. We aimed to examine the dose–response association of maternal smoking during each of the three trimesters of pregnancy with all-cause and cause-specific infant death.

Methods In this nationwide, population-based, retrospective cohort study, data were extracted from the U.S. National Vital Statistics System, 2015–2019. We included mother–infant pairs after excluding twin or multiple births, newborns with gestation age <37 weeks and those with low birthweight, mothers aged <18 years or ≥50 years, mothers with pre-existing hypertension or diabetes, and those with missing values for variables of interest. Poisson regression models were used to examine the association of different intensities and doses of maternal smoking during each of the three trimesters of pregnancy with all-cause and cause-specific infant death attributed to congenital anomalies, preterm birth, other perinatal conditions, sudden unexpected infant death, and infection.

Findings A total of 13,524,204 mother–infant pairs were included in our analyses. Maternal smoking during the entire pregnancy was associated with infant all-cause death (relative risk [RR] 1.88, 95% confidence interval [95% CI] 1.79–1.97), cause-specific death due to preterm birth (1.57, 1.25–1.98), perinatal conditions excluding preterm birth (1.35, 1.10–1.65), sudden unexpected infant death (2.56, 2.40–2.73), and infection (1.51, 1.20–1.88). The risk of infant all-cause death (RR values from 1.80 to 2.15) and cause-specific infant death by preterm birth (RR values from 1.42 to 1.74), perinatal conditions excluding preterm birth (RR values from 1.46 to 1.53), sudden unexpected infant death (RR values from 2.37 to 3.04), and infection (RR values from 1.48 to 2.69) increased with the intensity of maternal cigarette use during the entire pregnancy from 1–5 to ≥11 cigarettes. Compared with mothers who smoked during their entire pregnancy, those who smoked in the first trimester and then quit smoking in the second or third trimesters of pregnancy had a reduced risk of infant all-cause death (0.71, 0.65–0.78) and sudden unexpected infant death (0.64, 0.57–0.72).

Interpretation There was a dose–response association of maternal cigarette use during each of the three trimesters of pregnancy with all-cause and cause-specific infant death. In addition, mothers who are smokers in the first trimester and then quit smoking in the subsequent two trimesters are at decreased risk of infant all-cause mortality and sudden unexpected infant death compared with those who smoked during the entire pregnancy. These findings suggest that there is no safe level of maternal smoking in any trimester of pregnancy and maternal smokers should stop smoking during pregnancy to improve the survival of infants.

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Keywords: Maternal smoking; Infant death; Pregnancy; Dose–response association

Research in context

Evidence before this study

Although several studies have shown a positive association between maternal smoking during pregnancy and infant death, limited attention has been paid to the timing and intensity of maternal smoking during pregnancy.

Previous meta-analysis treated cigarette smoking as a categorical variable instead of a continuous number of cigarettes smoked.

Current ambiguous conclusions on safe levels of maternal smoking for infant death might inadvertently confuse messaging and prevent policymakers from making recommendations on the prevention of maternal smoking during pregnancy.

Added value of this study

Maternal smoking during pregnancy was associated with infant all-cause death and cause-specific death by preterm

birth, other perinatal conditions excluding preterm birth, sudden unexpected infant death, and infection.

The odds of infant death increased with higher intensity of maternal cigarette use during any trimester of pregnancy. There was a dose–response association of maternal smoking in any trimester of pregnancy with all-cause and cause-specific infant death.

Implications of all the available evidence

There is no safe level of maternal smoking in any trimester of pregnancy in consideration of infant health.

More efforts are needed to prevent smoking for never smokers or promote smoking cessation during pregnancy for smokers to decrease all-cause and cause-specific infant deaths.

Introduction

Infant death accounts for a large fraction of death for children under 5 years of age worldwide.¹ This is further exacerbated by the prevalence of infant mortality increasing from 2000 to 2017, globally, as a proportion of overall child death under 5 years.² The U.S. National Center for Health Statistics showed that the infant mortality rate was 5.66 per 1000 living births in 2019,³ significantly higher than 10 other high-income countries.⁴ In the USA, a decrease of 0.03 infant deaths per 1000 live births needs a \$0.3 per-person increase in environmental cost and at least \$0.7 per-person increase in social service cost.⁵ Therefore, identifying and preventing modifiable causes of infant death could substantially reduce the economic and health burden in the USA.

Maternal smoking during pregnancy is considered an important cause of adverse infant health outcomes, such as birth defects, preterm birth, and low birthweight.³ In 2016, about 7.2% of reproductive women who gave birth to children used cigarettes during pregnancy.³ Birth defects, preterm birth, low birthweight, sudden infant death syndrome, and maternal pregnancy complications are leading causes of infant death in the USA.⁶ Although earlier studies have focused on the association between maternal smoking during pregnancy and infant death,^{7–9} limited attention has been paid to the timing and intensity of maternal smoking during pregnancy; and where data exist there are conflicting findings. For example, a population-based cohort study in Sweden of 555,046 mother–infant pairs showed that a low level of cigarette use during pregnancy (1–9 cigarettes per day)

did not increase the risk of infant mortality.⁹ However, a retrospective cross-sectional study of 20,685,463 mother–infant pairs showed that use of 1 cigarette per day during pregnancy could significantly increase the risk of sudden unexpected infant death.⁷ In addition, a meta-analysis of 142 articles published between 1948 and 2011 on the association of active maternal smoking with infant death was limited to the main exposure, cigarette smoking, being treated as a categorical variable instead of a continuous number of cigarettes smoked while elements of timing of smoke exposure were unable to be examined fully.⁸ Besides, in terms of infant cause-specific death, several studies have assessed the association between maternal smoking during pregnancy and sudden unexpected infant death.^{7,10–16} For example, two recent studies based on the U.S. Centers for Disease Control and Prevention Birth Cohort Linked Birth/Infant Death Dataset (2007–2011) and the Chicago Infant Mortality Study (1993–1996) showed that there was a linear dose–response association between maternal smoking during pregnancy and sudden unexpected infant death.^{7,11} However, the data mentioned above are much old, and other infant cause-specific death such as death due to congenital anomalies, preterm-related conditions, and infection are rarely mentioned in previous studies. The ambiguous conclusion on association of maternal smoking with infant death might confuse and prevent policymakers from making recommendations on prevention of maternal smoking during pregnancy.

