Maternal cigarette smoking before or during pregnancy increases the risk of severe neonatal morbidity after delivery: a nationwide population-based retrospective cohort study

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ABSTRACT

Background The association of maternal cigarette smoking during pregnancy with severe neonatal morbidity (SNM) is still inconclusive. We aimed to examine the associations of the timing and the intensity of maternal cigarette smoking with infant SNM in the USA.

Methods We used birth certificate data of 12 150 535 women aged 18–49 years who had live singleton births from the 2016–2019 US National Vital Statistics System. Women self-reported the daily number of cigarettes they consumed before pregnancy and in each trimester of pregnancy. Composite SNM was defined as one or more of the following complications: assisted ventilation immediately following delivery, assisted ventilation for >6 hours, neonatal intensive care unit admission, surfactant replacement therapy, suspected neonatal sepsis, and seizure.

Results Maternal cigarette smoking either before pregnancy or during any trimester of pregnancy significantly increased the risk of infant SNM, even at a very low intensity (ie, 1–2 cigarettes per day). For example, compared with women who did not smoke before pregnancy, the adjusted odds ratios and 95% confidence intervals (OR, 95% CI) of composite SNM in the newborn from women who smoked 1–2, 3–5, 6–9, 10–19, and ≥20 cigarettes per day before pregnancy were 1.16 (1.13 to 1.19), 1.22 (1.20 to 1.24), 1.26 (1.23 to 1.29), 1.27 (1.25 to 1.28), and 1.31 (1.30 to 1.33), respectively. Furthermore, smokers who stopped smoking during pregnancy still had a higher risk of composite SNM than never smokers before and throughout pregnancy.

Conclusions Maternal cigarette smoking before or during pregnancy increased the risk of infant SNM, even at a low dose of 1–2 cigarettes/day. Interventions should emphasise the detrimental effects of even light smoking before and during pregnancy.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ To our knowledge, only a few studies have assessed the association between maternal cigarette smoking during pregnancy and severe neonatal morbidity (SNM) in offspring, with conflicting findings.
⇒ Studies quantifying the associations between the timing and intensity of maternal cigarette smoking during pregnancy and SNM in offspring are lacking.

WHAT THIS STUDY ADDS

⇒ In this large population-based cohort of 12 150 535 mother–infant pairs in the USA from 2016 to 2019, we found that maternal cigarette smoking either before pregnancy or in each of three trimesters of pregnancy was associated with an increased risk of infant composite SNM and individual components compared with maternal non-smoking in the considered specific period before and after conception.
⇒ The association was significant even for a low intensity of cigarette smoking (ie, 1–2 cigarettes per day).
⇒ Compared with never smokers before and throughout pregnancy, mothers who stopped smoking in each trimester of pregnancy still had a higher risk of infant composite SNM.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Women of reproductive age should abstain from cigarette smoking in relation to SNM, acknowledging that smoking is also detrimental from the perspective of other health outcomes (not examined in this study).

INTRODUCTION

Although advances in obstetric, intrapartum and neonatal care have contributed to a substantial decrease in neonatal mortality,[1] severe neonatal morbidity (SNM) after delivery, including admission to a neonatal intensive care unit (NICU), remains a serious public health concern. In the USA, the admission rate to NICU increased from 64.0 to 77.9 per 1000 live births from 2007 to 2012.[2] Affected newborns often need prolonged neonatal care and longer hospital stays. Furthermore, neurodevelopmental impairments related to infant SNM may persist into childhood and adulthood.[3] Thus, it is important to understand better the modifiable risk factors associated with infant SNM.

The prevalence of cigarette smoking is nearly 10% among pregnant women in the USA.[4] Smoking is a well-documented modifiable risk factor for

adverse birth outcomes, including preterm delivery, low birth weight, and intrauterine growth restriction.[5–8] However, only a few studies have assessed the association between maternal cigarette smoking and infant SNM, with conflicting findings.[9–11] For example, a retrospective population-based cohort study from the Finnish Medical Birth Register reported an increased risk of NICU admission in infants born to mothers who smoked cigarettes.[9] In contrast, another retrospective cohort study of singleton infants in Australia did not show a correlation between maternal cigarette smoking and infant composite SNM.[11] In addition, most previous studies were subject to some methodological issues, including a relatively small sample size of infant SNM cases,[10 11] insufficient adjustment for potential confounders,[9–11] or poor generalisability of the findings (eg, only included late preterm and early term births).[11] Furthermore, the associations between maternal cigarette smoking and other subtypes of SNM such as seizure or suspected neonatal sepsis have not been evaluated to date. Finally, studies quantifying the associations between the timing and intensity of maternal cigarette smoking and infant SNM are also lacking. This is an important issue as many women believe it is not hazardous to smoke cigarettes before conception or in the first trimester of pregnancy[12] or, at least, that light smoking causes little or no harm.[13]

Therefore, this study aims to assess the associations of the timing (before pregnancy, and in each trimester of pregnancy) and intensity (number of cigarettes per day) of maternal cigarette smoking with infant SNM based on large birth cohort data in the USA.

METHODS

Study population

We used nationwide birth certificate data from the US National Vital Statistics System (NVSS). The NVSS Natality File uses standard certificates (revised every 10–15 years) to collect maternal and infant demographic and health characteristics for all live births. Two standard worksheets were developed for the 2003 revised Standard Certificate of Live Birth, which offered expanded information on maternal cigarette smoking, and new information on other variables such as education, and weight and height before pregnancy.[14] As the 2003 revised birth certificate files have been completely implemented in all US states and in the District of Columbia since 2016, we used NVSS data from 2016 to 2019 in this study. Details about NVSS can be found at the official website (https://www.cdc.gov/nchs/nvss/births.htm).

In this study, we initially included 15 379 982 live births registered in the NVSS (2016–2019). We then excluded ineligible women if they: (1) were aged <18 or ≥50 years (n=200 589); (2) gave birth to twin or multiple births (n=516 374); (3) had pre-pregnancy hypertension or diabetes (n=396 691); and (4) were without data on cigarette smoking in any of the period (n=67 209), SNM (n=13 381) or selected covariates (n=2 035 203). Finally, 12 150 535 mother-infant pairs were available for data analyses (figure 1).

