

Birth-Certificate-Recorded Maternal HCV and Postneonatal Mortality in the United States

Sen Liang

Shandong Medical and Pharmaceutical University Hospital, Shandong Medical and Pharmaceutical University

Li Li

Shandong Medical and Pharmaceutical University Hospital, Shandong Medical and Pharmaceutical University

Chuanhou Zhang

wsbzls@163.com

Shandong Medical and Pharmaceutical University Hospital, Shandong Medical and Pharmaceutical University

Article

Keywords: maternal hepatitis C, postneonatal mortality, infant mortality, birth certificates, vital statistics

Posted Date: October 19th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-11164253/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Additional Declarations: No competing interests reported.

Abstract

Background

Maternal hepatitis C virus (HCV) has been associated with adverse birth outcomes and infant mortality, but overall infant mortality estimates may obscure differences across age-at-death windows. We estimated the association between birth-certificate-recorded maternal HCV and postneonatal mortality and assessed variation across infancy.

Methods

This population-based retrospective cohort included US resident live births in National Center for Health Statistics linked birth-infant death files, 2016–2022. The exposure was treated as a registry-based risk marker, not confirmed active infection. Modified Poisson regression, robust sandwich covariance, and marginal standardization estimated adjusted risks, risk differences (RDs), and risk ratios (RRs). A prespecified global test assessed heterogeneity across mutually exclusive windows.

Results

Among 26,066,234 births, 122,585 had recorded maternal HCV. For death at 28–364 days, standardized risks were 2.677 versus 1.907 per 1,000; adjusted RD was 0.770 per 1,000 (95% CI 0.563–0.977), and adjusted RR was 1.404 (95% CI 1.299–1.517). Adjusted RRs were 0.802 (95% CI 0.734–0.876) at 0–6 days, 1.159 (95% CI 0.999–1.344) at 7–27 days, and 1.058 (95% CI 1.003–1.117) at 0–364 days. Relative associations varied across mutually exclusive windows (Wald chi-square = 87.753; df = 2; $P = 8.80 \times 10^{-20}$). In the extended social and healthcare-detection model, the postneonatal RR attenuated to 1.278 (95% CI 1.183–1.382) and RD to 0.531 per 1,000 (95% CI 0.342–0.721).

Conclusions

Recorded maternal HCV was associated with higher postneonatal mortality, with attenuation after extended adjustment and potential residual confounding. This registry-based risk marker warrants surveillance and further follow-up research. The findings establish neither clinical predictive utility nor effects of active infection or vertical transmission.

Background

The epidemiology of hepatitis C virus (HCV) infection among pregnant people in the United States has changed alongside broader increases in infection among reproductive-aged adults. National Center for Health Statistics data showed that birth-certificate-reported maternal HCV rates rose from 421.4 per 100,000 births in 2016 to 506.5 per 100,000 in 2020, followed by a decline to 463.7 per 100,000 in 2021. In 2020, the Centers for Disease Control and Prevention (CDC) recommended HCV screening during each pregnancy, except in settings with an HCV prevalence below 0.1%. For infants born to people with current or probable HCV infection, CDC estimates that approximately 6%–7% acquire HCV perinatally and recommends nucleic acid testing for HCV RNA at age 2–6 months, partly because many exposed infants have historically not completed testing or linkage to care [1, 2, 3].

Previous studies have associated maternal HCV with preterm birth, impaired fetal growth, low birth weight, neonatal intensive care unit admission, and other adverse neonatal outcomes, although estimates vary across populations, exposure definitions, and adjustment strategies [4]. Rossi et al., using US birth records from 2009–2017, documented increasing birth-certificate-reported maternal HCV and included neonatal death recorded at birth-certificate filing among the studied outcomes [5]. More recent national natality and prospective multicenter studies have continued to identify associations with several adverse outcomes at or shortly after birth [6, 7]. Studies incorporating laboratory information further demonstrate

the importance of distinguishing HCV antibody positivity, resolved infection, and RNA-positive active infection—distinctions that are unavailable in birth-certificate data [8].

Evidence regarding mortality after birth is more limited. A 2025 Society for Maternal-Fetal Medicine conference abstract by Gedestad et al. used the 2015–2021 NCHS linked birth–infant death files and reported an association between maternal HCV status and overall infant mortality, but did not report mortality by neonatal and postneonatal intervals [9]. Weatherly et al. specifically examined sudden unexpected infant death (SUID) in the 2011–2015 linked files and reported an adjusted association with maternal HCV; the authors emphasized marked attenuation after socioeconomic and demographic adjustment and the likelihood of residual confounding [10]. Consequently, the unresolved question is not whether maternal HCV status is associated with infant mortality overall, but whether an overall estimate obscures variation across clinically distinct periods of infancy.

We therefore examined birth-certificate-recorded maternal HCV and infant mortality timing among US resident live births during 2016–2022. The primary objective was to estimate its association with unconditional cumulative all-cause mortality risk at 28–364 days, including standardized absolute risk and risk differences. Secondary objectives were to estimate associations for deaths at 0–6 days, 7–27 days, and 0–364 days and to formally evaluate heterogeneity across the three mutually exclusive mortality windows. Prespecified exploratory analyses described the cause-specific mortality structure.

Methods

Study design and data source

We conducted a population-based cohort study using the 2016–2022 US National Center for Health Statistics birth cohort linked birth–infant death files [14]. These files link information from live birth certificates to deaths occurring during the first year after birth. The study was designed as a vital-statistics-based risk-marker association study with surveillance relevance.

The 2023 linked cohort was used previously as a hypothesis-generating feasibility pilot and was not included in the present analytic cohort. For the 2016–2022 data, event feasibility and crude risks were examined before modeling; the statistical analysis plan, including the primary outcome, adjustment set, and modeling strategy, was frozen before adjusted results were run or reviewed.

Study population

The source population comprised all US resident live births from January 1, 2016, through December 31, 2022. Death information was obtained from the linked death numerator files. Deaths recorded in both the birth year and the subsequent calendar year were incorporated to provide complete follow-up through 364 days of age.

