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ORIGINAL RESEARCH ARTICLE

Comparative Safety Analysis of Opioid Agonist Treatment in Pregnant Women with Opioid Use Disorder: A Population-Based Study

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Abstract

Introduction and Objective Receipt of opioid agonist treatment during early and late pregnancy for opioid use disorder may relate to varying perinatal risks. We aimed to assess the effect of time-varying prenatal exposure to opioid agonist treatment using buprenorphine or methadone on adverse neonatal and pregnancy outcomes.

Methods We conducted a retrospective cohort study of pregnant women with opioid use disorder using Rhode Island Medicaid claims data and vital statistics during 2008–16. Time-varying exposure was evaluated in early (0–20 weeks) and late (≥ 21 weeks) pregnancy. Marginal structural models with inverse probability of treatment weighting were applied.

Results Of 400 eligible pregnancies, 85 and 137 individuals received buprenorphine and methadone, respectively, during early pregnancy. Compared with 152 untreated pregnancies with opioid use disorders, methadone exposure in both periods was associated with an increased risk of preterm birth (adjusted odds ratio [aOR]: 2.52; 95% confidence interval [CI] 1.07–5.95), low birth weight (aOR: 2.99; 95% CI 1.34–6.66), neonatal intensive care unit admission (aOR, 5.04; 95% CI 2.49–10.21), neonatal abstinence syndrome (aOR: 11.36; 95% CI 5.65–22.82), respiratory symptoms (aOR, 2.71; 95% CI 1.17–6.24), and maternal hospital stay > 7 days (aOR, 14.51; 95% CI 7.23–29.12). Similar patterns emerged for buprenorphine regarding neonatal abstinence syndrome (aOR: 10.27; 95% CI 4.91–21.47) and extended maternal hospital stay (aOR: 3.84; 95% CI 1.83–8.07). However, differences were found favoring the use of buprenorphine for preterm birth versus untreated pregnancies (aOR: 0.17; 95% CI 0.04–0.77), and for several outcomes versus methadone.

Conclusions Methadone and buprenorphine prescribed for the treatment of opioid use disorder during pregnancy are associated with varying perinatal risks. However, buprenorphine may be preferred in the setting of pregnancy opioid agonist treatment. Further research is necessary to confirm our findings and minimize residual confounding.

Key Points

In the context of pregnancy opioid agonist treatments, different agents prescribed for opioid use disorders are associated with varying perinatal risks; however, buprenorphine may be preferred to methadone.

Clinical practitioners must weigh the potentially undesired consequences of opioid agonist treatments for opioid use disorder in pregnancy against their effectiveness in reducing opioid use disorder-related morbidity and mortality.

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1 Introduction

Methadone and buprenorphine are commonly prescribed opioid agonist treatments (OATs) used for the treatment of opioid use disorder (OUD) with different pharmacological profiles [1]. Both have well-established benefits to minimize withdrawal symptoms and fatal overdose while encouraging adequate prenatal care among pregnant opioid-dependent individuals [2–4]. Comparative effects and safety of methadone or buprenorphine have been evaluated and are routinely accepted for use in pregnant women. However, conflicting findings regarding the associations between OATs and pregnancy and infant outcomes have been reported in the literature. Data based on multiple randomized controlled trials and a few observational studies suggested improved outcomes are associated with buprenorphine in regard to fetal heartbeat suppression and reactivity [5, 6], gestational age [7, 8], birth weight [8, 9], head circumference [9], incidences of neonatal abstinence syndrome (NAS) [10], the length of treatment for NAS [8, 11], and neonatal hospital stay compared with methadone [3, 10, 11]. In contrast, other studies using real-world data suggest the non-inferiority of methadone [12–14].

Despite adhering to standards of care with either opiate agonist [2, 3], the safety of their use for pregnant women and birth outcomes has yet to be evaluated comparing OAT-treated pregnancies to untreated pregnancies. Additionally, the timing of OAT use in (early or late) pregnancy has rarely been examined. Hence, this study aims to utilize Rhode Island (RI) Medicaid data linked to vital statistics to examine the association of neonatal and pregnancy outcomes with time-varying prenatal exposure to OAT using either buprenorphine or methadone when compared to untreated OUD pregnancies.