Therefore, we aimed to quantitatively examine the association of maternal smoking during the three

trimesters of pregnancy with all-cause and cause-specific infant mortality based on a nationwide population-based large cohort in the USA.

Methods

Study design and data source

The nationwide birth and death certificate data were from the National Vital Statistics System (NVSS), cooperated with the National Center for Health Statistics (NCHS) and the States in the USA.¹⁷ The collection of data and uniform registration followed standard forms and model procedures to promote uniformity across all registration areas.¹⁷ The vital statistic data include birth, death, maternal status, and other events. Mothers' and facility worksheets for the birth certificates developed for the widely implemented 2003 revisions of the USA, standard certificates were used to collect information on demographics, smoking during pregnancy, and parental complications and care.^{18,19} Data on infant mortality and causes of death were collected from the USA standard certificate of death.²⁰ A detailed description of the NVSS, data collection, and user's guide is available online.^{17,21}

In this study, we extracted records of all live single births between 2015 and 2019 from cohort-linked birth and death databases.²² Of 19,368,715 mother–infant pairs, we excluded 5,844,511 because of twin or multiple births, newborns with gestation age <37 weeks and those with low birthweight, mothers aged <18 years or ≥50 years, mothers with pre-existing hypertension or diabetes, and those with missing values for variables of interest, leaving 13,524,204 for analysis. The criteria of inclusion and exclusion of participants were based on previous publications.^{23–28} Of note, we did not include infants with low birthweight or preterm birth because both variables were viewed as potential mediating factors in the causal pathway between maternal smoking during pregnancy and infant death,^{27,28} and we aimed to examine an independent effect of maternal smoking during pregnancy. In addition, infants with preterm birth or low birthweight usually have less cigarette exposure especially in the third trimester compared with full-term infants,²⁹ precluding us from performing additional analyses on the intensity of maternal smoking during pregnancy. The flow chart of inclusion/exclusion of participants is provided in Fig. 1. We followed STROBE reporting guidelines for our methodology.

Ethics

The birth certificate data from the National Vital Statistics System are de-identified and do not include any protected health information. The data are publicly available and exempt under the ethical board review of the corresponding author's institution.

Exposure measurement

Maternal smoking during pregnancy was defined according to the question “How many cigarettes OR packs of cigarettes did you smoke on an average day during the first, second, and third trimesters of pregnancy (tobacco products only, not including e-cigarettes)?”¹⁸ Mothers who smoked at least one cigarette per day in these three periods were classified as smokers in the corresponding trimesters of pregnancy. We also defined the intensity of cigarette use in each trimester of pregnancy as 0, 1–5, 6–10, and ≥11, respectively. The intensity of maternal smoking was classified according to previous studies to ensure enough statistical power in each subgroup.³⁰ If mothers who smoked in the first trimester of pregnancy had no cigarette use in the second and third trimesters, they were defined as having quit. A similar definition was also used for change in cigarette use from the second trimester to the third trimester. If the daily number of cigarette use in the second and third trimesters of pregnancy was less than twice the number in the first trimester, the mothers were defined as reduced smokers.⁷ A similar definition was applied for third versus second trimester.

Outcome measurement

All-cause and cause-specific infant death was defined according to the Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10), as: congenital anomalies, preterm-related death, death due to other perinatal conditions (i.e., other perinatal cause of death based on ICD-10, irrespective of prematurity), sudden unexpected infant death, and death due to infection (Table S1).

Covariates

Maternal worksheet was used to collect the following covariates: maternal age at delivery (as a continuous variable), race/ethnicity (Hispanic, White, Black, or other), maternal education level (less than high school, high school, or more than high school), marital status (unmarried or married), pre-pregnancy body mass index (as a continuous variable), maternal smoking intensity before pregnancy (as a continuous variable), the total number of prenatal visits (0, 1–4, 5–9, or ≥10 times), gestational weight gain (as a continuous variable), parity (1, 2, 3, or ≥4), and infant sex (biological sex assigned at birth: boy or girl). Facility worksheet was used to collect data on birthplace (in or out of hospital), gestational diabetes (yes or no), gestational hypertension (yes or no), eclampsia (yes or no), and delivery mode (vaginal or cesarean section).

Statistical analysis

Characteristics of continuous variables were presented as median and interquartile range (IQR) and categorical variables were presented as n (%). Poisson regression analyses were used to examine the association of

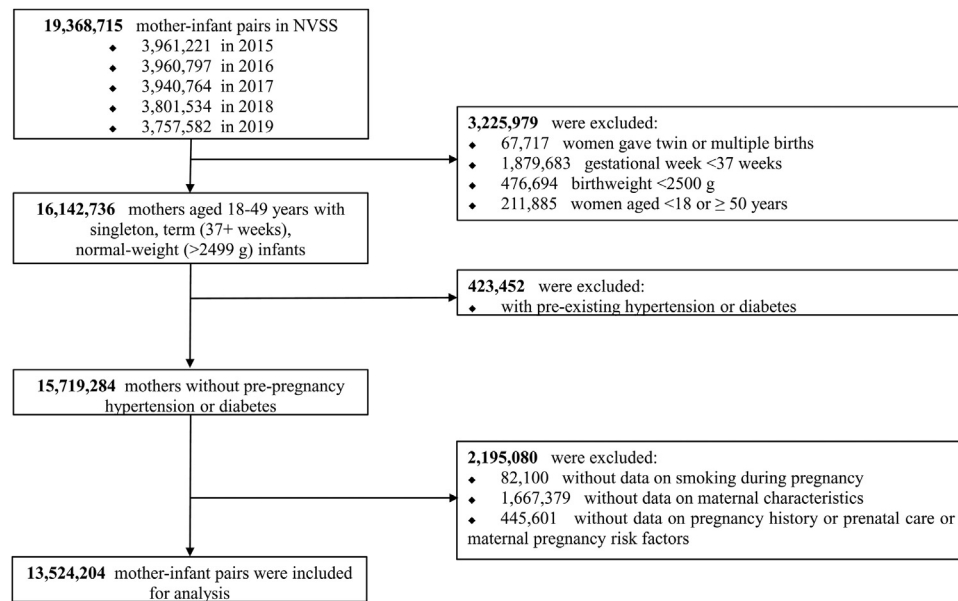


Fig. 1: Study profile.

maternal smoking during each trimester of pregnancy with all-cause and cause-specific infant death with adjustment of potential confounding factors including maternal age (as a continuous variable), race/ethnicity, education level, marital status, parity, the total number of prenatal care visits, weight gain during pregnancy (as a continuous variable), pre-pregnancy body mass index (as a continuous variable), maternal smoking intensity before pregnancy (as a continuous variable), gestational diabetes, gestational hypertension, eclampsia, infant sex, birthplace, and delivery method. Poisson regression analyses were repeated but stratified by the intensity of cigarette use at each trimester of pregnancy. We used logistic regression with restricted cubic splines to evaluate the dose–response association between maternal smoking at each trimester of pregnancy on a continuous scale and infant death with 3 knots 50th, 95th, and 97th percentiles of cigarette use per day. Imputation analyses based on the fully conditional specification method were used to fill missing data on variables of interest.³¹ We performed sensitivity analyses after imputing the missing data on variables of interest and with the inclusion of infants with preterm birth and low birthweight to test the stability of our main results. All analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC) and R version 4.4.2. A two-sided *P* value <0.05 indicated statistical significance.