The maternal hepatitis C reporting flag (F_IP_HEPC) was used to identify records for which the hepatitis C item was reportable. Records with F_IP_HEPC = 0 were excluded because absence of a reported positive result could not be interpreted as absence of maternal HCV. Among records with F_IP_HEPC = 1, those coded unknown for maternal HCV were also excluded. The final analytic risk set therefore compared records coded yes versus no for birth-certificate-recorded maternal HCV.

Exposure

The exposure was birth-certificate-recorded maternal HCV, defined using the birth-certificate item IP_HEPC among records with a valid reporting flag. Exposure status was obtained exclusively from the birth-year denominator record.

This variable identifies a positive HCV test documented on the birth certificate or its underlying medical record. It does not distinguish HCV antibody positivity from RNA-confirmed active infection and contains no information about viral load, spontaneous clearance, antiviral treatment, or vertical transmission. It was therefore analyzed as a recorded maternal risk marker rather than as a measure of active maternal infection.

Outcomes

The primary outcome was all-cause death at 28–364 days of age. The primary estimand was the unconditional cumulative mortality risk during this interval among all eligible live births, rather than mortality conditional on survival to day 28.

Prespecified secondary outcomes were death at 0–6 days, 7–27 days, and 0–364 days. Window-specific outcomes represented death within the specified interval among the complete eligible live-birth cohort. Age at death was derived from the official NCHS death-age fields according to the applicable annual record layouts.

Cause-of-death classification

Prespecified exploratory analyses classified deaths during infancy into seven mutually exclusive and collectively exhaustive categories based on the underlying cause of death: congenital anomalies, disorders related to preterm birth or low birth weight, infection or sepsis, other perinatal conditions, sudden unexpected infant death (SUID), external causes, and all other causes. The corresponding International Classification of Diseases, Tenth Revision (ICD-10) definitions are provided in Additional file 1, eTable 6.

These analyses were intended to describe the distribution of mortality associations and were not designed to identify biological or social mechanisms.

For the external-causes exploratory model only, triplet and quadruplet-plus births were combined as triplet_or_higher because the quadruplet-plus category had zero external-cause deaths and produced a boundary maximum-likelihood problem. No other cause-specific model used this collapse.

Covariates

The frozen primary adjustment set included birth-year fixed effects; maternal age; race/ethnicity; education; nativity; marital status; parity; prepregnancy body mass index (BMI); cigarette-smoking trajectory; pregestational diabetes; chronic hypertension; plurality; and infant sex (Table 1). Exact source fields and the actual categories and reference levels used in the effective final models are provided in eTable 1; the prespecified covariate framework is depicted in eFigure 1. The effective model retained separate master's and doctoral/professional education categories and separate parity categories of 7 and 8 or more; its reference categories were maternal age younger than 15 years, education of 8th grade or less, underweight BMI, and female infant sex. Covariates were selected before adjusted results were examined and were not selected according to statistical significance or changes in the exposure coefficient.

Table 1
Birth Cohort Characteristics by Recorded Maternal HCV Status, United States, 2016–2022

Characteristic	Level	Recorded maternal HCV, No. (%)	No recorded maternal HCV, No. (%)	Absolute SMD
Birth year	2016	15983 (13.0)	3782225 (14.6)	0.045
Birth year	2017	18086 (14.8)	3827438 (14.8)	0.000
Birth year	2018	18927 (15.4)	3764325 (14.5)	0.026
Birth year	2019	18917 (15.4)	3719152 (14.3)	0.031
Birth year	2020	18246 (14.9)	3583972 (13.8)	0.031
Birth year	2021	16923 (13.8)	3632523 (14.0)	0.006
Birth year	2022	15503 (12.6)	3634014 (14.0)	0.040
Maternal age, y	Under 15	9 (0.0)	13022 (0.1)	0.025
Maternal age, y	15–19	1613 (1.3)	1194710 (4.6)	0.195
Maternal age, y	20–24	18540 (15.1)	4898601 (18.9)	0.100
Maternal age, y	25–29	43683 (35.6)	7409616 (28.6)	0.152
Maternal age, y	30–34	38088 (31.1)	7578930 (29.2)	0.040
Maternal age, y	35–39	17346 (14.2)	3948340 (15.2)	0.030
Maternal age, y	40–44	3160 (2.6)	834673 (3.2)	0.038
Maternal age, y	45–49	125 (0.1)	58936 (0.2)	0.031
Maternal age, y	50–54	21 (0.0)	6821 (0.0)	0.006
Race/ethnicity	Non-Hispanic White	97088 (79.2)	13291398 (51.2)	0.614
Race/ethnicity	Non-Hispanic Black	6062 (4.9)	3740768 (14.4)	0.325
Race/ethnicity	Non-Hispanic American Indian or Alaska Native	3254 (2.7)	193418 (0.7)	0.148
Race/ethnicity	Non-Hispanic Asian	1444 (1.2)	1616484 (6.2)	0.270
Race/ethnicity	Non-Hispanic Native Hawaiian or Other Pacific Islander	68 (0.1)	67038 (0.3)	0.051
Race/ethnicity	Non-Hispanic multiracial	3555 (2.9)	584188 (2.3)	0.041
Race/ethnicity	Hispanic	9707 (7.9)	6215896 (24.0)	0.449
Race/ethnicity	Origin unknown	1407 (1.1)	234459 (0.9)	0.024
Maternal education	≤ 8th grade	3530 (2.9)	813998 (3.1)	0.015
Maternal education	9th–12th grade, no diploma	25581 (20.9)	2326983 (9.0)	0.339
Maternal education	High school graduate or GED	50386 (41.1)	6630788 (25.6)	0.334
Maternal education	Some college, no degree	28524 (23.3)	5012207 (19.3)	0.097
Maternal education	Associate degree	5869 (4.8)	2152912 (8.3)	0.142
Values are No. (%) within maternal-HCV group. Absolute standardized mean differences are category-specific absolute binary SMDs. No baseline hypothesis-testing P values are reported.				