Maternal cigarette smoking

Information about maternal cigarette smoking was collected using the mother's worksheet at the time of delivery. Women reported the number of cigarettes or packs of cigarettes they consumed on an average day during the 3 months before pregnancy, and in each of the three trimesters during pregnancy (ie, the timing of maternal cigarette smoking). In each time period, women who smoked 'one or more cigarettes per day' were considered as smokers, whereas women who smoked '0 cigarettes per day' were considered as non-smokers. The intensity of smoking was categorised into six subgroups: 0, 1–2, 3–5, 6–9, 10–19, and ≥20 cigarettes/day. To capture further the variability in the timing of maternal smoking around pregnancy, women were also divided into 16 mutually exclusive smoking status

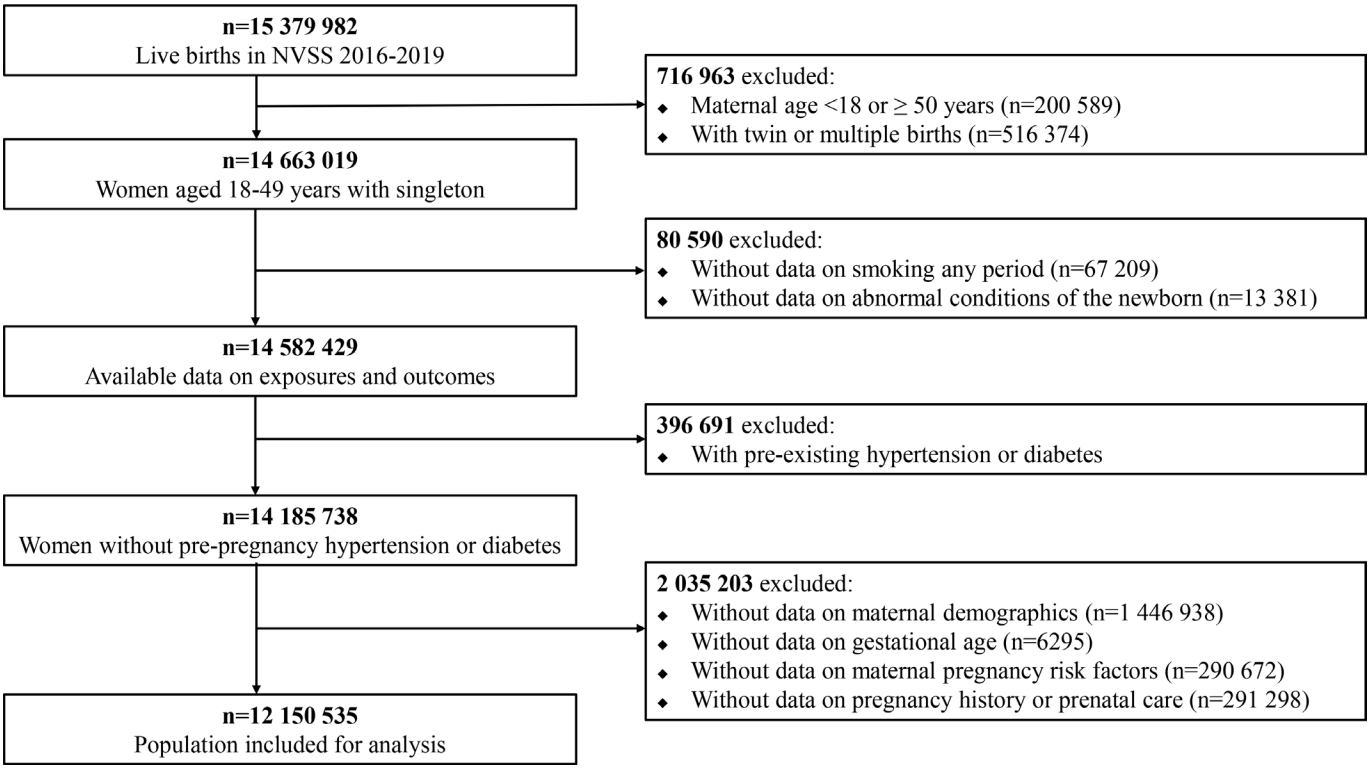
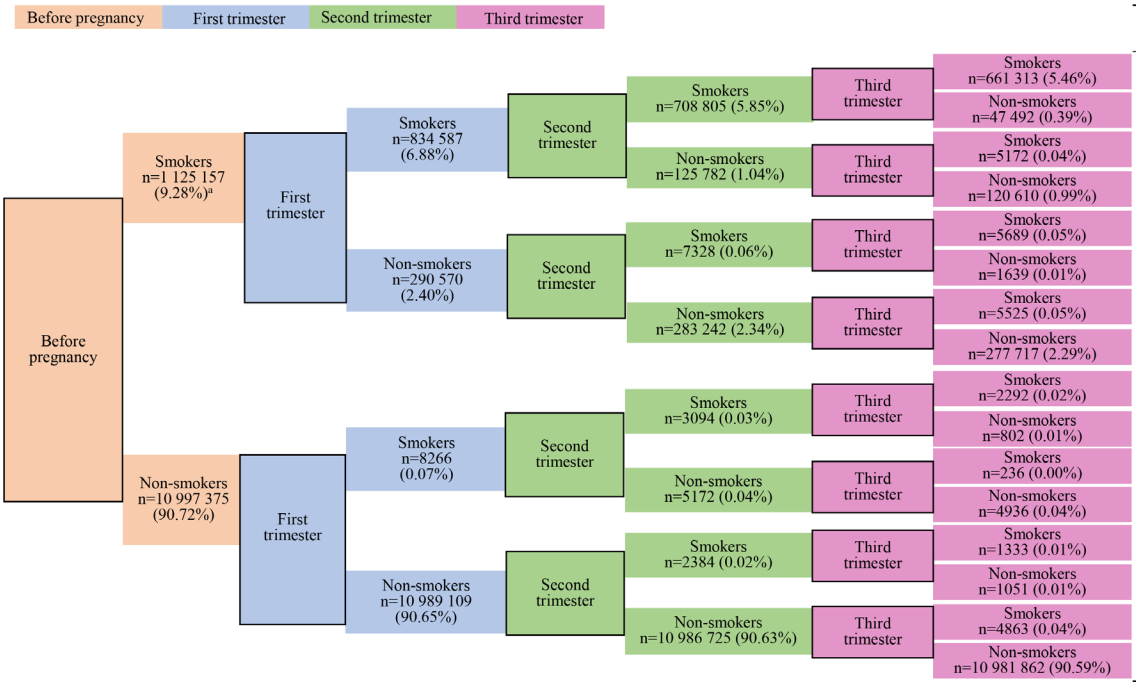


Figure 1 Flow chart of the inclusion/exclusion of the participants. NVSS, US National Vital Statistics System.



Group	Composite SNM[b]
1	1.33 (1.32 to 1.35)
2	1.31 (1.27 to 1.35)
3	1.33 (1.21 to 1.45)
4	1.21 (1.19 to 1.23)
5	1.05 (0.96 to 1.15)
6	1.02 (0.86 to 1.21)
7	1.14 (1.04 to 1.26)
8	1.12 (1.11 to 1.14)
9	1.27 (1.11 to 1.45)
10	1.08 (0.84 to 1.37)
11	1.20 (0.78 to 1.85)
12	1.23 (1.12 to 1.35)
13	1.23 (1.02 to 1.47)
14	1.40 (1.16 to 1.70)
15	1.21 (1.10 to 1.33)
16	1.00

Figure 2 Association of smoking cessation at different trimesters during pregnancy with infant composite SNM. [a]Number of participants and its proportion; [b]the adjusted OR (95% CI) of composite SNM for smoking cessation at various periods (groups 1–15) compared with never smokers (group 16). Adjusted covariates included maternal age at delivery, race/ethnicity, educational level, marital status, pre-pregnancy body mass index, sex of infant, gestational age at delivery, parity, total number of prenatal care visits, eclampsia, gestational hypertension, and gestational diabetes. For this analysis, we only included women who had complete data on cigarette smoking both before pregnancy and in each trimester (n=12 122 532). SNM, severe neonatal morbidity.

groups based on their smoking status before and during each trimester of pregnancy (figure 2).