2 Methods

2.1 Data Source

We conducted a retrospective cohort study using the RI Medicaid administrative claims database pertaining to mothers and newborns linked to vital statistics between 2008 and 2016, provided by the RI Department of Health and the RI Executive Office of Health & Human Services. Linkage between mothers and their offspring at the pregnancy level was provided along with the provision of the linked data. The Medicaid claims database contains the eligibility files and pharmacy and medical claims. Vital statistics include information on neonatal and pregnancy characteristics (e.g., date of delivery and ultrasound-based estimation of gestational age). The beginning of pregnancy was estimated by subtracting ultrasound-based estimates of gestational age from the date of delivery. This study was approved and granted a waiver of informed consent by the Institutional Review Board of The University of Rhode Island (IRB 1289357-4) and the RI Department of Health (IRB#: 2019-11).

2.2 Cohort Definition

The initial cohort included women aged 12–55 years who had live births between 1 January, 2008 and 31 December, 2016, and had continuous Medicaid enrollment from 3 months prior to the date of conception until 30 days postpartum. Women included into the final study cohort were required to have one or more medical claims indicating OUD or opioid dependence from 3 months prior to pregnancy until delivery (eFig. 1 of the Electronic Supplementary Material [ESM]). The operational definition of OUD using a claims database is provided in eTable 1 of the ESM.

2.3 Exposures

Exposure to methadone prescribed for OUD was determined using inpatient or outpatient medical claims coded by the International Classification of Disease, Ninth or Tenth Revision (ICD-9/10), Current Procedural Terminology, Fourth Edition, and the Health Common Procedure Coding System codes (H0020, J1230) [15]. To determine exposure to US Food and Drug Administration-approved buprenorphine maintenance treatment for OUD, we included generic and brand names (containing buprenorphine hydrochloride, buprenorphine-naloxone, Suboxone®, Subutex®, Zubsolv®, Sublocade®, and Bunavail®) based on pharmacy claims and verified by cross-referencing the data with National Drug Codes for each product [16]. Starting from the date of conception, exposure was time dependent and re-evaluated in two gestational periods, early (0–20 gestational weeks) and late pregnancy (21 gestational weeks to delivery). In a given gestational period, pregnancies with at least one dispensation of buprenorphine indicated for OUD were defined as exposed to buprenorphine, and those with at least one medical claim indicative of administration of methadone for OUD were defined as exposed to methadone. Pregnancies with potential for receiving both buprenorphine and methadone within any specified gestational period (i.e., early or late in pregnancy; $n = 14$) were excluded, while those who switched OATs during different gestational periods were captured. Pregnancies that did not receive OAT were defined as the untreated group. As a result, there were three possible values for early and late exposure: untreated, buprenorphine,

and methadone (eTable 2 of the ESM). The treatment pattern of using OATs for OUD is illustrated using a Sankey plot (eFig. 2 of the ESM).

2.4 Outcomes

Outcomes comprised adverse neonatal and pregnancy outcomes that were evaluated from the date of delivery up to 30 days postpartum. Adverse neonatal outcomes were preterm birth (< 37 weeks), low birth weight (< 2500 g), small for gestational age (SGA), feeding difficulties, respiratory symptoms (i.e., respiratory distress syndrome and transient tachypnea of newborn) after birth, neonatal intensive care unit admission (NICUa), and NAS. Adverse pregnancy outcomes included caesarean delivery, pre-eclampsia or eclampsia, postpartum hemorrhage, and extended length of maternal hospital stay (> 7 days). Outcomes were defined using data obtained from RI vital statistics or inpatient and outpatient medical claims pertaining to mothers or their offspring within 30 days after birth [17], coded by ICD-9/10 Clinical Modification diagnostic and procedural codes (operational definitions are provided in eTable 3 of the ESM).

2.5 Covariates

Based on subject matter knowledge and a literature review [18, 19], baseline time-invariant covariates and time-varying covariates at baseline and during pregnancy were identified using ICD-9/10 diagnostic and procedural codes and vital statistics data. Baseline covariates included demographic information [i.e., maternal age (categorical), race, and year of birth (< 2012 or ≥ 2012)], multi-fetal gestation, and pre-existing comorbidities (including depression, anxiety/post-traumatic stress disorder) [18, 19]. Numbers of outpatient visits and inpatient visits at baseline were also accounted for as proxies for disease burden and access to healthcare resources prior to pregnancy. Time-varying covariates comprised (i) concomitant use of opioid analgesics indicative of pain management, antidepressants, benzodiazepines, and anticonvulsants [20, 21], (ii) tobacco, alcohol, and non-opioid substance (including marijuana, hallucinogen, sedative, hypnotic, anxiolytic, or cocaine) abuse or dependence, and (iii) indicators of severity of OUD or addiction, which includes hepatitis C virus infection, opioid overdose, and injection drug use-related infection [22, 23]. Time-varying covariates were updated at baseline and both early and late in pregnancy. Infant sex was accounted for in the analysis of neonatal outcomes. A list of selected confounding variables is presented in Table 1.