Characteristic	Level	Recorded maternal HCV, No. (%)	No recorded maternal HCV, No. (%)	Absolute SMD
Maternal education	Bachelor's degree	4454 (3.6)	5398167 (20.8)	0.543
Maternal education	Master's degree	1328 (1.1)	2512942 (9.7)	0.388
Maternal education	Doctorate or professional degree	355 (0.3)	733008 (2.8)	0.206
Maternal education	Unknown or not stated	2558 (2.1)	362644 (1.4)	0.053
Maternal nativity	US-born	115597 (94.3)	20058437 (77.3)	0.502
Maternal nativity	Foreign-born	6147 (5.0)	5833262 (22.5)	0.524
Maternal nativity	Unknown or not stated	841 (0.7)	51950 (0.2)	0.073
Marital status	Married	28142 (23.0)	14001107 (54.0)	0.672
Marital status	Unmarried	90991 (74.2)	9320308 (35.9)	0.834
Marital status	Unknown or not stated	3452 (2.8)	2622234 (10.1)	0.300
Live birth order	1	27703 (22.6)	9871982 (38.1)	0.341
Live birth order	2	33803 (27.6)	8294633 (32.0)	0.096
Live birth order	3	27847 (22.7)	4397823 (17.0)	0.145
Live birth order	4	16931 (13.8)	1921041 (7.4)	0.209
Live birth order	5	8566 (7.0)	761959 (2.9)	0.187
Live birth order	6	3889 (3.2)	322765 (1.2)	0.132
Live birth order	7	1751 (1.4)	146837 (0.6)	0.087
Live birth order	8 or more	1492 (1.2)	158495 (0.6)	0.064
Live birth order	Unknown or not stated	603 (0.5)	68114 (0.3)	0.037
Prepregnancy BMI	Underweight	5508 (4.5)	770416 (3.0)	0.080
Prepregnancy BMI	Normal weight	56549 (46.1)	10433798 (40.2)	0.120
Prepregnancy BMI	Overweight	30951 (25.2)	6809875 (26.2)	0.023
Prepregnancy BMI	Obesity class I	14644 (11.9)	3954513 (15.2)	0.096
Prepregnancy BMI	Obesity class II	6094 (5.0)	1972834 (7.6)	0.109
Prepregnancy BMI	Obesity class III	3848 (3.1)	1424392 (5.5)	0.116
Prepregnancy BMI	Unknown or not stated	4991 (4.1)	577821 (2.2)	0.106
Cigarette smoking trajectory	No recorded smoking	46248 (37.7)	23851324 (91.9)	1.379
Cigarette smoking trajectory	Prepregnancy only	4319 (3.5)	457470 (1.8)	0.110
Cigarette smoking trajectory	Any smoking during pregnancy	69033 (56.3)	1421427 (5.5)	1.317
Values are No. (%) within maternal-HCV group. Absolute standardized mean differences are category-specific absolute binary SMDs. No baseline hypothesis-testing P values are reported.				

Characteristic	Level	Recorded maternal HCV, No. (%)	No recorded maternal HCV, No. (%)	Absolute SMD
Cigarette smoking trajectory	Unknown or not stated	2985 (2.4)	213428 (0.8)	0.128
Pregestational diabetes	No	120844 (98.6)	25674674 (99.0)	0.035
Pregestational diabetes	Yes	1432 (1.2)	258693 (1.0)	0.017
Pregestational diabetes	Unknown or not stated	309 (0.3)	10282 (0.0)	0.056
Chronic hypertension	No	117916 (96.2)	25340995 (97.7)	0.086
Chronic hypertension	Yes	4360 (3.6)	592372 (2.3)	0.076
Chronic hypertension	Unknown or not stated	309 (0.3)	10282 (0.0)	0.056
Plurality	Singleton	117763 (96.1)	25089207 (96.7)	0.034
Plurality	Twin	4708 (3.8)	831388 (3.2)	0.035
Plurality	Triplet	114 (0.1)	21892 (0.1)	0.003
Plurality	Quadruplet or higher	0 (0.0)	1162 (0.0)	0.009
Infant sex	Male	62748 (51.2)	13267294 (51.1)	0.001
Infant sex	Female	59837 (48.8)	12676355 (48.9)	0.001
Values are No. (%) within maternal-HCV group. Absolute standardized mean differences are category-specific absolute binary SMDs. No baseline hypothesis-testing P values are reported.				

Table 2

All-Cause Infant Mortality According to Age-at-Death Window and Birth-Certificate-Recorded Maternal HCV Status

Age-at-death window	Designation	Recorded maternal HCV events/N	No recorded maternal HCV events/N	Standardized risk: recorded maternal HCV, per 1000	Standardized risk: no recorded maternal HCV, per 1000	Adjusted RD per 1000 (95% CI)	Adjusted RR (95% CI)
28–364 days	Primary	679/122585	49221/25943649	2.677	1.907	0.770 (0.563 to 0.977)	1.404 (1.299 to 1.517)
0–6 days	Secondary	509/122585	74853/25943649	2.322	2.896	-0.574 (-0.778 to -0.369)	0.802 (0.734 to 0.876)
7–27 days	Secondary	180/122585	18902/25943649	0.847	0.731	0.116 (-0.010 to 0.242)	1.159 (0.999 to 1.344)
0–364 days	Overall	1368/122585	142976/25943649	5.858	5.535	0.323 (0.006 to 0.641)	1.058 (1.003 to 1.117)
Risks are unconditional cumulative risks among all eligible live births. The 0-6-, 7-27-, and 28-364-day outcomes are mutually exclusive; 0-364 days is their composite. Global heterogeneity: Wald chi-square = 87.753, df = 2, P = 8.80 x 10 ⁻²⁰ . No pairwise comparisons were prespecified.							