Severe neonatal morbidity

Information on infant SNM was collected from the medical records using the facility worksheet. Infant SNM included assisted ventilation immediately following delivery, assisted ventilation for more than 6 hours, NICU admission for continuous mechanical ventilation, surfactant replacement therapy, suspected neonatal sepsis, and seizure or serious neurologic dysfunction.[15–18] Infant composite SNM was defined as the presence of one or more of the above outcomes in the study.

Study covariates

Maternal age at delivery was categorised as 18–29, 30–39, and 40–49 years old. Education was classified as less than high school, high school, and more than high school. Race/ethnicity was divided into non-Hispanic white, non-Hispanic black, Hispanic, and other. Maternal pre-pregnancy body mass index (BMI) was categorised according to the WHO[19] as <18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, 35.0–39.9, and ≥40 kg/m^2. Parity included 1, 2, 3, and ≥4 pregnancies and total number of prenatal care visits included 0, 1–4, 5–9, and ≥10. Other covariates were dichotomous, including marital status (married or unmarried), eclampsia (yes or no), gestational hypertension (yes or no), gestational diabetes (yes or no), and sex of infant (male or female). These covariates were selected based on their established/hypothesised associations with maternal smoking and SNM, and the information available in the worksheet, consistent with our previous research.[20 21]

Statistical analysis

Baseline characteristics of participants are presented according to maternal cigarette smoking status before pregnancy and in each pregnancy trimester. Continuous variables are expressed as median (interquartile range [IQR]) and categorical variables as n (%). First, we performed logistic regression models to estimate the associations between the timing of maternal cigarette smoking and infant composite SNM, as well as individual components, with non-smoking women in the specific period as the reference. The magnitudes of the associations were assessed using odds ratios (OR) and 95% confidence intervals (95% CI). Second, we performed logistic regression models to assess the associations between the intensity of maternal cigarette smoking and infant composite SNM, as well as individual components. Third, we performed logistic regression models to examine the associations of smoking cessation before pregnancy and during different pregnancy trimesters with infant composite SNM. Fourth, we performed subgroup analyses of the associations between the timing of maternal cigarette smoking and infant composite SNM as well as individual components by maternal age at delivery, race/ethnicity, and infant birth year. Finally, we did four sensitivity analyses to validate the robustness of our main findings (ie, the associations between the timing of maternal cigarette smoking and infant composite SNM as well as individual components), including: (1) by excluding women with eclampsia, gestational hypertension or diabetes; (2) by excluding women with caesarean section; (3) by excluding women with preterm birth (ie, <37 weeks pregnancy); and (4) the use of multiple imputation to deal with missing data on selected covariates. All models were adjusted for the aforementioned covariates.

All analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC, USA). A two-sided $p<0.05$ was considered as statistical significance. The Bonferroni correction method was used for multiple comparisons.

RESULTS

Population baseline characteristics

A total of 12 150 535 women aged 18–49 years with singleton births were included in the study (figure 1). Among them, 9.3%, 7.0%, 6.0%, and 5.7% reported smoking cigarettes before pregnancy, and in the first, second, and third trimester, respectively. Compared with non-smokers, women who smoked cigarettes tended to be younger, non-Hispanic white, unmarried, and obese, and to have low education, more parities, and fewer number of prenatal care visits (table 1). The overall prevalence of infant SNM was 9.4%.

Association between the timing of maternal cigarette smoking and infant SNM

After adjusting for all potential covariates and compared with non-smokers in specific period, infants born to women who smoked cigarettes before pregnancy or in each pregnancy

Table 1 Baseline characteristics of the study population by the timing of maternal cigarette smoking