2.6 Statistical Analyses

Baseline characteristics were summarized by exposure in both early and late pregnancy, respectively. Continuous variables were compared using an analysis of variance or a Mann–Whitney *U* test, while categorical variables were compared using the Chi square or Fisher exact test.

To assess prenatal OAT risks of adverse neonatal and pregnancy outcomes, we fitted marginal structural models (MSMs) using stabilized inverse probability of treatment weighting (IPTW) with two time periods to account for time-varying exposure and confounding [24]. We estimated crude and adjusted odds ratios (aORs) with 95% confidence intervals (CIs) for each outcome. We developed two stabilized IPTWs for both early and late exposure by fitting numerator and denominator models using multinomial logistic regression models, respectively. Specifically, the numerator model accounted for baseline covariates (i.e., maternal age, race, year of birth, multifetal gestation, pre-existing comorbid conditions, and healthcare resource utilization at baseline), and the denominator model accounted for time-varying comedication use, substance use, and markers of severity of OUD, in additional to baseline covariates. Previous exposure history was included in the numerator and denominator models for late exposure. A product of two stabilized IPTWs associated with early and late exposure was used as the final weight in outcome models. Analysis of final stabilized IPTW distribution showed convergence towards one, suggesting no substantial evidence of model misspecification or violation of positivity assumption [24]. Generalized estimation equations with logit link and final stabilized IPTWs were fitted to obtain aORs and 95% CI for each outcome. Baseline covariates were included in outcome models. Robust variance estimates were adopted to account for implementation of IPTW. To avoid adjusting for intermediate variables that occur after the time-varying exposure, we accounted for time-varying covariates in a time interval preceding the occurrence of exposure. All analyses were performed using SAS, version 9.4 (SAS Inc., Cary, NC, USA). All statistical tests were two-sided with a significance level of 0.05.

2.6.1 Primary and Secondary Analyses

In the primary analysis, the effect of prenatal buprenorphine and methadone exposure during both early and late pregnancy time periods, early (alone) or late (alone), on adverse outcomes was assessed, comparing OAT-treated

Table 1 Selected baseline and time-varying characteristics of buprenorphine-treated, methadone-treated, and untreated pregnancies with opioid use disorder

Characteristics	Exposure early in pregnancy (0–20 gestational weeks)[a,b]				Exposure late in pregnancy (>20 gestational weeks)[a,b]			
	Untreated (N = 178)	Buprenorphine (N = 85)	Methadone (N = 137)	P-value	Untreated (N = 184)	Buprenorphine (N = 72)	Methadone (N = 144)	P-value
Maternal age, years (mean, SD)	28.04 (5.26)	30.01 (5.31)	29.64 (4.32)	0.002	28.18 (5.50)	30.18 (4.80)	29.48 (4.34)	0.0060
Maternal age, years, *n* (%)								
< 20	< 11	< 11	< 11	< 0.0001	< 11	< 11	< 11	0.0373
20–34	141 (79.21)	59 (69.41)	113 (82.48)		143 (77.72)	52 (72.22)	118 (81.94)	
> 34	30 (16.85)	24 (28.24)	22 (16.06)		32 (17.39)	20 (27.78)	24 (16.67)	
Race, *n* (%)								
Black	15 (8.43)	< 11	< 11	< 0.0001	14 (7.61)	< 11	< 11	< 0.0001
Other	32 (17.98)	< 11	23 (16.79)		36 (19.57)	< 11	22 (15.28)	
White	131 (73.60)	72 (84.71)	109 (79.56)		134 (72.83)	62 (86.11)	116 (80.56)	
Birth year, *n* (%)								
2008–11	63 (35.39)	13 (15.29)	40 (29.20)	0.0035	70 (38.04)	< 11	40 (27.78)	< 0.0001
2012–16	115 (64.61)	72 (84.71)	97 (70.80)	0.0035	114 (61.96)	66 (91.67)	104 (72.22)	< 0.001
Multifetal gestation, *n* (%)	< 11	< 11	< 11	0.1098	< 11	< 11	< 11	0.0137
Infant sex, male, *n* (%)	85 (47.75)	44 (51.76)	67 (48.91)	0.8506	89 (48.37)	35 (48.61)	72 (50.00)	0.9554
Pre-existing comorbidities, *n* (%)								
Depression	56 (31.46)	31 (36.47)	32 (23.36)	0.0923	60 (32.61)	24 (33.33)	35 (24.31)	0.2015
Anxiety/ PTSD	62 (34.83)	32 (37.65)	38 (27.74)	0.2446	65 (35.33)	27 (37.50)	40 (27.78)	0.2362
Healthcare resource utilization at baseline, *n* (%)								
Number of outpatient visits (all-cause), mean (SD)	13.15 (18.69)	12.25 (9.05)	54.23 (80.26)	< 0.0001	12.93 (15.23)	12.65 (9.17)	52.22 (79.67)	< 0.0001
Number of inpatient visits (all-cause), mean (SD)	1.09 (2.14)	2.61 (3.89)	2.01 (3.14)	< 0.0001	1.04 (1.85)	2.89 (4.23)	2.03 (3.22)	< 0.0001
Use of substances at 3-month baseline, *n* (%)								
Tobacco use disorder/ abuse	20 (11.24)	11 (12.94)	20 (14.60)	0.6735	19 (10.33)	11 (15.28)	21 (14.58)	0.4024
Alcohol use disorder/ abuse	14 (7.87)	< 11	< 11	0.0234	14 (7.61)	< 11	< 11	0.0306