Table 3

Prespecified Exploratory Cause-Specific Infant Mortality According to Birth-Certificate-Recorded Maternal HCV Status

Cause category	Recorded maternal HCV deaths	No recorded maternal HCV deaths	Standardized risk: recorded maternal HCV, per 1000	Standardized risk: no recorded maternal HCV, per 1000	Adjusted RD per 1000 (95% CI)	Adjusted RR (95% CI)
Congenital anomalies	181	29422	1.065	1.136	-0.071 (-0.229 to 0.087)	0.938 (0.809 to 1.087)
Preterm/LBW	128	23613	0.601	0.913	-0.312 (-0.418 to -0.207)	0.658 (0.552 to 0.784)
Infection/sepsis	67	8356	0.346	0.323	0.023 (-0.061 to 0.107)	1.071 (0.840 to 1.365)
Other perinatal conditions	310	41117	1.391	1.591	-0.200 (-0.357 to -0.043)	0.875 (0.781 to 0.979)
SUID	475	23789	1.504	0.924	0.580 (0.440 to 0.721)	1.628 (1.483 to 1.789)
External causes	100	4844	0.333	0.188	0.145 (0.077 to 0.213)	1.773 (1.445 to 2.177)
Other causes	107	11835	0.532	0.458	0.074 (-0.029 to 0.177)	1.162 (0.958 to 1.410)
Prespecified exploratory analysis. Categories are mutually exclusive and collectively exhaustive. Cause-specific associations do not establish HCV-specific mechanisms.						

Gestational age, birth weight, and congenital anomalies were excluded from the primary adjustment set because they could reflect pregnancy or neonatal pathways occurring after ascertainment of the maternal risk marker. Variables included only in the extended social/detection model were likewise excluded from the primary model.

Statistical analysis

We summarized exposure counts and deaths within each prespecified mortality window. Associations between birth-certificate-recorded maternal HCV and mortality were estimated using modified Poisson regression with robust sandwich standard errors and the frozen adjustment set, including birth-year fixed effects.

Adjusted risks were obtained through marginal standardization by predicting mortality for the analytic population under each exposure level and averaging the resulting predicted risks. We report standardized risks per 1,000 live births, adjusted risk differences (RDs) per 1,000 live births, adjusted risk ratios (RRs), and 95% confidence intervals. RR confidence intervals were Wald intervals on the log-RR scale; RD confidence intervals used the analytic gradient of the standardized RD with the HC0 sandwich covariance matrix.

Variation in the adjusted relative association across the three mutually exclusive mortality windows—0–6, 7–27, and 28–364 days—was evaluated using a prespecified global 2-df Wald test. The test was implemented using stacked estimating equations and an infant-clustered HC0 joint sandwich covariance matrix, thereby retaining cross-window covariance. No pairwise comparisons between individual windows were prespecified.

Cause-specific analyses used the same frozen primary adjustment framework and were designated exploratory.

Ethics

Ethics approval and consent to participate: This study used publicly available, deidentified data from the National Center for Health Statistics. Institutional review board review was not required. Informed consent was not required because the study involved secondary analysis of publicly available, deidentified data.

Sensitivity analyses

A prespecified extended social/detection model added payer, participation in the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC), prenatal-care initiation, hepatitis B, syphilis, gonorrhea, and chlamydia to evaluate attenuation after additional control for measured social and healthcare-detection characteristics. This model was not interpreted causally.

Separate pathway-attenuation models sequentially added gestational age, birth weight, and congenital anomalies to the primary model. These models were used only to describe changes in the association after conditioning on these variables; they were not mediation analyses and did not estimate direct effects.

Data processing and reproducibility

Annual fixed-width denominator and linked death numerator files were processed using year-specific official record layouts. Exposure status was obtained from denominator records, whereas death status, age at death, and underlying cause were obtained from linked numerator records. Cohort construction incorporated deaths occurring in the calendar year following birth when required for complete infant follow-up.

Source-level validation included reproduction of official cohort counts, verification of reporting flags and exposure coding, assessment of duplicate and invalid records, and confirmation that deaths across the three mutually exclusive age windows summed to total infant deaths. The global heterogeneity test and cause-of-death classification were independently verified.

Variable definitions, annual source mapping, and locked supplementary results are provided in Additional file 1. Analysis code and supporting reproducibility materials are available from the corresponding author on reasonable request.

Values are No. (%) within maternal-HCV group. Absolute standardized mean differences are category-specific absolute binary SMDs. No baseline hypothesis-testing P values are reported.

Risks are unconditional cumulative risks among all eligible live births. The 0-6-, 7-27-, and 28-364-day outcomes are mutually exclusive; 0-364 days is their composite. Global heterogeneity: Wald chi-square = 87.753, df = 2, P = 8.80×10^{-20} . No pairwise comparisons were prespecified.

Prespecified exploratory analysis. Categories are mutually exclusive and collectively exhaustive. Cause-specific associations do not establish HCV-specific mechanisms.

Results

The 2016–2022 source population included 26,286,324 US resident live births. The maternal HCV item was not reportable (F_IP_HEPC=0) for 138,662 births. Among births for which the item was reportable, 81,428 had unknown HCV status and were excluded.

The final analytic risk set included 26,066,234 births: 122,585 with and 25,943,649 without birth-certificate-recorded maternal HCV. Among exposed and unexposed births, respectively, there were 509 and 74,853 deaths at 0–6 days, 180 and 18,902 deaths at 7–27 days, and 679 and 49,221 deaths at 28–364 days. Overall, 1,368 exposed and 142,976 unexposed infants died during days 0–364 (Figure 1; Table 1). Expanded cohort characteristics and missingness are provided in eTable 2, and annual exposure and linked-mortality counts are provided in eTable 3.

For death at 28–364 days, the standardized risks were 2.677 per 1,000 births with birth-certificate-recorded maternal HCV and 1.907 per 1,000 births without recorded maternal HCV. The adjusted RD was 0.770 deaths per 1,000 births (95% CI, 0.563–0.977), and the adjusted RR was 1.404 (95% CI, 1.299–1.517; Table 2; Figure 2).