	Smoking before pregnancy		Smoking in the first trimester		Smoking in the second trimester		Smoking in the third trimester	
Characteristics	No	Yes	No	Yes	No	Yes	No	Yes
N	11 016 709	1 130 448	11 300 697	846 606	11 422 615	724 265	11 438 428	687 387
Maternal age at delivery, years								
Median (IQR)	29.0 (25.0–33.0)	27.0 (23.0–31.0)	29.0 (25.0–33.0)	27.0 (23.0–31.0)	29.0 (25.0–33.0)	27.0 (23.0–31.0)	29.0 (25.0–33.0)	27.0 (23.0–31.0)
Category, n (%)								
18–29	5 856 447 (53.2)	777 483 (68.8)	6 054 255 (53.6)	579 747 (68.5)	6 142 004 (53.8)	491 699 (67.9)	6 156 610 (53.8)	465 130 (67.7)
30–39	4 823 271 (43.8)	336 064 (29.7)	4 905 592 (43.4)	253 821 (30.0)	4 938 088 (43.2)	221 199 (30.5)	4 939 612 (43.2)	211 370 (30.8)
40–49	336 991 (3.1)	16 901 (1.5)	340 850 (3.0)	13 038 (1.5)	342 523 (3.0)	11 367 (1.6)	342 206 (3.0)	10 887 (1.6)
Race/ethnicity, n (%)								
Hispanic	2 516 481 (22.8)	78 774 (7.0)	2 547 825 (22.6)	47 581 (5.6)	2 559 058 (22.4)	36 286 (5.0)	2 557 362 (22.4)	33 489 (4.9)
Non-Hispanic white	5 845 570 (53.1)	857 398 (75.9)	6 046 146 (53.5)	656 756 (77.6)	6 132 075 (53.7)	570 582 (78.8)	6 151 304 (53.8)	544 103 (79.2)
Non-Hispanic black	1 649 749 (15.0)	125 389 (11.1)	1 682 897 (14.9)	92 306 (10.9)	1 698 939 (14.9)	76 205 (10.5)	1 696 351 (14.8)	71 096 (10.3)
Other	1 004 909 (9.1)	68 887 (6.1)	1 023 829 (9.1)	49 963 (5.9)	1 032 543 (9.0)	41 192 (5.7)	1 033 411 (9.0)	38 699 (5.6)
Educational level, n (%)								
<High school	1 213 330 (11.0)	233 610 (20.7)	1 247 589 (11.0)	199 343 (23.6)	1 266 377 (11.1)	180 462 (24.9)	1 270 002 (11.1)	174 012 (25.3)
High school	2 666 838 (24.2)	471 744 (41.7)	2 772 495 (24.5)	366 170 (43.3)	2 821 883 (24.7)	316 607 (43.7)	2 830 442 (24.8)	300 759 (43.8)
>High school	7 136 541 (64.8)	425 094 (37.6)	7 280 613 (64.4)	281 093 (33.2)	7 334 355 (64.2)	227 196 (31.4)	7 337 984 (64.2)	212 616 (30.9)
Marital status, n (%)								
Married	7 080 442 (64.3)	335 002 (29.6)	7 185 953 (63.6)	229 447 (27.1)	7 220 599 (63.2)	194 699 (26.9)	7 220 341 (63.1)	185 828 (27.0)
Unmarried	3 936 267 (35.7)	795 446 (70.4)	4 114 744 (36.4)	617 159 (72.9)	4 202 016 (36.8)	529 566 (73.1)	4 218 087 (36.9)	501 559 (73.0)
Pre-pregnancy BMI, kg/m^2								
Median (IQR)	25.4 (22.1–30.2)	25.8 (21.9–31.3)	25.5 (22.1–30.3)	25.7 (21.8–31.1)	25.5 (22.1–30.3)	25.6 (21.7–31.1)	25.5 (22.1–30.3)	25.6 (21.7–31.0)
Category, n (%)								
<18.5	338 426 (3.1)	60 252 (5.3)	349 804 (3.1)	48 879 (5.8)	355 625 (3.1)	43 046 (5.9)	356 997 (3.1)	40 961 (6.0)
18.5–24.9	4 810 704 (43.7)	448 527 (39.7)	4 917 952 (43.5)	341 283 (40.3)	4 964 751 (43.5)	294 296 (40.6)	4 972 527 (43.5)	279 711 (40.7)
25.0–29.9	2 948 468 (26.8)	278 525 (24.6)	3 022 192 (26.7)	204 848 (24.2)	3 052 551 (26.7)	174 388 (24.1)	3 055 871 (26.7)	165 622 (24.1)
30.0–34.9	1 616 335 (14.7)	177 973 (15.7)	1 663 825 (14.7)	130 528 (15.4)	1 683 890 (14.7)	110 400 (15.2)	1 685 819 (14.7)	104 613 (15.2)
35.0–39.9	774 449 (7.0)	95 544 (8.5)	799 971 (7.1)	70 043 (8.3)	810 774 (7.1)	59 198 (8.2)	811 609 (7.1)	55 962 (8.1)
≥40	528 327 (4.8)	69 627 (6.2)	546 953 (4.8)	51 025 (6.0)	555 024 (4.9)	42 937 (5.9)	555 605 (4.9)	40 518 (5.9)
Eclampsia, n (%)	27 293 (0.3)	2880 (0.3)	28 081 (0.3)	2081 (0.3)	28 408 (0.3)	1750 (0.2)	28 333 (0.3)	1628 (0.2)
Gestational hypertension, n (%)	748 202 (6.8)	80 897 (7.2)	772 338 (6.8)	56 798 (6.7)	782 504 (6.9)	46 591 (6.4)	783 616 (6.9)	43 449 (6.3)
Gestational diabetes, n (%)	697 459 (6.3)	69 298 (6.1)	717 575 (6.4)	49 201 (5.8)	725 873 (6.4)	40 872 (5.6)	727 502 (6.4)	38 657 (5.6)
Parity, n (%)								
1	4 228 391 (38.4)	377 304 (33.4)	4 361 975 (38.6)	243 891 (28.8)	4 414 861 (38.7)	190 835 (26.4)	4 419 083 (38.6)	176 225 (25.6)
2	3 607 141 (32.7)	334 829 (29.6)	3 689 858 (32.7)	252 099 (29.8)	3 725 026 (32.6)	216 792 (29.9)	3 730 757 (32.6)	206 020 (30.0)
3	1 865 471 (16.9)	223 808 (19.8)	1 907 423 (16.9)	181 840 (21.5)	1 927 466 (16.9)	161 750 (22.3)	1 931 055 (16.9)	155 328 (22.6)
≥4	1 315 706 (11.9)	194 507 (17.2)	1 341 441 (11.9)	168 776 (19.9)	1 355 262 (11.9)	154 888 (21.4)	1 357 533 (11.9)	149 814 (21.8)
Sex of infant, n (%)								
Male	5 636 183 (51.2)	577 952 (51.1)	5 780 747 (51.2)	433 489 (51.2)	5 845 894 (51.2)	371 117 (51.2)	5 850 637 (51.2)	352 040 (51.2)
Female	5 380 526 (48.8)	552 496 (48.9)	5 519 950 (48.9)	413 117 (48.8)	5 579 721 (48.9)	353 148 (48.8)	5 587 791 (48.9)	335 347 (48.8)
Gestational age at delivery, weeks								
Median (IQR)	39.0 (38.0–40.0)	39.0 (38.0–39.0)	39.0 (38.0–40.0)	39.0 (38.0–39.0)	39.0 (38.0–40.0)	39.0 (38.0–39.0)	39.0 (38.0–40.0)	39.0 (38.0–39.0)
Total number of prenatal care visits, n (%)								
0	157 807 (1.4)	34 649 (3.1)	160 897 (1.4)	31 544 (3.7)	162 771 (1.4)	29 659 (4.1)	161 657 (1.4)	28 527 (4.2)
1–4	374 516 (3.4)	79 302 (7.0)	384 457 (3.4)	69 357 (8.2)	390 344 (3.4)	63 448 (8.8)	385 919 (3.4)	60 284 (8.8)
5–9	2 231 800 (20.3)	280 172 (24.8)	2 288 257 (20.3)	223 801 (26.4)	2 315 666 (20.3)	196 280 (27.1)	2 316 967 (20.3)	186 233 (27.1)
≥10	8 252 586 (74.9)	736 325 (65.1)	8 467 086 (74.9)	521 904 (61.7)	8 553 834 (74.9)	434 878 (60.0)	8 573 885 (75.0)	412 343 (60.0)

BMI, body mass index.