Role of funding source

The funder of the study had no role in study design, data collection, data analyses, data interpretation, or writing of the report.

Results

A total of 13,524,204 mother–infant pairs (infant boys: 51.2%) were included, and the prevalence of cigarette smoking during the entire pregnancy, the first, second, and third trimesters of pregnancy was 6.68%, 6.51%, 5.51%, and 5.24%, respectively. Mothers who smoked in each trimester of pregnancy were more likely to be younger, non-Hispanic whites, and unmarried, and to have a lower educational level, more parities, fewer prenatal care visits, and more cesarean section and post-neonatal death (Table 1).

Among mothers who smoked during pregnancy, 4196, 384, 161, 216, 2530, and 178 infant deaths were attributed to all causes, congenital anomalies, preterm birth, other perinatal conditions excluding preterm birth, sudden unexpected infant death, and infection, respectively. After adjustment for potential covariates, maternal smoking during the entire pregnancy was associated with infant all-cause death (relative risk [RR] = 1.88, 95% confidence interval [CI] = 1.79–1.97) and cause-specific death by preterm birth (1.57, 1.25–1.98), perinatal death excluding preterm birth (1.35, 1.10–1.65), sudden unexpected infant death (2.56, 2.40–2.73), and infection (1.51, 1.20–1.88). Similar results were found in the first, second, and third trimesters of pregnancy (Table 2). Sensitivity analyses showed similar results after the imputation of missing values on variables of interest (Table S2) and with the inclusion of infants with preterm birth and low birthweight (Table S3).

When stratified by the intensity of cigarette use per day, the odds of infant all-cause death and cause-specific

Characteristics	Total	Smoking during pregnancy		Smoking in the first trimester		Smoking in the second trimester		Smoking in the third trimester	
		No	Yes	No	Yes	No	Yes	No	Yes
N	13,524,204	12,620,765	903,424	12,642,566	880,986	12,778,056	744,867	12,813,957	709,069
Maternal age at delivery, years									
Median (IQR)	29 (25–33)	29 (25–33)	26 (23–30)	29 (25–33)	26 (23–30)	29 (25–33)	26 (23–30)	29 (25–33)	26 (23–30)
Category, n (%)									
18–29	7,420,395 (54.9)	6,781,914 (53.7)	638,472 (70.7)	6,797,914 (53.8)	622,023 (70.6)	6,897,326 (54.0)	522,180 (70.1)	6,924,201 (54.0)	495,359 (69.9)
30–39	5,731,035 (42.4)	5,478,024 (43.4)	253,005 (28.0)	5,483,558 (43.4)	247,294 (28.1)	5,518,013 (43.2)	212,643 (28.6)	5,526,649 (43.1)	204,052 (28.8)
40–49	372,774 (2.8)	360,827 (2.9)	11,947 (1.3)	361,094 (2.9)	11,669 (1.3)	362,717 (2.8)	10,044 (1.4)	363,107 (2.8)	9658 (1.4)
Race/ethnicity, n (%)									
Hispanic	2,943,680 (21.8)	2,892,724 (22.9)	50,950 (5.6)	2,894,419 (22.9)	49,215 (5.6)	2,906,853 (22.8)	36,704 (4.9)	2,909,619 (22.7)	33,946 (4.8)
Non-Hispanic White	7,584,397 (56.1)	6,874,253 (54.5)	710,141 (78.6)	6,889,550 (54.5)	694,404 (78.8)	6,987,037 (54.7)	596,520 (80.1)	7,013,555 (54.7)	570,060 (80.4)
Non-Hispanic Black	1,792,723 (13.3)	1,703,473 (13.5)	89,246 (9.9)	1,706,605 (13.5)	86,030 (9.8)	86,030 (9.8)	69,908 (9.4)	1,726,872 (13.5)	65,698 (9.3)
Other	1,203,404 (8.9)	1,150,315 (9.1)	53,087 (5.9)	1,151,992 (9.1)	51,337 (5.8)	1,161,519 (9.1)	41,735 (5.6)	1,163,911 (9.1)	39,365 (5.6)
Educational level, n (%)									
Less than high school	1,577,579 (11.7)	1,371,159 (10.9)	206,418 (22.9)	1,376,186 (10.9)	201,204 (22.8)	1,396,530 (10.9)	180,749 (24.3)	1,402,431 (10.9)	174,903 (24.7)
High school	3,392,433 (25.1)	3,004,194 (23.8)	388,234 (43.0)	3,013,215 (23.8)	378,935 (43.0)	3,067,623 (24.0)	324,269 (43.5)	3,082,932 (24.1)	309,004 (43.6)
More than high school	8,554,192 (63.3)	8,245,412 (65.3)	308,772 (34.2)	8,253,165 (65.3)	300,847 (34.2)	8,313,903 (65.1)	239,849 (32.2)	8,328,594 (65.0)	225,162 (31.8)
Marital status, n (%)									
Married	8,441,506 (62.4)	8,188,649 (64.9)	252,851 (28.0)	8,194,784 (64.8)	246,568 (28.0)	8,234,394 (64.4)	206,793 (27.8)	8,243,213 (64.3)	197,994 (27.9)
Unmarried	5,082,698 (37.6)	4,432,116 (35.1)	650,573 (72.0)	4,447,782 (35.2)	634,418 (72.0)	4,543,662 (35.6)	538,074 (72.2)	4,570,744 (35.7)	511,075 (72.1)
Pre-pregnancy body mass index (BMI), kg/m², median (IQR)	25.3 (22.1–30.1)	25.3 (22.1–30.1)	25.8 (21.9–31.3)	25.3 (22.1–30.1)	25.8 (21.9–31.3)	25.3 (22.1–30.1)	25.7 (21.9–31.2)	25.3 (22.1–30.1)	25.7 (21.9–31.2)
Smoking before pregnancy, n (%)									
Yes	1,207,835 (8.9)	320,652 (2.5)	887,183 (98.2)	334,971 (2.6)	872,214 (99.0)	467,379 (3.7)	739,186 (99.2)	506,673 (4.0)	700,017 (98.7)
No	12,316,369 (91.1)	12,300,113 (97.5)	16,241 (1.8)	12,307,595 (97.4)	8772 (1.0)	12,310,677 (96.3)	5681 (0.8)	12,307,284 (96.0)	9052 (1.3)
Parity, n (%)									
1	5,130,991 (37.9)	4,861,231 (38.5)	269,754 (29.9)	4,868,469 (38.5)	262,325 (29.8)	4,928,633 (38.6)	201,885 (27.1)	4,943,336 (38.6)	187,212 (26.4)
2	4,466,016 (33.0)	4,189,329 (33.2)	276,682 (30.6)	4,195,839 (33.2)	270,006 (30.7)	4,235,360 (33.1)	230,292 (30.9)	4,246,144 (33.1)	219,526 (31.0)
3	2,319,382 (17.2)	2,127,608 (16.9)	191,770 (21.2)	2,131,853 (16.9)	187,380 (21.3)	2,153,486 (16.9)	165,670 (22.2)	2,159,732 (16.9)	159,445 (22.5)
≥4	1,607,815 (11.9)	1,442,597 (11.4)	165,218 (18.3)	1,446,405 (11.4)	161,275 (18.3)	1,460,577 (11.4)	147,020 (19.7)	1,464,745 (11.4)	142,886 (20.2)
Total number of prenatal care visits, n (%)									
0	164,422 (1.2)	141,777 (1.1)	22,642 (2.5)	22,642 (2.5)	22,159 (2.5)	143,658 (1.1)	20,736 (2.8)	144,115 (1.1)	20,287 (2.9)
1–4	413,465 (3.1)	354,959 (2.8)	58,504 (6.5)	356,361 (2.8)	57,041 (6.5)	361,418 (2.8)	51,955 (7.0)	363,156 (2.8)	50,233 (7.1)
5–9	2,558,589 (18.9)	2,338,036 (18.5)	220,551 (24.4)	2,343,543 (18.5)	214,858 (24.4)	2,371,258 (18.6)	187,007 (25.1)	2,379,789 (18.6)	178,501 (25.2)
≥10	10,387,728 (76.8)	9,785,993 (77.5)	601,727 (66.6)	9,800,423 (77.5)	586,928 (66.6)	9,901,722 (77.5)	485,169 (65.3)	9,926,897 (77.5)	460,048 (64.9)
Weight gain during pregnancy, pounds, median (IQR)	30 (20–39)	30 (21–39)	30 (19–41)	30 (21–39)	30 (19–41)	30.0 (21–39)	29 (18–40)	30 (21–39)	29 (18–40)
Gestational diabetes, n (%)	808,690 (6.0)	757,189 (6.0)	51,498 (5.7)	758,369 (6.0)	50,284 (5.7)	767,220 (6.0)	41,391 (5.6)	769,347 (6.0)	39,277 (5.5)