For death at 0–6 days, the standardized risks were 2.3222 and 2.8960 per 1,000 births with and without birth-certificate-recorded maternal HCV, respectively. The adjusted RD was –0.574 per 1,000 births (95% CI, –0.778 to –0.369), and the adjusted RR was 0.802 (95% CI, 0.734–0.876).

For death at 7–27 days, the adjusted RD was 0.116 per 1,000 births (95% CI, –0.010 to 0.242), and the adjusted RR was 1.159 (95% CI, 0.999–1.344).

Across the full 0–364-day period, the adjusted RD was 0.323 per 1,000 births (95% CI, 0.006–0.641), and the adjusted RR was 1.058 (95% CI, 1.003–1.117).

The adjusted relative association varied across mortality windows (global Wald $\chi^2=87.753$; df=2; P= 8.80×10^{-20}). The 28–364-day interval had the largest positive adjusted point estimate. No prespecified pairwise tests were conducted to compare individual windows.

In prespecified exploratory analyses, the adjusted RRs were 0.938 (95% CI, 0.809–1.087) for congenital anomalies, 0.658 (95% CI, 0.552–0.784) for preterm birth or low birth weight, 1.071 (95% CI, 0.840–1.365) for infection or sepsis, and 0.875 (95% CI, 0.781–0.979) for other perinatal conditions.

The adjusted RRs were 1.628 (95% CI, 1.483–1.789) for SUID, 1.773 (95% CI, 1.445–2.177) for external causes, and 1.162 (95% CI, 0.958–1.410) for other causes. These cause-specific estimates were exploratory and were not used to infer underlying mechanisms (Table 3; eTable 6).

After additional adjustment for the prespecified social and healthcare-detection variables, the association with death at 28–364 days was attenuated but remained positive. The adjusted RR was 1.278 (95% CI, 1.183–1.382), and the adjusted RD was 0.531 per 1,000 births (95% CI, 0.342–0.721; eTable 4).

The primary adjusted RR for death at 28–364 days was 1.404. After sequential inclusion of gestational age, the RR was 1.306 (95% CI, 1.209–1.412); after inclusion of birth weight, it was 1.292 (95% CI, 1.195–1.396); and after subsequent inclusion of congenital anomalies, it was 1.277 (95% CI, 1.181–1.381). These models describe attenuation after conditioning on the added variables and were not interpreted as mediation or direct-effect estimates (eTable 5).

Discussion

In this nationwide cohort of more than 26 million US resident live births, birth-certificate-recorded maternal HCV was associated with a higher adjusted observed risk of death at 28–364 days. Standardized postneonatal mortality risks were 2.677 and 1.907 per 1,000 births with and without recorded maternal HCV, respectively, corresponding to an adjusted RD of 0.770 per 1,000 births and an adjusted RR of 1.404. The adjusted relative association varied across mortality windows, with the 28–364-day interval having the largest positive adjusted point estimate. In contrast, the adjusted RR was 0.802 at 0–6 days and 1.159 at 7–27 days, whereas the association across the entire first year was comparatively small (RR, 1.058). These findings indicate that an aggregate infant mortality estimate can obscure substantial temporal heterogeneity.

Our findings extend, rather than replace, previous evidence. Rossi et al. described increasing birth-certificate-reported maternal HCV in the United States and reported an association with neonatal death recorded at birth-certificate filing, alongside preterm birth, small-for-gestational-age birth, neonatal intensive care, and assisted ventilation [5]. A 2025 analysis of the 2016–2021 natality files likewise reported associations with several adverse outcomes occurring at or near birth but did not evaluate linked mortality through the first year [6]. Gedestad et al. subsequently reported higher overall infant mortality in the 2015–2021 linked files in a conference abstract, establishing that the association was not confined to outcomes documented at delivery [9]. Our principal addition is the prespecified characterization of mortality timing, including postneonatal absolute risk and RD and a formal test of heterogeneity across mortality windows. It is not the first study of maternal HCV and infant mortality.

The small association for 0–364-day mortality should be interpreted in the context of the divergent window-specific estimates. Overall infant mortality is a cumulative contrast combining deaths arising during periods with different baseline risks and different adjusted associations; it is not a simple average of the three window-specific RRs. The relatively numerous deaths during the first week, together with an adjusted estimate below 1.0 in that interval, offset part of the positive postneonatal association. The resulting near-null overall RR therefore does not contradict the postneonatal finding. Instead, the global heterogeneity test supports the more specific conclusion that the adjusted relative association varied across mortality windows. Because pairwise comparisons were not prespecified, the results do not establish that the postneonatal association was statistically greater than each individual earlier-window association.

The direction change for deaths at 0–6 days—from a positive crude comparison to an adjusted RR of 0.802 in the same eligible cohort—was technically verified and is consistent with substantial confounding reversal arising from differences in measured baseline-risk characteristics. Nevertheless, this inverse adjusted estimate should not be interpreted as evidence that HCV prevents early neonatal death. Birth-certificate-recorded maternal HCV is nonrandomly ascertained, important social and substance-use characteristics remain unavailable, and restriction to live births may introduce selection concerns when a prenatal characteristic is associated with fetal survival [11]. Exposure misclassification and differential detection may also contribute. The early neonatal result is therefore best regarded as one component of the observed temporal heterogeneity rather than as a clinically beneficial association.

The exposure should be interpreted as a registry-recorded risk marker rather than a measure of active infection. NCHS instructs that the birth-certificate item be marked when a positive HCV test during pregnancy is documented in the medical record, but the item cannot distinguish antibody positivity from RNA-confirmed current infection [2]. Other surveillance work

has shown that birth certificates incompletely identify maternal HCV documented through laboratory reporting systems [12]. Moreover, studies with laboratory data demonstrate that pregnancy characteristics and outcomes can differ between RNA-positive and nonviremic individuals [8]. Birth-certificate-recorded maternal HCV may therefore mark a heterogeneous combination of infection history, screening and documentation, healthcare contact, and correlated clinical or social circumstances. It cannot identify infant HCV infection or vertical transmission.