Table 1 (continued)

Characteristics	Exposure early in pregnancy (0–20 gestational weeks)[a,b]				Exposure late in pregnancy (>20 gestational weeks)[a,b]			
	Untreated (N = 178)	Buprenorphine (N = 85)	Methadone (N = 137)	P-value	Untreated (N = 184)	Buprenorphine (N = 72)	Methadone (N = 144)	P-value
Substance use disorder/abuse	44 (24.72)	19 (22.35)	12 (8.76)	0.0010	48 (26.09)	14 (19.44)	13 (9.03)	0.0004
Use of substances early in pregnancy, *n* (%)								
Tobacco use disorder/abuse					28 (15.22)	11 (15.28)	22 (15.28)	0.9999
Alcohol use disorder/abuse					14 (7.61)	< 11	< 11	0.0234
Substance use disorder/abuse					49 (26.63)	15 (20.83)	23 (15.97)	0.0660
Concomitant medication uses at 3-month baseline, *n* (%)								
Benzodiazepines	33 (18.54)	20 (23.53)	33 (24.09)	0.4327	39 (21.20)	16 (22.22)	31 (21.53)	0.9839
Antidepressants	42 (23.60)	32 (37.65)	34 (24.82)	0.0436	45 (24.46)	27 (37.50)	36 (25.00)	0.0853
Opioid analgesics	45 (25.28)	15 (17.65)	23 (16.79)	0.0019	48 (26.09)	12 (16.67)	23 (15.97)	0.0008
Anticonvulsants	20 (11.24)	< 11	< 11	0.4975	18 (9.78)	< 11	13 (9.03)	0.9711
Concomitant medication uses early in pregnancy, *n* (%)								
Benzodiazepines					35 (19.02)	19 (26.39)	33 (22.92)	0.4005
Antidepressants					42 (22.83)	27 (37.50)	34 (23.61)	0.0415
Opioid analgesics					31 (16.85)	< 11	12 (8.33)	0.0006
Anticonvulsants					17 (9.24)	< 11	< 11	0.6992

PTSD post-traumatic stress disorder, *SD* standard deviation

[a]Small cell count < 11 was suppressed

[b]Markers of severity of opioid use disorder (including injection drug use-related infection, opioid-related overdose, and hepatitis C virus infection) at baseline and early in pregnancy were included as time-varying covariates in models for inverse probability of treatment weighting; however, descriptive statistics were not reported because of the small counts (i.e., < 11)

and untreated pregnancies. In the secondary analysis, we compared the risks of adverse neonatal and pregnancy outcomes among women exposed to buprenorphine versus those exposed to methadone both early and late, early (alone), or late (alone) in pregnancy.

2.6.2 Sensitivity Analyses

Several sensitivity analyses were conducted. First, maternal age was restricted to ≥18 years because of the inconsistent minimum eligible age for the receipt of OAT therapy [19, 25]. Second, to address exposure misclassification, women had to have two or more records of dispensing for OAT with buprenorphine or two or more documented office visits indicating methadone administration during each of the prespecified gestational periods. Women with only one dispensation of OAT with buprenorphine or only one office visit associated with methadone administration were excluded from the analytical cohort. Third, cohort inclusion criteria were refined to having two or more medical claims indicating OUD at a 3-month baseline or during pregnancy to address potential false-positive cases of OUD. Last, to quantify uncertainties associated with unmeasured confounding, we computed *E*-values (eTables 5 and 6 of the ESM) for comparisons that achieved statistical significance. E-values can provide an estimate of the minimum strength of the association that unmeasured confounding needs to have with both exposure and outcome to drive the estimated exposure-outcome association toward null [26].