(Table 1 continues on next page)

Characteristics	Total	Smoking during pregnancy		Smoking in the first trimester		Smoking in the second trimester		Smoking in the third trimester	
		No	Yes	No	Yes	No	Yes	No	Yes
(Continued from previous page)									
Gestational hypertension, n (%)	753,742 (5.6)	703,113 (5.6)	50,624 (5.6)	704,281 (5.6)	49,426 (5.6)	713,850 (5.6)	39,805 (5.3)	716,358 (5.6)	37,295 (5.3)
Eclampsia, n (%)	21,859 (0.2)	20,417 (0.2)	1442 (0.2)	20,451 (0.2)	1407 (0.2)	20,698 (0.2)	1156 (0.2)	20,770 (0.2)	1086 (0.2)
Infant sex, n (%)									
Boy	6,924,492 (51.2)	6,458,061 (51.2)	466,419 (51.6)	6,469,095 (51.2)	455,059 (51.7)	6,538,253 (51.2)	385,577 (51.8)	6,556,723 (51.2)	367,156 (51.8)
Girl	6,599,712 (48.8)	6,162,704 (48.8)	437,005 (48.4)	6,173,471 (48.8)	425,927 (48.3)	6,239,803 (48.8)	359,290 (48.2)	6,257,234 (48.8)	341,913 (48.2)
Birth place, n (%)									
In hospital	13,278,897 (98.2)	12,379,742 (98.1)	899,141 (99.5)	12,401,436 (98.1)	876,820 (99.5)	12,536,235 (98.1)	741,396 (99.5)	12,571,947 (98.1)	705,790 (99.5)
Not in hospital	245,307 (1.8)	241,023 (1.9)	4283 (0.5)	241,130 (1.9)	4166 (0.5)	241,821 (1.9)	3471 (0.5)	242,010 (1.9)	3179 (0.5)
Delivery method, n (%)									
Vaginal	9,614,636 (71.1)	8,987,509 (71.2)	627,117 (69.4)	9,003,033 (71.2)	611,130 (69.4)	9,096,853 (71.2)	516,862 (69.4)	9,121,574 (71.2)	492,202 (69.4)
Cesarean	3,909,568 (28.9)	3,633,256 (28.8)	276,307 (30.6)	3,639,533 (28.8)	269,856 (30.6)	3,681,203 (28.8)	228,005 (30.6)	3,692,383 (28.8)	216,867 (30.6)
Age of death (alive infants are not included), days									
Median (IQR)	67 (16–141)	65 (13–142)	73 (34–137)	65 (13–142)	73 (34–137)	65 (13–141)	74 (35–137)	66 (13–141)	74 (35–137)
Category, n (%)									
0–6 days (early neonatal) ^a	4014 (17.3)	3660 (19.3)	354 (8.4)	3672 (19.3)	342 (8.4)	3729 (19.2)	284 (7.7)	3735 (19.1)	278 (7.8)
7–27 days (late neonatal) ^b	3148 (13.6)	2608 (13.8)	540 (12.9)	2622 (13.7)	525 (12.8)	2679 (13.8)	469 (12.7)	2695 (13.7)	453 (12.8)
28–366 days (postneonatal) ^c	15,995 (69.1)	12,693 (66.9)	3302 (78.7)	12,772 (67.0)	3221 (78.8)	13,039 (67.1)	2951 (79.7)	13,170 (67.2)	2822 (79.4)
IQR, interquartile range. ^a Early neonatal, deaths occurring within 0–6 days of birth. ^b Late neonatal, deaths occurring within 7–27 days of birth. ^c Postneonatal, deaths occurring within 28 days–12 months of birth.									