Additional adjustment for measured social and healthcare-detection characteristics attenuated the postneonatal RR from 1.404 to 1.278 and the RD from 0.770 to 0.531 per 1,000 births. This attenuation indicates that the magnitude of the association was sensitive to the added measured characteristics, but it cannot quantify their contribution or remove residual confounding. In a three-state surveillance cohort of pregnancies with HCV, reported substance use was common, illustrating the close co-occurrence of HCV and substance-related circumstances in some populations [13]. The present data lacked detailed information about opioid exposure, injection-drug use, treatment, housing, household conditions, and postdischarge healthcare access. Persistence of an association after measured adjustment therefore does not establish a causal relationship.

Sequential conditioning on gestational age, birth weight, and congenital anomalies also attenuated the postneonatal RR, from 1.404 to 1.306, 1.292, and 1.277, respectively. These changes show that the estimate was sensitive to variables strongly related to infant mortality and pregnancy outcome. Because these variables may occur after ascertainment of the maternal risk marker and because the models were not designed for mediation analysis, the attenuation cannot be interpreted as mediation, a direct association, or a partition of pathways.

The exploratory cause-specific results provide descriptive context but do not identify why the timing pattern occurred. Positive adjusted associations were observed for SUID and external causes, whereas several predominantly perinatal categories had null or inverse estimates. Weatherly et al. previously reported an association between maternal HCV and SUID and specifically cautioned that residual socioeconomic and demographic confounding was likely [10]. Our SUID finding should therefore be considered supportive evidence in a more recent national cohort rather than a novel primary observation. The SUID and external-cause estimates are compatible with a broad postnatal vulnerability marker, but they do not demonstrate an HCV-specific mechanism. Unmeasured substance exposure, infant sleep and household environments, caregiver circumstances, and postdischarge healthcare access remain plausible sources of residual confounding. In addition, because the cause-specific analyses covered the full first year rather than decomposing each cause within every mortality window, they should not be presented as a statistical explanation for the postneonatal association.

Strengths of this study include its nationwide population base, inclusion of more than 26 million live births, linked birth and infant death information, prespecified mortality windows, reporting of both absolute and relative risks, and formal assessment of cross-window heterogeneity accounting for within-infant covariance. The primary outcome, adjustment framework, and modeling strategy were frozen before adjusted results were run or viewed, and the exposure, death-age construction, cause classification, cohort counts, and heterogeneity test underwent source-level and independent technical verification. These procedures reduce risks arising from outcome-driven modeling and data-processing errors.

Several limitations warrant emphasis. First, the birth-certificate exposure is subject to underascertainment and misclassification and cannot distinguish HCV antibody positivity from RNA-positive active infection, resolved infection, or a false-positive result. Information on viral load, treatment, spontaneous clearance, infant HCV status, and vertical transmission was unavailable. Second, screening practices changed during the study period, potentially altering which pregnancies were identified, and the HCV reporting item was not reportable for a subset of 2016 records. Although analyses were restricted to reportable records and included birth-year adjustment, calendar-time differences in ascertainment may remain. Third, detailed opioid and injection-drug use, other substance exposures, social and household environments, infant sleep circumstances, and longitudinal healthcare use were not available, leaving substantial potential for residual confounding. Fourth, vital records may contain errors in clinical variables, record linkage, age at death, and underlying cause-of-death classification despite the completed validation procedures. Fifth, the estimand applies to live-born infants; it does

not address fetal deaths, and conditioning on live birth limits causal interpretation of prenatal characteristics, particularly for early neonatal outcomes [11]. Finally, the 2023 feasibility pilot informed development of the timing question, and event counts and crude risks in the 2016–2022 cohort were reviewed before the adjusted analysis plan was frozen. The study should therefore not be characterized as an entirely untouched confirmatory analysis, although adjusted specifications were prospectively frozen relative to adjusted-result review.

Conclusion

Birth-certificate-recorded maternal HCV was associated with higher unconditional cumulative mortality risk at 28–364 days among US resident live births, and the adjusted relative association varied across mortality windows. The comparatively small overall infant mortality association obscured a larger positive postneonatal estimate and an inverse adjusted early neonatal estimate. Attenuation after extended adjustment and the potential for residual confounding limit interpretation. These findings support population surveillance and further follow-up research on a registry-based risk marker. Predictive performance and intervention effects were not evaluated, so the results do not establish clinical screening or risk-stratification utility. They do not establish that active HCV infection or vertical transmission caused infant deaths.

Abbreviations

BMI

Body mass index

CDC

Centers for Disease Control and Prevention

CI

Confidence interval

HCV

Hepatitis C virus

ICD-10

International Classification of Diseases, Tenth Revision

LBW

Low birth weight

NCHS

National Center for Health Statistics

RD

Risk difference

RR

Risk ratio

SMD

Standardized mean difference

SUID

Sudden unexpected infant death

WIC

Special Supplemental Nutrition Program for Women, Infants, and Children

Declarations

Ethics approval and consent to participate

This study used publicly available, deidentified data from the National Center for Health Statistics. Institutional review board review was not required. Informed consent was not required because the study involved secondary analysis of publicly

available, deidentified data.

Consent for publication

Not applicable.

Availability of data and materials

The public-use National Center for Health Statistics linked birth and infant death data files for 2016–2022 are available through the NCHS Linked Birth and Infant Death Data webpage (<https://www.cdc.gov/nchs/nvss/linked-birth.htm>), which provides access to downloadable public-use data files [14]. Analysis code and supporting reproducibility materials are available from the corresponding author on reasonable request; no public code repository DOI or URL has been assigned.

Competing interests

The authors declare that they have no competing interests.

Funding

No funding.