3 Results

Out of 400 eligible pregnancies, 85 (21.3%) pregnancies were initially exposed to buprenorphine or a combination of buprenorphine and naloxone, and 137 (34.3%) were exposed to methadone early in pregnancy (eFig. 1 of the ESM). When compared with pregnancies treated with methadone, pregnancies treated with buprenorphine or untreated were more likely to have pre-existing comorbidities, including depression and nonopioid substance dependence, and had more frequent concomitant use of antidepressants. In addition, compared with women who received OAT, the untreated pregnancies were more likely to be younger, African American, with concomitant alcohol use disorder, or use of opioid analgesics (Table 1).

When compared with infants of untreated mothers, those with prenatal methadone exposure during both gestational periods were associated with an increased risk of preterm birth [methadone: 31 (24.8%); untreated: 22 (14.47%); aOR: 2.52; 95% CI 1.07–5.95], low birth weight [methadone: 35 (28%); untreated: 23 (15.13%); aOR: 2.99; 95% CI 1.34–6.66], NAS [methadone: 75 (60%); untreated: 19 (12.5%); aOR: 11.36; 95% CI 5.65–22.82], NICUa [methadone: 69 (55.2%); untreated: 27 (17.76%); aOR: 5.04; 95% CI 2.49–10.21], respiratory symptoms [methadone: 29 (23.2%); untreated: 17 (11.18%); aOR: 2.71; 95% CI 1.17–6.24], small for gestational age [methadone: 19 (15.2%); untreated: 11 (7.24%); aOR: 3.54; 95% CI 1.23–10.22], and extended maternal delivery hospital stay (> 7 days) [methadone: 91 (72.8%); untreated: 29 (19.08%); aOR: 14.51; 95% CI 7.23–29.12] (Table 2). In contrast to untreated pregnancies, continuous buprenorphine use during both gestational periods was associated with an increased risk of NAS [buprenorphine: 37 (56.92%); untreated: 19 (12.5%); aOR: 10.27; 95% CI 4.91–21.47] and extended maternal delivery hospital stay (> 7 days) [buprenorphine: 28 (43.08%); untreated: 29 (19.08%); aOR: 3.84; 95% CI 1.83–8.07]; however, continuous buprenorphine use demonstrated a reduced risk of preterm birth [buprenorphine: < 11; untreated: 22 (14.47%); aOR: 0.17; 95% CI 0.04–0.77].

Results were largely similar when comparing untreated pregnancies to early (alone) pregnancy exposure to both opioid agonists (Table 3). However, early (alone) pregnancy exposure to methadone was associated with a higher risk of SGA (aOR: 4.45; 95% CI 1.38–14.33), extended maternal hospitalization > 7 days (aOR: 2.76; 95% CI 1.11–6.88), and a reduced risk of feeding difficulties (aOR: 0.12; 95% CI 0.04–0.38). Further, late (alone) pregnancy exposure to methadone was associated with a significantly increased risk of preterm birth (aOR: 4.53; 95% CI 1.39–14.76), NAS (aOR: 18.39; 95% CI 5.74–58.98), NICUa (aOR: 3.58; 95% CI 1.51–8.45), feeding difficulties (aOR: 4.68; 95% CI 1.63–13.45), and extended maternal hospitalization > 7 days (aOR: 5.26; 95% CI 2.12–13.06) when compared with untreated pregnancies. Late (alone) pregnancy exposure to buprenorphine was associated with an increased risk of NAS (aOR: 7.04; 95% CI 2.03–24.43) and SGA (aOR: 3.45; 95% CI 1.47–8.05) compared with untreated pregnancies. Counts and percentages of events were not reported because of a small count < 11.

When evaluating prenatal buprenorphine exposure during early and late pregnancy, infants with exposure to methadone in both gestational periods experienced a substantially higher risk of preterm birth (< 37 gestational weeks) [methadone: 31 (24.8%); buprenorphine: < 11; aOR: 14.49; 95% CI 3.20–65.57], low birth weight [methadone: 35 (28%); buprenorphine: < 11; aOR: 7.36; 95% CI 2.18–24.87], NICUa [methadone: 69 (55.2%); buprenorphine: 18 (27.69%); aOR: 2.83; 95% CI 1.23–6.48], and extended maternal hospitalization (> 7 days) [methadone: 91 (72.8%); buprenorphine: 28 (43.08%); aOR: 3.77; 95% CI 1.80–7.70] (Table 4). A similar estimate emerged for the effect of late (alone) pregnancy exposure to methadone on preterm birth (aOR: 7.74; 95% CI 1.26–47.41) versus late (alone) pregnancy exposure to buprenorphine (Table 5). Additionally, early (alone) methadone use was linked to a higher risk of SGA (aOR: 4.68; 95% CI 1.39–17.01) (Table 5). Conversely, significant differences were found in favor of continuous methadone use during both early and late gestational periods for feeding difficulties [methadone:

Table 2 Crude and adjusted (inverse probability-weighted) ORs of adverse neonatal and pregnancy outcomes associated with prenatal exposure to buprenorphine or methadone both early and late in pregnancy compared with untreated pregnancies

Neonatal outcomes	Exposure to OATs in both early and late pregnancy[a,b]		
	Cases, *n* (%)	Crude OR (95% CI)	Weighted OR (95% CI)
Preterm birth (< 37 weeks)			
Buprenorphine	< 11	0.26 (0.07–1.00)	0.17 (0.04–0.77)
Methadone	31 (24.8)	2.03 (1.08–3.84)	2.52 (1.07–5.95)
Untreated	22 (14.47)	Ref.	Ref.
Low birthweight (< 2500 g)			
Buprenorphine	<11	0.32 (0.11–0.93)	0.41 (0.12–1.40)
Methadone	35 (28)	2.13 (1.18–3.82)	2.99 (1.34–6.66)
Untreated	23 (15.13)	Ref.	Ref.
Neonatal intensive care unit admission			
Buprenorphine	18 (27.69)	1.83 (0.92–3.65)	1.78 (0.77–4.14)
Methadone	69 (55.2)	5.90 (3.40–10.23)	5.04 (2.49–10.21)
Untreated	27 (17.76)	Ref.	Ref.
Neonatal abstinence syndrome			
Buprenorphine	37 (56.92)	8.28 (4.23–16.19)	10.27 (4.91–21.47)
Methadone	75 (60)	10.50 (5.90–18.68)	11.36 (5.65–22.82)
Untreated	19 (12.5)	Ref.	Ref.
Respiratory symptoms			
Buprenorphine	11 (16.92)	1.51 (0.67–3.39)	1.79 (0.67–4.76)
Methadone	29 (23.2)	2.39 (1.28–4.47)	2.71 (1.17–6.24)
Untreated	17 (11.18)	Ref.	Ref.
Feeding difficulties			
Buprenorphine	18 (27.69)	1.20 (0.63–2.30)	1.52 (0.65–3.57)
Methadone	16 (12.8)	0.49 (0.26–0.90)	0.57 (0.27–1.21)
Untreated	36 (23.68)	Ref.	Ref.
Small for gestational age			
Buprenorphine	<11	2.46 (0.90– 6.77)	3.15 (1.00–9.94)
Methadone	19 (15.2)	2.65 (1.14–6.21)	3.54 (1.23–10.22)
Untreated	11 (7.24)	Ref.	Ref.
Maternal and obstetrical complications			
Length of maternal hospital stay (> 7 days)[c]			
Buprenorphine	28 (43.08)	3.35 (1.79–6.28)	3.84 (1.83–8.07)
Methadone	91 (72.8)	11.60 (6.62–20.31)	14.51 (7.23–29.12)
Untreated	29 (19.08)	Ref.	Ref.
Caesarean delivery			
Buprenorphine	23 (35.38)	1.07 (0.60–1.93)	1.08 (0.54–2.14)
Methadone	34 (27.2)	0.62 (0.37–1.04)	0.79 (0.41–1.52)
Untreated	55 (36.18)	Ref.	Ref.
Pre-eclampsia			
Buprenorphine	< 11	0.86 (0.13–5.60)	0.66 (0.08–5.34)
Methadone	< 11	1.60 (0.45–5.67)	1.69 (0.43–6.68)
Untreated	< 11	Ref.	0.66 (0.08–5.34)
Postpartum hemorrhage			
Buprenorphine	< 11	2.14 (0.54–8.49)	1.51 (0.33–6.89)
Methadone	< 11	0.62 (0.13–3.04)	0.65 (0.13–3.14)
Untreated	< 11	Ref.	Ref.