Table 1: Characteristics of the study population, by timing of maternal cigarette smoking.

Cause of infant death	Smoking during entire pregnancy		Smoking in the first trimester		Smoking in the second trimester		Smoking in the third trimester	
	No	Yes	No	Yes	No	Yes	No	Yes
All-cause								
n (/10,000)	18,961 (15.02)	4196 (46.45)	19,066 (15.08)	4088 (46.40)	19,447 (15.22)	3704 (49.73)	19,600 (15.30)	3553 (50.11)
RR (95% CI)	1.00	1.88 (1.79–1.97)	1.00	1.85 (1.76–1.94)	1.00	1.90 (1.81–2.00)	1.00	1.87 (1.78–1.96)
P-value		<0.001		<0.001		<0.001		<0.001
Congenital anomalies								
n (/10,000)	4595 (3.64)	384 (4.25)	4603 (3.64)	376 (4.27)	4658 (3.65)	320 (4.30)	4680 (3.65)	298 (4.20)
RR (95% CI)	1.00	0.94 (0.81–1.08)	1.00	0.94 (0.81–1.09)	1.00	0.93 (0.80–1.08)	1.00	0.89 (0.76–1.03)
P-value		0.373		0.405		0.340		0.125
Preterm-related								
n (/10,000)	843 (0.67)	161 (1.78)	850 (0.67)	154 (1.75)	871 (0.68)	133 (1.79)	874 (0.68)	130 (1.83)
RR (95% CI)	1.00	1.57 (1.25–1.98)	1.00	1.48 (1.18–1.86)	1.00	1.42 (1.12–1.79)	1.00	1.47 (1.16–1.86)
P-value		<0.001		<0.001		0.004		0.001
Other perinatal conditions								
n (/10,000)	1850 (1.47)	216 (2.39)	1856 (1.47)	210 (2.38)	1893 (1.48)	173 (2.32)	1896 (1.48)	170 (2.40)
RR (95% CI)	1.00	1.35 (1.10–1.65)	1.00	1.33 (1.08–1.62)	1.00	1.20 (0.98–1.48)	1.00	1.27 (1.03–1.56)
P-value		0.003		0.006		0.079		0.023
Sudden unexpected infant death (SUID)								
n (/10,000)	6930 (5.49)	2530 (28.00)	6995 (5.53)	2464 (27.97)	7191 (5.63)	2266 (30.42)	7277 (5.68)	2180 (30.74)
RR (95% CI)	1.00	2.56 (2.40–2.73)	1.00	2.49 (2.34–2.66)	1.00	2.56 (2.40–2.74)	1.00	2.52 (2.36–2.69)
P-value		<0.001		<0.001		<0.001		<0.001
Infection								
n (/10,000)	1014 (0.80)	178 (1.97)	1020 (0.81)	171 (1.94)	1027 (0.80)	164 (2.20)	1038 (0.81)	154 (2.17)
RR (95% CI)	1.00	1.51 (1.20–1.88)	1.00	1.49 (1.19–1.88)	1.00	1.78 (1.41–2.24)	1.00	1.61 (1.28–2.02)
P-value		<0.001		<0.001		<0.001		<0.001

CI, confidence interval; RR, risk ratio. Poisson regression models were adjusted for maternal age (as a continuous variable), race/ethnicity, education level, marital status, parity, total number of prenatal care visits, weight gain during pregnancy (as a continuous variable), pre-pregnancy body mass index (as a continuous variable), maternal smoking intensity before pregnancy (as a continuous variable), gestational diabetes, gestational hypertension, eclampsia, infant sex, birthplace, and delivery method. Preterm-related death in this analysis was defined by ICD 10 codes of K550, P000, P010, P011, P015, P020, P021, P027, P070–P073, P102, P220–229, P250–279, P280, P281, P360–369, P520–523, or P77.

Table 2: Association between timing of maternal cigarette smoking during each trimester of pregnancy and infant death.

death by preterm birth, perinatal death excluding preterm birth, sudden unexpected infant death, and infection significantly increased with higher intensity of cigarette use during the entire pregnancy (Table 3). Similar results were found for maternal cigarette use in the first, second, and third trimesters of pregnancy (Tables S4–S6).

Logistic regression with restricted spines showed a dose–response association between maternal cigarette use during pregnancy and infant all-cause death (Fig. 2) and cause-specific death by preterm birth, perinatal death excluding preterm birth, sudden unexpected, and infection, regardless of trimesters of pregnancy (Figs. S1–S4).

Among 242,014 and 190,307 mothers, respectively, who smoked in the first trimester and then reduced and quit smoking in the subsequent trimesters, 1172 and 627 infants, respectively, died due to all-cause, respectively. Compared with mothers who smoked during their entire pregnancy, those who smoked in the first trimester and then quit smoking in the subsequent two trimesters of pregnancy had a reduced risk of infant

all-cause death (0.71, 0.65–0.78) and sudden unexpected infant death (0.64, 0.57–0.72) (Table 4). However, there was no significant change in the odds of all-cause among those who smoked in the second trimester and then reduced or quit smoking in the third trimester (Table S7).

Discussion

In this large-scale nationwide population-based retrospective cohort study including 13,524,204 USA mother–infant pairs between 2015 and 2019, maternal smoking during pregnancy was associated with increased odds of infant all-cause death and cause-specific death by preterm birth, other perinatal conditions excluding preterm birth, sudden unexpected infant death, and infection. The odds of infant death increased with the intensity of maternal cigarette use during each trimester of pregnancy. In addition, there was a dose–response association of maternal smoking in any trimester of pregnancy with all-cause and cause-specific infant death.