Authors' contributions

S.L. contributed to conceptualization, methodology, software, formal analysis, visualization, and writing the original draft. L.L. contributed to investigation, data curation, validation, and reviewing and editing the manuscript. C.Z. contributed to conceptualization, methodology, formal analysis, supervision, and reviewing and editing the manuscript. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

References

1. Schillie, S., Wester, C., Osborne, M., Wesolowski, L. & Ryerson, A. B. CDC recommendations for hepatitis C screening among adults—United States, 2020. *MMWR Recomm Rep.* **69** (2), 1–17. <https://doi.org/10.15585/mmwr.rr6902a1> (2020).
2. Ely, D. M. & Gregory, E. C. W. Trends and characteristics in maternal hepatitis C virus infection rates during pregnancy: United States, 2016–2021. *Natl. Vital Stat. Rep.* **72** (3), 1–12 (2023).
3. Panagiotakopoulos, L. et al. CDC recommendations for hepatitis C testing among perinatally exposed infants and children—United States, 2023. *MMWR Recomm Rep.* **72** (4), 1–21. <https://doi.org/10.15585/mmwr.rr7204a1> (2023).
4. Shen, G. F., Ge, C. H., Shen, W., Liu, Y. H. & Huang, X. Y. Association between hepatitis C infection during pregnancy with maternal and neonatal outcomes: a systematic review and meta-analysis. *Eur. Rev. Med. Pharmacol. Sci.* **27** (8), 3475–3488. https://doi.org/10.26355/eurev_202304_32120 (2023).

5. Rossi, R. M. et al. Reported prevalence of maternal hepatitis C virus infection in the United States. *Obstet. Gynecol.* **135** (2), 387–395. <https://doi.org/10.1097/AOG.0000000000003644> (2020).
6. Gulersen, M., Lenchner, E., Grunebaum, A., Chervenak, F. A. & Bornstein, E. Risk factors and adverse outcomes associated with hepatitis C virus in pregnancy. *J. Perinat. Med.* **53** (7), 821–826. <https://doi.org/10.1515/jpm-2025-0146> (2025).
7. Hughes, B. L. et al. NICHD Maternal-Fetal Medicine Units Network. Pregnancy outcomes in patients with hepatitis C virus infection. *Obstet. Gynecol.* **144** (4), 501–506. <https://doi.org/10.1097/AOG.0000000000005703> (2024).
8. Kushner, T. et al. Influence of hepatitis C viral parameters on pregnancy complications and risk of mother-to-child transmission. *J. Hepatol.* **77** (5), 1256–1264. <https://doi.org/10.1016/j.jhep.2022.05.016> (2022).
9. Gedestad, I. et al. The association between hepatitis C virus infection during pregnancy and risk of infant death [conference abstract, Poster 505]. *Pregnancy. ;1 Suppl 1*:e12026. (2025). <https://doi.org/10.1002/pmf2.12026>
10. Weatherly, M. et al. Maternal infections in pregnancy and the risk of sudden unexpected infant death in the offspring in the U.S., 2011–2015. *PLoS One.* **18** (4), e0284614. <https://doi.org/10.1371/journal.pone.0284614> (2023).
11. Liew, Z., Olsen, J., Cui, X., Ritz, B. & Arah, O. A. Bias from conditioning on live birth in pregnancy cohorts: an illustration based on neurodevelopment in children after prenatal exposure to organic pollutants. *Int. J. Epidemiol.* **44** (1), 345–354. <https://doi.org/10.1093/ije/dyu249> (2015).
12. Gowda, C. et al. Enhanced identification of maternal hepatitis C virus infection using existing public health surveillance systems. *Paediatr. Perinat. Epidemiol.* **32** (4), 401–410. <https://doi.org/10.1111/ppe.12481> (2018).
13. Woodworth, K. R. et al. Birth outcomes among people with hepatitis C in pregnancy—Three U.S. states, 2018–2021. *Matern Child. Health J.* **28** (6), 979–983. <https://doi.org/10.1007/s10995-024-03917-3> (2024).
14. National Center for Health Statistics. Linked Birth and Infant Death Data. <https://www.cdc.gov/nchs/nvss/linked-birth.htm>. Accessed 24 September 2026.