CI confidence intervals, *OR* odds ratio, *OATs* opioid agonist treatments, *Ref.* reference

[a]Small cell count < 11 was suppressed

[b]Stabilized inverse probability of treatment weightings of early and late exposure were computed with the numerator model adjusting for baseline covariates (i.e., maternal age, race, year of birth, multiple gestation, pre-existing comorbid conditions, and healthcare resource utilization at baseline), and the denominator model adjusting for additional time-varying comedication use, substance use, and markers of opioid use disorder severity. Previous exposure history was included in the models for late exposure. Infant sex was included for adverse neonatal outcomes. A product of stabilized inverse probability of treatment weighting for early and late exposure was used in the outcome models

[c]Missing values were ≤ 0.5% and only complete cases were analyzed

Table 3 Crude and adjusted (inverse probability-weighted) ORs of adverse neonatal and pregnancy outcomes associated with prenatal exposure to buprenorphine or methadone early (alone) or late (alone) in pregnancy compared with untreated pregnancies

	Exposure to OAT in early pregnancy only		Exposure to OAT in late pregnancy only	
	Crude OR (95% CI)	Weighted OR (95% CI)	Crude OR (95% CI)	Weighted OR (95% CI)
Neonatal outcomes				
Preterm birth (< 37 weeks)				
Buprenorphine	0.53 (0.16–1.73)	0.30 (0.08–1.11)	0.50 (0.13–1.88)	0.58 (0.14–2.38)
Methadone	0.80 (0.37–1.76)	0.56 (0.16–1.97)	2.53 (1.15–5.60)	4.53 (1.39–14.76)
Untreated	Ref.	Ref.	Ref.	Ref.
Low birthweight (< 2500 g)				
Buprenorphine	0.78 (0.18–3.30)	1.18 (0.21–6.60)	0.40 (0.08–2.17)	0.34 (0.05–2.30)
Methadone	1.95 (0.78–4.87)	0.95 (0.21–4.32)	1.09 (0.44–2.72)	3.14 (0.78–12.69)
Untreated	Ref.	Ref.	Ref.	Ref.
Neonatal intensive care unit admission				
Buprenorphine	0.69 (0.25–1.88)	0.71 (0.19–2.59)	2.66 (0.96–7.33)	2.51 (0.67–9.42)
Methadone	1.64 (0.77–3.52)	1.41 (0.59–3.35)	3.59 (1.66–7.75)	3.58 (1.51–8.45)
Untreated	Ref.	Ref.	Ref.	Ref.
Neonatal abstinence syndrome				
Buprenorphine	1.07 (0.41–2.80)	1.46 (0.43–4.91)	7.76 (2.95–20.45)	7.04 (2.03–24.43)
Methadone	0.71 (0.26–1.91)	0.62 (0.19–1.97)	14.85 (5.28–41.72)	18.39 (5.74–58.98)
Untreated	Ref.	Ref.	Ref.	Ref.
Respiratory symptoms				
Buprenorphine	0.95 (0.30–2.97)	1.23 (0.31–4.85)	1.60 (0.50–5.13)	1.45 (0.35–6.08)
Methadone	1.61 (0.53–4.88)	1.58 (0.48–5.16)	1.48 (0.49–4.52)	1.72 (0.53–5.58)
Unexposed	Ref.	Ref.	Ref.	Ref.
Feeding difficulties				
Buprenorphine	1.02 (0.40–2.56)	0.90 (0.36–2.24)	1.18 (0.45–3.08)	1.69 (0.61–4.75)
Methadone	0.33 (0.12–0.92)	0.12 (0.04–0.38)	1.49 (0.55–4.02)	4.68 (1.63–13.45)
Unexposed	Ref.	Ref.	Ref.	Ref.
Small for gestational age				
Buprenorphine	0.88 (0.44–1.76)	0.91 (0.42–2.64)	2.80 (1.39–5.66)	3.45 (1.47–8.05)
Methadone	4.49 (1.59–12.66)	4.45 (1.38–14.33)	0.59 (0.22–1.62)	0.80 (0.26–2.46)
Unexposed	Ref.	Ref.	Ref.	Ref.
Maternal and obstetrical complications				
Length of maternal hospital stay (> 7 days)[c]				
Buprenorphine	0.68 (0.24–1.88)	1.04 (0.28–3.82)	4.95 (1.77–13.84)	3.71 (0.98–13.99)
Methadone	1.78 (0.80–3.96)	2.76 (1.11–6.88)	6.51 (2.93–14.44)	5.26 (2.12–13.06)
Unexposed	Ref.	Ref.	Ref.	Ref.
Caesarean delivery				
Buprenorphine	0.36 (0.13–1.01)	0.51 (0.16–1.59)	2.98 (1.06–8.35)	2.10 (0.65–6.78)
Methadone	1.10 (0.52–2.32)	1.38 (0.53–3.60)	0.56 (0.27–1.19)	0.58 (0.23–1.47)
Unexposed	Ref.	Ref.	Ref.	Ref.