Table 2 Association of the timing of maternal cigarette smoking with SNM

	Smoking before pregnancy		Smoking in the first trimester		Smoking in the second trimester		Smoking in the third trimester	
Outcomes	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**
Assisted ventilation immediately following delivery								
n (%)	404 007 (3.7)	61 627 (5.5)	417 880 (3.7)	47 812 (5.7)	424 728 (3.7)	40 925 (5.7)	418 745 (3.7)	37 129 (5.4)
OR (95% CI)	1.00	1.28 (1.27 to 1.30)	1.00	1.29 (1.28 to 1.31)	1.00	1.28 (1.26 to 1.29)	1.00	1.25 (1.23 to 1.26)
P value		<0.0001		<0.0001		<0.0001		<0.0001
Assisted ventilation for >6 hours								
n (%)	128 751 (1.2)	20 494 (1.8)	133 149 (1.2)	16 095 (1.9)	135 379 (1.2)	13 856 (1.9)	130 968 (1.1)	12 059 (1.8)
OR (95% CI)	1.00	1.27 (1.25 to 1.29)	1.00	1.26 (1.24 to 1.29)	1.00	1.26 (1.23 to 1.28)	1.00	1.23 (1.20 to 1.25)
P value		<0.0001		<0.0001		<0.0001		<0.0001
NICU admission for continuous mechanical ventilation								
n (%)	791 750 (7.2)	110 531 (9.8)	813 953 (7.2)	88 400 (10.4)	824 824 (7.2)	77 478 (10.7)	816 290 (7.1)	71 578 (10.4)
OR (95% CI)	1.00	1.24 (1.23 to 1.25)	1.00	1.30 (1.29 to 1.31)	1.00	1.32 (1.31 to 1.33)	1.00	1.31 (1.30 to 1.32)
P value		<0.0001		<0.0001		<0.0001		<0.0001
Surfactant replacement therapy								
n (%)	37 449 (0.3)	6278 (0.6)	38 694 (0.3)	5034 (0.6)	39 342 (0.3)	4380 (0.6)	35 696 (0.3)	3485 (0.5)
OR (95% CI)	1.00	1.25 (1.21 to 1.29)	1.00	1.25 (1.21 to 1.30)	1.00	1.29 (1.24 to 1.33)	1.00	1.28 (1.23 to 1.33)
P value		<0.0001		<0.0001		<0.0001		<0.0001
Suspected neonatal sepsis								
n (%)	210 911 (1.9)	30 687 (2.7)	218 016 (1.9)	23 588 (2.8)	221 300 (1.9)	20 270 (2.8)	218 644 (1.9)	18 499 (2.7)
OR (95% CI)	1.00	1.30 (1.28 to 1.31)	1.00	1.31 (1.29 to 1.33)	1.00	1.32 (1.30 to 1.34)	1.00	1.31 (1.29 to 1.33)
P value		<0.0001		<0.0001		<0.0001		<0.0001
Seizure or serious neurologic dysfunction								
n(‰)	3486 (3.2)	682 (6.0)	3630 (3.2)	537 (6.3)	3683 (3.2)	483 (6.7)	3668 (3.2)	453 (6.6)
OR (95% CI)	1.00	1.54 (1.41 to 1.68)	1.00	1.58 (1.43 to 1.74)	1.00	1.66 (1.50 to 1.84)	1.00	1.67 (1.50 to 1.85)
P value		<0.0001		<0.0001		<0.0001		<0.0001
Composite SNM*								
n (%)	998 056 (9.1)	140 587 (12.4)	1 027 746 (9.1)	111 008 (13.1)	1 042 124 (9.1)	96 556 (13.3)	1 034 094 (9.0)	89 572 (13.0)
OR (95% CI)	1.00	1.27 (1.26 to 1.28)	1.00	1.31 (1.30 to 1.32)	1.00	1.32 (1.31 to 1.33)	1.00	1.31 (1.30 to 1.32)
P value		<0.0001		<0.0001		<0.0001		<0.0001

Logistic regression models were adjusted for maternal age at delivery, race/ethnicity, educational level, marital status, pre-pregnancy body mass index, sex of infant, gestational age at delivery, parity, total number of prenatal care visits, eclampsia, gestational hypertension, and gestational diabetes.
*Composite SNM was defined as having one or more of the above outcomes.
NICU, neonatal intensive care unit; SNM, severe neonatal morbidity.

trimester had higher risks of composite SNM and individual components (table 2). The adjusted OR (95% CI) of composite SNM for infants born to women who smoked cigarettes before pregnancy, and in the first, second, and third pregnancy trimester were 1.27 (1.26 to 1.28), 1.31 (1.30 to 1.32), 1.32 (1.31 to 1.33), and 1.31 (1.30 to 1.32), respectively (all p<0.0001). Regarding individual components, taking infant NICU admission for example, the corresponding OR (95% CI) were 1.24 (1.23 to 1.25), 1.30 (1.29 to 1.31), 1.32 (1.31 to 1.33), and 1.31 (1.30 to 1.32), respectively (all p<0.0001).

Maternal cigarette smoking before and during pregnancy was associated with infant composite SNM and individual components in most subgroups even after the Bonferroni correction (online supplemental table S1). Sensitivity analyses yielded consistent results by excluding women with eclampsia, gestational hypertension, or diabetes, excluding women who underwent caesarean section, or excluding women with preterm birth. In addition, imputation of missing values for the variables of interest also did not alter the findings (all p<0.0001) (online supplemental table S2).

Considering the variability in the timing of maternal smoking, women who smoked only before pregnancy (group 8), or only during the first (group 12), second (group 14), or third (group 15) trimester had higher OR of infant composite SNM than women who did not smoke before and throughout pregnancy. Adjusted OR (95% CI) were 1.12 (1.11 to 1.14), 1.23 (1.12 to 1.35), 1.40 (1.16 to 1.70), and 1.21 (1.10 to 1.33), respectively. Statistically or marginally significant associations were also observed for the remaining 11 smoking cessation patterns (figure 2).

Association between the intensity of maternal cigarettes smoking and infant SNM

Compared with non-smokers, infants born to women who consumed any number of cigarettes per day before or during pregnancy, even at a low dose of 1–2 cigarettes per day, were at increased risks of composite SNM and individual components (table 3). For example, compared with women who did not smoke before pregnancy, the adjusted OR (95% CI) of composite SNM in the newborn born to women who smoked 1–2, 3–5, 6–9, 10–19, and ≥20 cigarettes per day before pregnancy were 1.16 (1.13 to 1.19), 1.22 (1.20 to 1.24), 1.26 (1.23 to 1.29), 1.27 (1.25 to 1.28), and 1.31 (1.30 to 1.33), respectively (all p<0.0001). There was a potential dose-response association between smoking intensity and infant SNM, with the OR increasing with smoking intensity from 1 to 2 cigarettes/day to ≥20 cigarettes/day.

Regarding individual components, taking infant NICU admission for example, compared with non-smokers, the corresponding adjusted OR (95% CI) of infant NICU admission were 1.13 (1.10 to 1.16), 1.19 (1.17 to 1.21), 1.22 (1.19 to 1.26), 1.24 (1.22 to 1.25), and 1.29 (1.28 to 1.31), respectively, for women who smoked before pregnancy (all p<0.0001). The