Figures

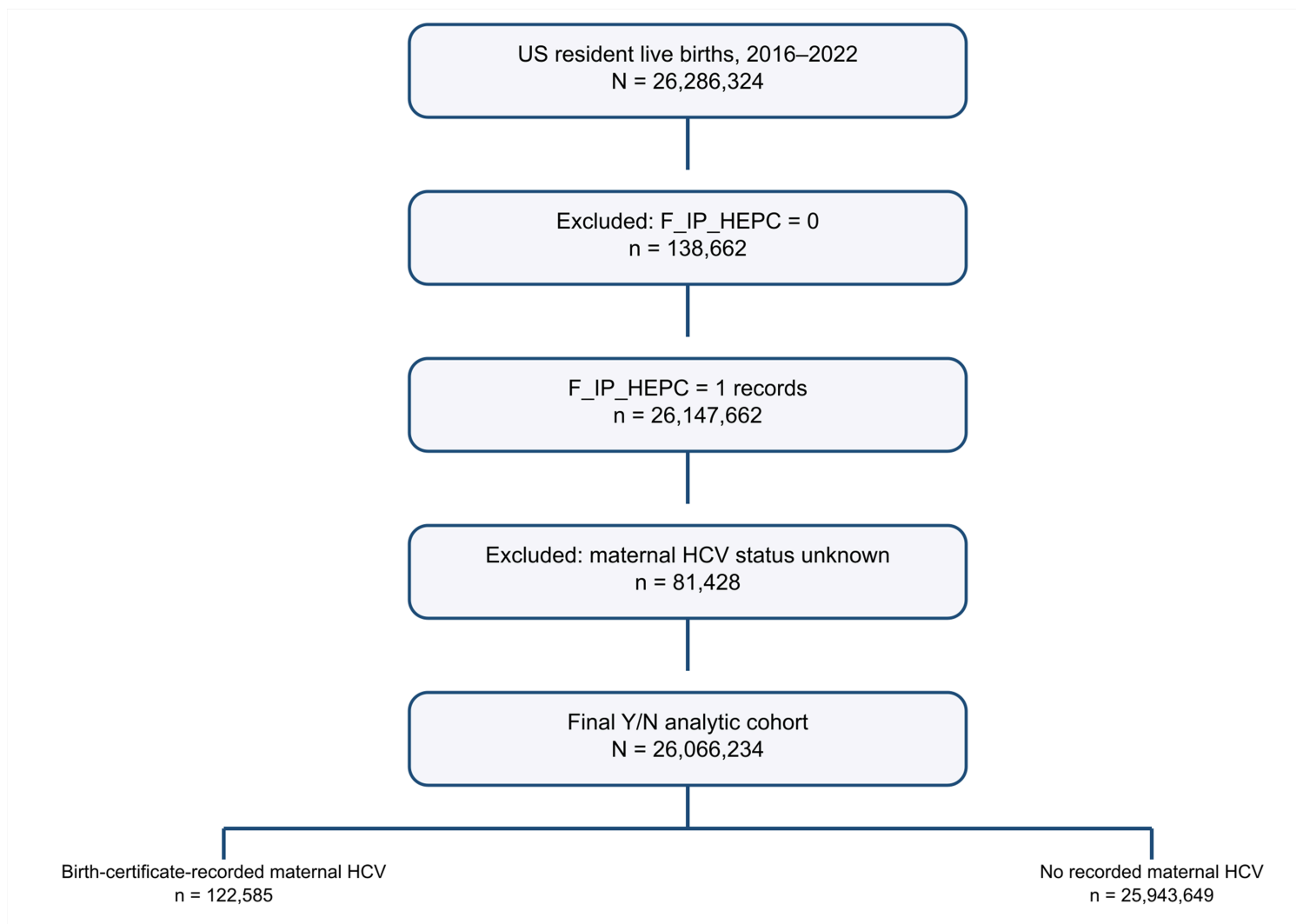


Figure 1

Construction of the Analytic Birth Cohort. Exposure status was obtained from birth-year denominator records. Infant deaths were identified from linked death numerator records. F_IP_HEPC=0 records and records with unknown maternal HCV status were excluded before the final Y/N analytic cohort was defined.

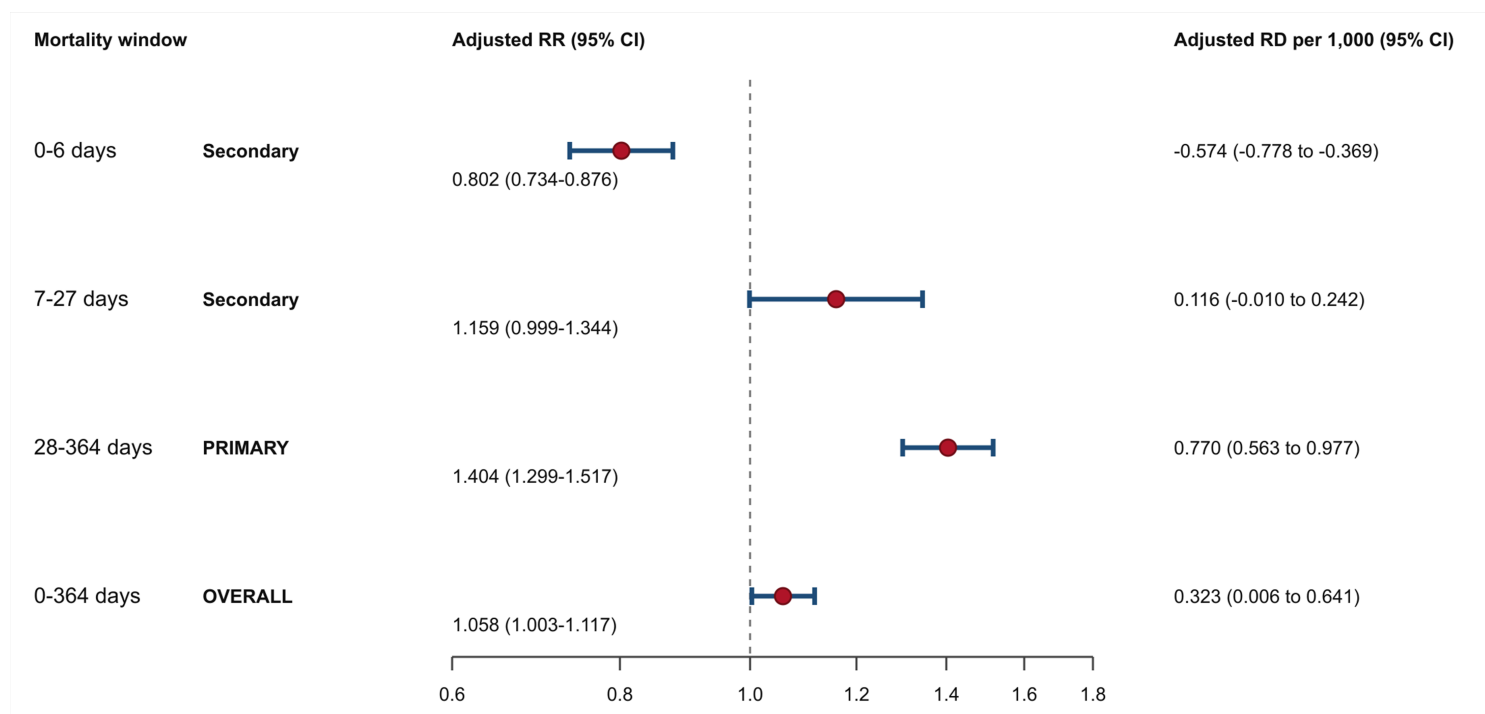


Figure 2

Adjusted Associations Between Recorded Maternal HCV and Infant Mortality Across Age Windows. Estimates are from the frozen primary modified Poisson model with robust sandwich covariance and marginal standardization. The 0-6-, 7-27-, and 28-364-day windows are mutually exclusive. The 0-364-day estimate is an overlapping overall outcome. Global heterogeneity: Wald chi-square=87.753; df=2; $P=8.80 \times 10^{-20}$. No pairwise comparisons were prespecified.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Listofadditionalfileslegends.docx](#)
- [SupplementaryMaterialv1.1.docx](#)