Cause of infant death	Number of cigarettes consumed per day					P for trend
	Continuous	0	1-5	6-10	≥11	
All-cause						
n (/10,000)	4152 (46.72)	18,998 (15.04)	1544 (41.57)	1540 (48.04)	1068 (54.31)	<0.001
RR (95% CI)	1.02 (1.02-1.02)	1.00	1.80 (1.70-1.90)	2.00 (1.87-2.13)	2.15 (1.96-2.35)	
P-value	<0.001		<0.001	<0.001	<0.001	
Congenital anomalies						
n (/10,000)	375 (4.22)	4603 (3.64)	164 (4.41)	127 (3.96)	84 (4.27)	0.143
RR (95% CI)	1.00 (0.99-1.00)	1.00	1.03 (0.88-1.21)	0.87 (0.73-1.04)	0.90 (0.72-1.12)	
P-value	0.321		0.713	0.135	0.326	
Preterm-related						
n (/10,000)	158 (1.78)	846 (0.67)	54 (1.45)	58 (1.81)	46 (2.34)	<0.001
RR (95% CI)	1.01(0.99-1.02)	1.00	1.42(1.06-1.91)	1.62(1.19-2.21)	1.74(1.16-2.60)	
P-value	0.241		0.020	0.002	0.007	
Other perinatal conditions						
n (/10,000)	215 (2.42)	1851 (1.47)	94 (2.53)	67 (2.09)	54 (2.75)	0.015
RR (95% CI)	1.01 (0.99-1.03)	1.00	1.46 (1.16-1.84)	1.20 (0.89-1.60)	1.53 (1.05-2.23)	
P-value	0.208		0.001	0.233	0.028	
Sudden unexpected infant death						
n (/10,000)	2507 (28.21)	6949 (5.50)	898 (24.17)	958 (29.89)	651 (33.11)	<0.001
RR (95% CI)	1.02 (1.02-1.03)	1.00	2.37 (2.19-2.56)	2.86 (2.62-3.12)	3.04 (2.69-3.43)	
P-value	<0.001		<0.001	<0.001	<0.001	
Infection						
n (/10,000)	176 (1.98)	1015 (0.80)	63 (1.70)	57 (1.78)	56 (2.85)	<0.001
RR (95% CI)	1.02 (1.01-1.04)	1.00	1.48 (1.11-1.96)	1.60 (1.14-2.23)	2.69 (1.75-4.15)	
P-value	0.004		0.007	0.006	<0.001	

CI, confidence interval; RR, risk ratio. Poisson regression models were adjusted for maternal age (as a continuous variable), race/ethnicity, education level, marital status, parity, total number of prenatal care visits, weight gain during pregnancy (as a continuous variable), pre-pregnancy body mass index (as a continuous variable), maternal smoking intensity before pregnancy (as a continuous variable), gestational diabetes, gestational hypertension, eclampsia, infant sex, birthplace, and delivery method. Preterm-related death in this analysis was defined by ICD 10 codes of K550, P000, P010, P011, P015, P020, P021, P027, P070-P073, P102, P220-229, P250-279, P280, P281, P360-369, P520-523, or P77.

Table 3: Association of intensity of maternal smoking with infant death across entire pregnancy.

The main strength of our study is that it was based on a large-scale national database, which provided strong statistical power to evaluate the timing of maternal smoking during pregnancy and cause-specific infant deaths. In addition, we examined the dose-response association between maternal smoking and infant cause-specific death during each trimester of pregnancy. However, several limitations should be considered. First, the information on maternal smoking during pregnancy was self-reported, which might cause misclassification of smoking status because several mothers may be reluctant to report their smoking to clinicians during prenatal care. However, it has been shown that maternal self-reported cigarette use is highly corrected with objectively measured cotinine levels.³² Second, we did not classify the timing of infant death (e.g., neonatal death 0-27 days after birth and post-neonatal death 28 days-11 months after birth) due to the rare cases of infant death at different time stages. Third, although we adjusted for several potential confounders, confounding from other unmeasured covariates during pregnancy such as lifestyle factors (e.g., alcohol

drinking, dietary intake, and physical activity),^{10,33,34} drug use (e.g., cocaine, supplements),^{11,35} and environmental factors (e.g., air pollution, extreme temperature)^{36,37} cannot be completely ruled out. Fourth, we only included live births, then congenital anomalies among stillbirth and pregnancy terminations might be uncaptured, which might result in selection bias. Fifth, we can not assess the long-term benefits of quitting smoking in the first trimester because of limited accessed data. A critical review reported that the effect of smoking cessation during and after pregnancy on long-term health for mothers and offspring remains inconclusive.³⁸ However, based on previous studies, about 50-90% of pregnant women who quit smoking might relapse to cigarette use within the period of 6 months-1 year postpartum.³⁸⁻⁴⁰ In addition, compared with mothers who remained abstinent during and after pregnancy, those who had relapsed after delivery may pose future adverse effects to their babies by breastmilk, and the adverse health consequences include severe asthma attacks and developmental problems.³⁸ These findings need to be validated in future well-designed