Table 3 Association of the intensity of maternal cigarette smoking with SNM

	Number of cigarettes consumed per day					
Outcomes	**0**	**1–2**	**3–5**	**6–9**	**10–19**	**≥20**
Before pregnancy						
Assisted ventilation immediately following delivery						
n (%)	404 007 (3.7)	3886 (5.0)	11 336 (5.3)	4128 (5.2)	19 208 (5.5)	23 069 (5.7)
OR (95% CI)	1.00	1.20 (1.16 to 1.24)	1.27 (1.24 to 1.30)	1.28 (1.23 to 1.32)	1.28 (1.26 to 1.30)	1.31 (1.29 to 1.33)
P value		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Assisted ventilation for >6 hours						
n (%)	128 751 (1.2)	1357 (1.8)	3832 (1.8)	1345 (1.7)	6322 (1.8)	7638 (1.9)
OR (95% CI)	1.00	1.26 (1.19 to 1.34)	1.28 (1.24 to 1.33)	1.25 (1.17 to 1.32)	1.24 (1.20 to 1.27)	1.29 (1.26 to 1.32)
P value		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
NICU admission for continuous mechanical ventilation						
n (%)	791 750 (7.2)	7233 (9.3)	20 421 (9.5)	7483 (9.5)	33 962 (9.6)	41 432 (10.2)
OR (95% CI)	1.00	1.13 (1.10 to 1.16)	1.19 (1.17 to 1.21)	1.22 (1.19 to 1.26)	1.24 (1.22 to 1.25)	1.29 (1.28 to 1.31)
P value		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Surfactant replacement therapy						
n (%)	37 449 (0.3)	402 (0.5)	1207 (0.6)	422 (0.5)	1981 (0.6)	2266 (0.6)
OR (95% CI)	1.00	1.16 (1.04 to 1.29)	1.29 (1.21 to 1.38)	1.28 (1.15 to 1.43)	1.24 (1.18 to 1.31)	1.24 (1.18 to 1.30)
P value		0.0081	<0.0001	<0.0001	<0.0001	<0.0001
Suspected neonatal sepsis						
n (%)	210 911 (1.9)	2098 (2.7)	5847 (2.7)	2141 (2.7)	9362 (2.7)	11 239 (2.8)
OR (95% CI)	1.00	1.24 (1.19 to 1.30)	1.28 (1.25 to 1.32)	1.32 (1.26 to 1.38)	1.29 (1.26 to 1.32)	1.32 (1.29 to 1.35)
P value		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Seizure or serious neurologic dysfunction						
n (‰)	3486 (3.2)	30 (3.9)	117 (5.4)	42 (5.3)	217 (6.2)	276 (6.8)
OR (95% CI)	1.00	1.03 (0.72 to 1.48)	1.44 (1.20 to 1.74)	1.41 (1.04 to 1.92)	1.57 (1.36 to 1.81)	1.68 (1.48 to 1.92)
P value		0.8626	0.0001	0.0266	<0.0001	<0.0001
Composite SNM*						
n (%)	998 056 (9.1)	9132 (11.8)	25 916 (12.1)	9557 (12.1)	43 424 (12.3)	52 558 (12.9)
OR (95% CI)	1.00	1.16 (1.13 to 1.19)	1.22 (1.20 to 1.24)	1.26 (1.23 to 1.29)	1.27 (1.25 to 1.28)	1.31 (1.30 to 1.33)
P value		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
In the first trimester						
Assisted ventilation immediately following delivery						
n (%)	417 880 (3.7)	3836 (5.3)	11 190 (5.5)	3614 (5.4)	17 467 (5.7)	11 705 (6.0)
OR (95% CI)	1.00	1.23 (1.19 to 1.28)	1.27 (1.25 to 1.30)	1.25 (1.21 to 1.29)	1.29 (1.27 to 1.31)	1.35 (1.32 to 1.38)
P value		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Assisted ventilation for >6 hours						
n (%)	133 149 (1.2)	1265 (1.8)	3774 (1.9)	1221 (1.8)	5855 (1.9)	3980 (2.1)
OR (95% CI)	1.00	1.18 (1.11 to 1.26)	1.25 (1.20 to 1.29)	1.23 (1.15 to 1.31)	1.25 (1.21 to 1.28)	1.34 (1.29 to 1.39)
P value		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
NICU admission for continuous mechanical ventilation						
n (%)	813 953 (7.2)	7104 (9.9)	20 237 (9.9)	6829 (10.2)	31 929 (10.3)	22 301 (11.5)
OR (95% CI)	1.00	1.18 (1.14 to 1.21)	1.22 (1.20 to 1.24)	1.27 (1.24 to 1.31)	1.31 (1.29 to 1.32)	1.43 (1.41 to 1.45)
P value		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Surfactant replacement therapy						
n (%)	38 694 (0.3)	390 (0.5)	1167 (0.6)	426 (0.6)	1827 (0.6)	1224 (0.6)
OR (95% CI)	1.00	1.12 (1.00 to 1.25)	1.20 (1.12 to 1.28)	1.38 (1.25 to 1.54)	1.23 (1.17 to 1.30)	1.35 (1.26 to 1.44)
P value		0.0500	<0.0001	<0.0001	<0.0001	<0.0001
Suspected neonatal sepsis						
n (%)	218 016 (1.9)	2066 (2.9)	5567 (2.7)	1816 (2.7)	8354 (2.7)	5785 (3.0)
OR (95% CI)	1.00	1.29 (1.24 to 1.35)	1.26 (1.22 to 1.30)	1.28 (1.22 to 1.34)	1.29 (1.26 to 1.32)	1.40 (1.37 to 1.44)
P value		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Seizure or serious neurologic dysfunction						
n (‰)	3630 (3.2)	20 (2.8)	125 (6.1)	33 (4.9)	221 (7.2)	138 (7.1)
OR (95% CI)	1.00	0.71 (0.46 to 1.10)	1.56 (1.30 to 1.87)	1.25 (0.89 to 1.77)	1.78 (1.54 to 2.05)	1.72 (1.44 to 2.05)
P value		0.1270	<0.0001	0.1989	<0.0001	<0.0001
Composite SNM*						

Continued

Table 3 Continued

Outcomes	Number of cigarettes consumed per day					
	0	1–2	3–5	6–9	10–19	≥20
n (%)	1 027 746 (9.1)	9030 (12.5)	25 629 (12.6)	8578 (12.8)	40 151 (13.0)	27 620 (14.2)
OR (95% CI)	1.00	1.22 (1.19 to 1.25)	1.25 (1.23 to 1.27)	1.29 (1.26 to 1.32)	1.32 (1.30 to 1.33)	1.42 (1.40 to 1.44)
P value		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
In the second trimester						
Assisted ventilation immediately following delivery						
n (%)	424 728 (3.7)	3803 (5.6)	11 330 (5.5)	3487 (5.4)	15 150 (5.6)	7155 (6.2)
OR (95% CI)	1.00	1.27 (1.22 to 1.31)	1.25 (1.23 to 1.28)	1.24 (1.19 to 1.28)	1.27 (1.25 to 1.29)	1.35 (1.32 to 1.39)
P value		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Assisted ventilation for >6 hours						
n (%)	135 379 (1.2)	1305 (1.9)	3841 (1.9)	1168 (1.8)	5070 (1.9)	2472 (2.2)
OR (95% CI)	1.00	1.27 (1.20 to 1.35)	1.24 (1.20 to 1.28)	1.22 (1.14 to 1.30)	1.24 (1.20 to 1.28)	1.34 (1.28 to 1.40)
P value		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
NICU admission for continuous mechanical ventilation						
n (%)	824 824 (7.2)	7063 (10.3)	21 194 (10.3)	6697 (10.3)	28 393 (10.5)	14 131 (12.3)
OR (95% CI)	1.00	1.21 (1.18 to 1.24)	1.26 (1.24 to 1.28)	1.30 (1.26 to 1.34)	1.33 (1.31 to 1.35)	1.50 (1.47 to 1.53)
P value		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Surfactant replacement therapy						
n (%)	39 342 (0.3)	387 (0.6)	1184 (0.6)	415 (0.6)	1610 (0.6)	784 (0.7)
OR (95% CI)	1.00	1.18 (1.06 to 1.32)	1.21 (1.14 to 1.29)	1.46 (1.31 to 1.62)	1.30 (1.23 to 1.37)	1.36 (1.26 to 1.47)
P value		0.0031	<0.0001	<0.0001	<0.0001	<0.0001
Suspected neonatal sepsis						
n (%)	221 300 (1.9)	2002 (2.9)	5658 (2.8)	1787 (2.7)	7212 (2.7)	3611 (3.1)
OR (95% CI)	1.00	1.31 (1.25 to 1.38)	1.27 (1.24 to 1.31)	1.31 (1.25 to 1.38)	1.29 (1.26 to 1.32)	1.47 (1.42 to 1.52)
P value		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Seizure or serious neurologic dysfunction						
n (‰)	3683 (3.2)	23 (3.4)	149 (7.2)	37 (5.7)	188 (7.0)	86 (7.5)
OR (95% CI)	1.00	0.85 (0.57 to 1.29)	1.83 (1.55 to 2.17)	1.44 (1.04 to 2.00)	1.73 (1.49 to 2.02)	1.79 (1.44 to 2.23)
P value		0.4503	<0.0001	0.0275	<0.0001	<0.0001
Composite SNM*						
n (%)	1 042 124 (9.1)	8920 (13.1)	26 527 (12.9)	8380 (12.9)	35 494 (13.2)	17 235 (15.0)
OR (95% CI)	1.00	1.25 (1.22 to 1.28)	1.27 (1.26 to 1.29)	1.30 (1.27 to 1.34)	1.33 (1.31 to 1.34)	1.47 (1.44 to 1.49)
P value		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
In the third trimester						
Assisted ventilation immediately following delivery						
n (%)	418 745 (3.7)	4592 (5.3)	11 360 (5.2)	2865 (5.1)	12 372 (5.4)	5940 (6.1)
OR (95% CI)	1.00	1.25 (1.22 to 1.29)	1.23 (1.21 to 1.26)	1.21 (1.16 to 1.25)	1.24 (1.21 to 1.26)	1.32 (1.28 to 1.36)
P value		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Assisted ventilation for >6 hours						
n (%)	130 968 (1.1)	1471 (1.7)	3598 (1.7)	921 (1.7)	4067 (1.8)	2002 (2.0)
OR (95% CI)	1.00	1.26 (1.20 to 1.34)	1.20 (1.16 to 1.25)	1.18 (1.10 to 1.26)	1.21 (1.17 to 1.26)	1.29 (1.23 to 1.36)
P value		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
NICU admission for continuous mechanical ventilation						
n (%)	816 290 (7.1)	8778 (10.0)	21 587 (9.9)	5664 (10.1)	23 606 (10.4)	11 943 (12.2)
OR (95% CI)	1.00	1.24 (1.21 to 1.27)	1.26 (1.24 to 1.28)	1.31 (1.27 to 1.35)	1.31 (1.29 to 1.33)	1.49 (1.45 to 1.52)
P value		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Surfactant replacement therapy						
n (%)	35 696 (0.3)	357 (0.4)	1005 (0.5)	298 (0.5)	1217 (0.5)	608 (0.6)
OR (95% CI)	1.00	1.14 (1.02 to 1.27)	1.24 (1.16 to 1.33)	1.41 (1.25 to 1.60)	1.30 (1.22 to 1.38)	1.36 (1.25 to 1.49)
P value		0.0223	<0.0001	<0.0001	<0.0001	<0.0001
Suspected neonatal sepsis						
n (%)	218 644 (1.9)	2415 (2.8)	5703 (2.6)	1453 (2.6)	5900 (2.6)	3028 (3.1)
OR (95% CI)	1.00	1.32 (1.26 to 1.37)	1.28 (1.24 to 1.31)	1.28 (1.22 to 1.35)	1.27 (1.24 to 1.31)	1.46 (1.40 to 1.52)
P value		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Seizure or serious neurologic dysfunction						
n (‰)	3668 (3.2)	41 (4.7)	151 (6.9)	30 (5.4)	163 (7.1)	68 (6.9)

Continued

Table 3 Continued

Outcomes	Number of cigarettes consumed per day					
	0	1–2	3–5	6–9	10–19	≥20
OR (95% CI)	1.00	1.21 (0.89 to 1.65)	1.78 (1.51 to 2.11)	1.38 (0.96 to 1.98)	1.79 (1.52 to 2.11)	1.68 (1.31 to 2.15)
P value		0.2272	<0.0001	0.0816	<0.0001	<0.0001
Composite SNM*						
n (%)	1 034 094 (9.0)	11 119 (12.7)	27 289 (12.5)	7118 (12.7)	29 496 (12.9)	14 550 (14.8)
OR (95% CI)	1.00	1.27 (1.24 to 1.30)	1.27 (1.26 to 1.29)	1.31 (1.28 to 1.35)	1.30 (1.28 to 1.32)	1.45 (1.42 to 1.48)
P value		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

Logistic regression models were adjusted for maternal age at delivery, race/ethnicity, educational level, marital status, pre-pregnancy body mass index, sex of infant, gestational age at delivery, parity, total number of prenatal care visits, eclampsia, gestational hypertension, and gestational diabetes.
*Composite SNM was defined as having one or more of the above outcomes.
NICU, neonatal intensive care unit; SNM, severe neonatal morbidity.

statistical significance existed for most individual components after the Bonferroni correction.

DISCUSSION

In this large population-based cohort of 12 150 535 mother-infant pairs in the USA, we found that maternal cigarette smoking before or during pregnancy increased the risk of infant composite SNM and individual components compared with maternal non-smoking in the considered specific period, even at a low dose of 1–2 cigarettes/day, suggesting there is no safe period and no safe level of cigarette smoking shortly before or during pregnancy. Compared with never smokers before and throughout pregnancy, mothers who stopped smoking in each trimester still had a higher risk of infant composite SNM.

Comparisons with other studies

Our findings expand the available evidence about adverse effects of maternal cigarette smoking before and during pregnancy on infant SNM. We found an increased risk of composite SNM in infants born to women who smoked cigarettes during pregnancy, inconsistent with a previous retrospective cohort study in Australia,[11] which reported no increased risk of overall SNM among women who smoked cigarettes during pregnancy (late preterm: OR 0.77, 95% CI 0.46 to 1.29; early term: OR 1.26, 95% CI 0.79 to 2.00). However, the Australia study included a smaller sample size (n=6243) than ours (recognising that large sample sizes are needed to study rare events such as SNM). Besides, in the Australia study the associations were estimated with adjustment for gestational age only, and participants were limited to late preterm and early term infants.[11] Finally, it is important to acknowledge that there is no 'gold standard' definition for composite SNM and therefore comparisons between studies should be made with caution.