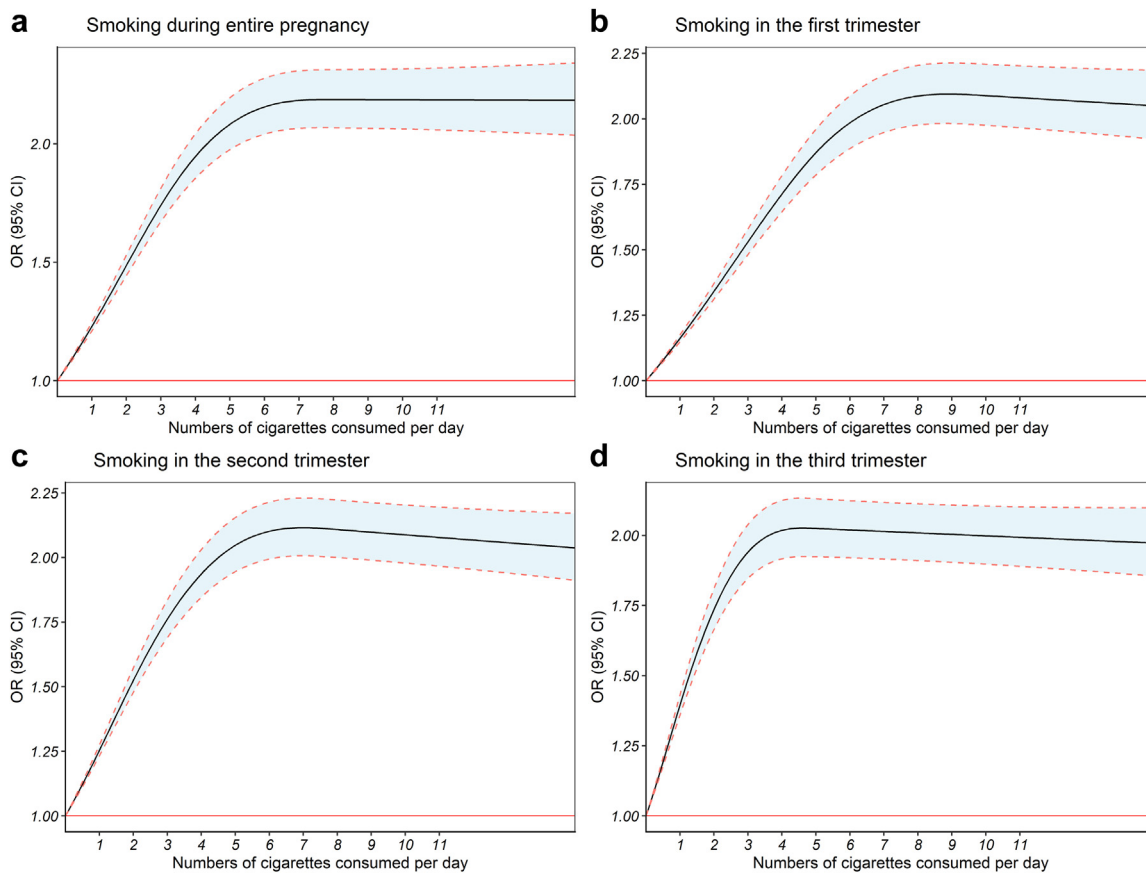


Fig. 2: Dose-response association between number of cigarettes consumed per day and infant deaths during: (a) the entire pregnancy; (b) first trimester; (c) second trimester; and (d) third trimester of pregnancy. Logistic regression models were adjusted for maternal age (as a continuous variable), race/ethnicity, education level, marital status, parity, total number of prenatal care visits, weight gain during pregnancy (as a continuous variable), pre-pregnancy body mass index (as a continuous variable), maternal smoking intensity before pregnancy (as a continuous variable), gestational diabetes, gestational hypertension, eclampsia, infant sex, birthplace, and delivery method. OR, odds ratio.

cohort studies. Sixth, the sample used in this study can represent the general population in the USA, although our results can not be generalised to populations of

other race/ethnicity such as Asian population. Seventh, in consideration of limited statistical power for death cases, we did not perform subgroup analysis stratified

Cause of infant death	Smoking status in the subsequent trimesters						P for trend
	Continued		Reduced		Quit		
	Case/total	RR (95% CI)	Case/total	RR (95% CI)	Case/total	RR (95% CI)	
All-cause	2285/447,497	1.00	1172/242,014	0.96 (0.89–1.03)	627/190,307	0.71 (0.65–0.78)	<0.001
Congenital anomalies	206/445,418	1.00	86/240,928	0.78 (0.60–1.01)	83/189,763	1.03 (0.79–1.35)	0.780
Preterm-related	79/445,291	1.00	44/240,886	0.96 (0.66–1.40)	31/189,711	0.98 (0.63–1.51)	0.880
Other perinatal conditions	118/445,330	1.00	47/240,889	0.73 (0.52–1.04)	45/189,725	0.91 (0.64–1.30)	0.357
Sudden unexpected infant death	1,386/446,598	1.00	735/241,577	1.00 (0.91–1.09)	340/190,020	0.64 (0.57–0.72)	<0.001
Infection	91/445,303	1.00	57/240,899	1.18 (0.83–1.66)	23/189,703	0.67 (0.42–1.08)	0.253

CI, confidence interval; RR, risk ratio. Poisson regression models were adjusted for maternal age (as a continuous variable), race/ethnicity, education level, marital status, parity, total number of prenatal care visits, weight gain during pregnancy (as a continuous variable), pre-pregnancy body mass index (as a continuous variable), maternal smoking intensity before pregnancy (as a continuous variable), gestational diabetes, gestational hypertension, eclampsia, infant sex, birthplace, and delivery method. Preterm-related death in this analysis was defined by ICD 10 codes of K550, P000, P010, P011, P015, P020, P021, P027, P070–P073, P102, P220–229, P250–279, P280, P281, P360–369, P520–523, or P77.

Table 4: Association of change of smoking status in the subsequent trimesters of pregnancy with infant death among mothers who smoked in the first trimester.

by infant sex. Further studies with sufficient statistical power are needed to validate our findings.

A meta-analysis of data from 142 articles by Pineles et al.⁸ reported that the associations were not statistically significant between maternal smoking of 1–10 cigarettes/day and stillbirth (RR = 1.10, 95% CI = 0.98–1.24) and neonatal death (RR = 1.06, 95% CI = 0.90–1.26), but were statistically significant for perinatal death and maternal smoking of 11–20 cigarettes/day, and >20 cigarettes/day. However, a recent study of 4,503,197 single births in California showed that infants whose mothers smoked during the first and second trimesters of pregnancy had a 75% increased risk of mortality compared with those whose mothers were nonsmokers.⁴¹ A recent umbrella review reported that the exposure window is an important gap for health outcomes of infants whose mothers smoke during pregnancy.⁴² Consistent with the study in California, we found that even 1–5 cigarettes per day could increase the risk of infant death during each trimester of pregnancy. The discrepancy in findings between ours and the previous meta-analysis might be due to the differences in outcomes (i.e., outcomes of stillbirth, neonatal death, and perinatal death in that meta-analysis versus infant death in our study). In addition, the number of cigarettes smoked was estimated by the midpoint of categories from most included studies in the Pineles meta-analysis, which might not best represent the actual values.⁸ Our findings suggest there is no safe level of maternal cigarette smoking in relation to infant survival during any trimester of pregnancy. As such, our results are consistent with messaging to expecting mothers or those planning pregnancies that any maternal smoking, even in the first trimester of pregnancy, can significantly increase the risk of infant death.