With respect to individual SNM components, NICU admission has been the most frequently studied in relation to maternal cigarette smoking, but the findings in several previous studies have also been inconclusive.[9 10 22] A previous study using data from the NHS Foundation Trust in the UK (2017–2018; n=4465) showed no significant association between maternal cigarette smoking during pregnancy and infant admission to NICU.[10] In contrast, a nationwide population-based cohort study using data from the Finnish Medical Birth Register from 1991 to 2010 (n=1 164 953) showed that maternal smoking cessation in the first trimester (ie, smoking exposure during early pregnancy) was associated with an increased risk of infant NICU admission (OR 1.27, 95% CI 1.25 to 1.30).[9] Of note, the above mentioned studies included relatively small samples[10 22] or included adjustment for no covariate[10 22] or only a few covariates (ie, maternal age, parity, sex, pre-eclampsia, and gestational diabetes).[9] Our study was based on the largest sample size to date and showed a significant association between maternal cigarette smoking before and during pregnancy and infant NICU admission after adjusting for a fairly large number of potential confounders (n=12). One possible explanation is that maternal cigarette smoking can increase the risk of intrauterine growth restriction,[7 8 23] which in turn will increase the risk of infant NICU admission after delivery.[24]

We also observed a significant association between maternal cigarette smoking before and during pregnancy and seizure or serious neurologic dysfunction. One study used the same datasets (2013–2017) as the one used in this study and also reported that maternal smoking during pregnancy was associated with neonatal seizures (OR 1.50, 95% CI 1.33 to 1.69) at term.[25] However, the study only included term births, whereas preterm births were at a higher risk of neonatal seizures.[26 27] Several previous studies focused on febrile seizures in childhood (3 months to 5 years) showed an increased risk for children whose mothers smoked cigarettes during pregnancy,[28–30] which also support our findings. A biological mechanism may be that maternal cigarette smoking during pregnancy can alter brain structures of the fetus, including decreasing cortical thickness in the perisylvian and lateral occipital cortices, decreasing volume in the anterior cingulate, and increasing volume in the frontal regions.[31]

In addition, we observed an increased risk of suspected neonatal sepsis in offspring born to women who smoked cigarettes before or during pregnancy, which has been seldom reported in previous studies. This may indicate a potential link between maternal cigarette smoking and maternal immune response or placental function. A large cohort of infants born in Upstate New York reported that maternal cigarette smoking throughout pregnancy could alter cytokine signalling (eg, interleukin-8 (IL-8)) in newborns, which is a pro-inflammatory chemokine linked to various pathological conditions, such as impaired lung function and respiratory disorders.[32] Other novel findings of our study also include the associations of maternal cigarette smoking with assisted ventilation immediately following delivery, assisted ventilation for more than 6 hours, and surfactant replacement therapy. Our results suggest that maternal cigarette smoking before and during pregnancy can potentially serve as a marker of an increased risk of these neonatal morbidities.

It is worth mentioning that the previous studies above did not distinguish the effects of the timing of maternal cigarette smoking (before pregnancy or in different trimesters) on infant SNM. They

also did not explore in detail the associations between the intensity of maternal cigarette smoking and infant SNM. Our study showed that maternal cigarette smoking before pregnancy or in any trimester was associated with an increased risk of infant SNM, even at a low smoking intensity of 1–2 cigarettes per day. Another important finding of our study is that for mothers who smoked before pregnancy, smoking cessation during subsequent trimesters did not substantially decrease the risk of infant SNM. However, for a few smoking cessation subgroups (ie, groups 6, 10, and 11), the associations were only marginally (not statistically) significant, which may be attributed to the limited statistical power in these subgroups. Several large cohort studies[5 20 21 33] focusing on other neonatal outcomes (eg, preterm birth and congenital anomalies) also showed an elevated risk among women who smoked during pregnancy regardless of the timing and doses consumed. Overall, these data suggest that there is no safe period and no safe level of cigarettes consumed shortly before or during pregnancy.

Our findings re-emphasise the need to prevent smoking initiation for non-smokers and to promote smoking cessation for smokers. Interventions should also highlight the adverse effects of light smoking for pregnant women. Actually, numerous efforts have been done to promote smoking cessation among pregnant women in the USA. For example, in 2015, the US Preventive Services Task Force issued a clinical guideline on interventions for smoking cessation in adults, including pregnant women.[34] The guideline recommends that obstetricians should routinely ask pregnant women regarding smoking, advise those who smoke to stop immediately, and offer evidence-based cessation interventions.[34] Yet, the prevalence of maternal smoking before and during pregnancy remained high in our study. Therefore, it is imperative that strong tobacco control policies, such as strict national tobacco control laws and higher adherence to the WHO Framework Convention on Tobacco Control, are put into place in the USA.

Strengths and limitations

The major strengths of this study are that we used the largest sample size to date with over 12 million mother–infant pairs, which allowed us to examine thoroughly the associations of the timing (per trimester) and intensity (number of cigarettes per day) of maternal cigarette smoking with composite SNM and individual components (given that SNM is a relatively rare outcome), and that we could adjust for a fairly large number of potential confounders.

However, a few limitations exist. First, information on maternal cigarette smoking was self-reported by the mothers, which may introduce information bias. However, a previous study showed that self-reported maternal smoking was well correlated with objectively measured cotinine during pregnancy.[35] Second, for 'maternal prepregnancy smoking', the NVSS only collected data during the 3 months before pregnancy, making it impossible to distinguish between women who never smoked and those who ceased smoking before pregnancy. Third, the NVSS did not provide information on women's exposure to secondhand smoke, hindering us from examining the association between maternal secondhand smoke exposure during pregnancy and SNM in offspring. Finally, although we have adjusted for many potential confounders in this study, we cannot completely rule out residual confounding from unmeasured or unknown confounders.

CONCLUSIONS

Based on a large, population-based, birth cohort study, we found that maternal cigarette smoking, even at a low dose (1–2 cigarettes per day), either before pregnancy or in any pregnancy trimester, increased the risk of infant SNM. Our findings further support the advice that women of reproductive age should abstain from cigarette smoking in relation to SNM.

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Contributors BX conceptualised the study. LY (Lili Yang) drafted the manuscript. LY (Liu Yang) and HW analysed the data. BX, PB, YG and MZ critically revised the manuscript for key intellectual content. All authors approved the final version of the manuscript. BX is the guarantor. LY (Lili Yang) and LY (Liu Yang) are co-first authors.

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Patient consent for publication Not applicable.

Ethics approval This study involves human participants but 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. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. The birth certificate data from the National Vital Statistics System are available at the official website (https:// www.cdc.gov/nchs/nvss/births.htm).

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