In terms of infant cause-specific death, a retrospective, cross-sectional study of 20,685,463 mother–infant pairs conducted between 2007 and 2011 based on the USA national vital statistic data showed that maternal smoking during any trimester of pregnancy significantly increased sudden unexpected infant death.⁷ Studies from Germany, the U.K., and other countries found a similar positive association of maternal smoking with sudden unexpected infant death,^{12–15,43} even for low-dose consumption of cigarettes (i.e., 1–5 cigarettes per day) during pregnancy.^{7,14} A recent study based on a USA urban black population showed an increased risk of sudden unexpected infant death for maternal smoking during pregnancy.¹¹ However, the results were limited to the black population, and maternal smoking during pregnancy seems more common in non-Hispanic whites compared with non-Hispanic blacks.⁴⁴ Maternal smoking has previously been reported to be associated with infant death caused by respiratory disease and infection,^{45,46} and hospitalization and mortality due to infectious disease.⁴⁷ However, these studies did not consider the timing of smoking during pregnancy or the intensity of cigarette use, and most were case-control

studies, which provide limited or lower quality of scientific evidence for policymakers. We used updated and nationwide NVSS data (2010–2013) including Hispanic, White, and Black populations and showed a similar association between maternal smoking during any trimester of pregnancy and sudden unexpected infant death, as well as other cause-specific infant death by preterm birth, other perinatal conditions excluding preterm birth, and infection. In addition, we found that the odds of cause-specific infant death increased with the intensity of maternal cigarette use from 1–5 to ≥ 11 cigarettes per day during any trimester of pregnancy.

One study based on data from the Centers for Disease Control and Prevention Birth Cohort Linked Birth/Infant Death Set (2007–2011) showed no significant dose–response association between maternal smoking during pregnancy and infant preterm-related death.⁷ However, a Chilean study of data from 2008 to 2012 reported that the population-attributable fraction for maternal smoking during pregnancy was 11.9% for infant preterm-related death (adjusted OR = 1.5)⁴⁸. The discrepancy might be due to differences in study period and adjustment for potential confounders. However, our use of large-scale national data to support that maternal smoking during pregnancy is associated with preterm-related infant death, regardless of trimesters of pregnancy lends support to the hypothesis that even low levels of maternal smoking negatively impact infant health, likely acting via multiple etiological factors.

Consistent with prior meta-analysis on the association of maternal smoking during pregnancy with neonatal death,⁸ we found a dose–response association between maternal smoking during any trimester of pregnancy and infant all-cause death and cause-specific death with significantly increased odds starting from 1 cigarette per day. Moreover, the curve for infant all-cause death and cause-specific death by sudden unexpected infant death began to level off at approximately 7 cigarettes per day during pregnancy. Previous meta-analysis also showed higher odds of perinatal death from about 7 cigarettes per day.⁴⁹ These findings reinforce that efforts aimed at smoking cessation among expectant mothers, even if light smokers, during any, but best done in the first, trimester of pregnancy are likely highly effective means of reducing all-cause and cause-specific infant death.

Our finding that smoking cessation after the first trimester of pregnancy significantly reduced the risk of infant all-cause death and sudden unexpected infant death is consistent with those suggesting a beneficial effect of quitting smoking on infant death.⁹ However, the benefits of quitting smoking on infant all-cause death do not appear to extend after the second trimester. Our findings support that mothers who smoked during pregnancy should be strongly advised and supported to quit smoking earlier. However, given the difficulty of nicotine dependence, attempting to

maintain abstinence during the entire pregnancy can be difficult for some mothers.²⁷ Nicotine replacement therapy and bupropion might be appropriate pharmacotherapies to help mothers who smoke but are unable to quit.^{50,51} A population-based retrospective cohort study of 529,317 live births in Scotland conducted between 1994 and 2003 showed that maternal smoking during pregnancy accounted for 31% of the social inequality in infant death.²⁷ Therefore, in addition to strategies and measures on preventing maternal smoking during pregnancy, efforts that adapt cessation programs for pregnant smokers to improve social support and circumstances are needed.⁵² In addition, our findings imply that disseminating the hazard message of even 1 cigarette use per day during pregnancy through text messaging, web-based communication, and preconception counseling by clinicians and healthcare teams might be effective in preventing reproductive women who are non-smokers from starting smoking. For reproductive women who are current smokers, behavioral counseling might aid in successful smoking cessation that the hazard of smoking during pregnancy can be reduced to the minimum if they quit smoking early in the first trimester.^{53,54} In addition, findings on dose–response associations imply that the risk of infant death can be lowered largely by decrease in even one cigarette consumed per day (from about seven cigarettes) among current smokers.

It is biologically plausible that maternal smoking during pregnancy is associated with infant death. First, epigenetic modifications including DNA methylation involved in maternal smoking during pregnancy play an important role with potential lifelong consequences. The significant CpG sites associated with maternal smoking during pregnancy are enriched in several biological processes related to organ, tissue, and cell development, proliferation, differentiation, and growth.⁴⁹ Second, polymorphisms of the serotonin transporter gene 5-HTT caused by maternal smoking may lead to infant death.⁵⁵ Third, there is an adverse effect of smoke exposure in utero on the infant immune system through reducing leukocytes⁵⁶ and impairing toll-like-receptor-mediated immune responses in neonates,⁵⁷ predisposing infants to infection. Fourth, placental function might be damaged because of maternal smoking by impairing function of placental macrophages.⁵⁸ Fifth, $\alpha 7$ nicotinic receptors in lung vessel walls and lung epithelial cells might mediate the effect of maternal smoking during pregnancy on unexplained infant death.^{59,60}

In conclusion, maternal smoking during any trimester of pregnancy was associated with infant all-cause death and cause-specific infant death by preterm birth, perinatal conditions excluding preterm-related death, sudden unexpected infant death, and infection, in a dose–response manner, suggesting no safe period or level for maternal smoking during pregnancy. Our

findings suggest that more efforts are needed to promote smoking cessation during pregnancy to prevent all-cause and cause-specific infant deaths.

Contributors

B.X. contributed to the study design, and interpretation of the data analysis and revised the manuscript. J.S. drafted the manuscript. X.L. analysed the data and contributed to the interpretation of the data. C.G.M. contributed to the interpretation of the data and revised the manuscript. M.Z. contributed to the study design, the interpretation of the data and revised the manuscript. X.L. and J.S. accessed and verified the data. The corresponding author, B.X., had full access to all data used in the study and had final responsibility for the decision to submit for publication. All authors read and approved the final version of the manuscript.

Data sharing statement

Data from the National Vital Statistics System are publicly available online (<https://www.cdc.gov/nchs/nvss/births.htm>).

Declaration of interests

We declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.eclim.2023.101858>.

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