CI confidence interval, *OAT* opioid agonist treatment, *OR* odds ratio, *Ref.* reference

[a]Counts and percentages of events were not reported because of the small counts (< 11) for most of the outcomes of interest

[b]Stabilized inverse probability of treatment weightings of early and late exposure were computed with the numerator model adjusting for baseline covariates (i.e., maternal age, race, year of birth, multiple gestation, pre-existing comorbid conditions, and healthcare resource utilization at baseline), and the denominator model adjusting for additional time-varying comedication use, substance use, and markers of opioid use disorder severity. Previous exposure history was included in the models for late exposure. Infant sex was included for adverse neonatal outcomes. A product of stabilized inverse probability of treatment weighting for early and late exposure was used in the outcome models

[c]Missing values were ≤ 0.5% and only complete cases were analyzed

Table 4 Crude and adjusted (inverse probability-weighted) ORs of adverse neonatal and pregnancy outcomes associated with prenatal exposure to methadone both early and late in pregnancy compared with buprenorphine both early and late in pregnancy

Neonatal outcomes	Exposure to OATs in both early and late pregnancy[a,b]		
	Cases, *n* (%)	Crude OR (95% CI)	Weighted OR (95% CI)
Preterm birth (< 37 weeks)			
Buprenorphine	< 11	Ref.	Ref.
Methadone	31 (24.8)	7.77 (2.14–28.18)	14.49 (3.20–65.57)
Low birthweight (< 2500 g)			
Buprenorphine	< 11	Ref.	Ref.
Methadone	35 (28)	6.75 (2.32–19.66)	7.36 (2.18–24.87)
Neonatal intensive care unit admission			
Buprenorphine	18 (27.69)	Ref.	Ref.
Methadone	69 (55.2)	3.23 (1.71–6.06)	2.83 (1.23–6.48)
Neonatal abstinence syndrome			
Buprenorphine	37 (56.92)	Ref.	Ref.
Methadone	75 (60)	1.27 (0.70–2.30)	1.11 (0.54–2.28)
Respiratory symptoms			
Buprenorphine	11 (16.92)	Ref.	Ref.
Methadone	29 (23.2)	1.58 (0.75–3.34)	1.51 (0.55–4.12)
Feeding difficulties			
Buprenorphine	18 (27.69)	Ref.	Ref.
Methadone	16 (12.8)	0.40 (0.20–0.83)	0.37 (0.15–0.92)
Small for gestational age			
Buprenorphine	< 11	Ref.	Ref.
Methadone	19 (15.2)	1.08 (0.46–2.53)	1.12 (0.43–2.96)
Maternal and obstetrical complications			
Length of maternal hospital stay (> 7 days)[c]			
Buprenorphine	28 (43.08)	Ref.	Ref.
Methadone	91 (72.8)	3.46 (1.86–6.42)	3.77 (1.80–7.90)
Caesarean delivery			
Buprenorphine	23 (35.38)	Ref.	Ref.
Methadone	34 (27.2)	0.57 (0.31–1.07)	0.74 (0.35–1.57)
Preeclampsia			
Buprenorphine	< 11	Ref.	Ref.
Methadone	< 11	1.86 (0.33–10.60)	2.56 (0.45–14.43)
Postpartum hemorrhage			
Buprenorphine	< 11	Ref.	Ref.
Methadone	< 11	0.29 (0.06–1.37)	0.43 (0.07–2.45)

CI confidence interval, *OATs* opioid agonist treatments, *OR* odds ratio, *Ref.* reference

[a]Small cell count < 11 was suppressed

[b]Stabilized inverse probability of treatment weightings of early and late exposure were computed with the numerator model adjusting for baseline covariates (i.e., maternal age, race, year of birth, multiple gestation, pre-existing comorbid conditions, and healthcare resource utilization at baseline), and the denominator model adjusting for additional time-varying comedication use, substance use, and markers of opioid use disorder severity. Previous exposure history was included in the models for late exposure. Infant sex was included for adverse neonatal outcomes. A product of stabilized inverse probability of treatment weighting for early and late exposure was used in the outcome models

[c]Missing values were ≤ 0.5% and only complete cases were analyzed

16 (12.8%); buprenorphine: 18 (27.69%); aOR: 0.37; 95% CI 0.15–0.92] (Table 4).

Sensitivity analyses were mainly consistent with the primary analyses and were presented in eTable 4 of the ESM.

Prenatal methadone exposure both early and late during pregnancy was associated with an increased risk of preterm birth, low birth weight, NICUa, NAS, respiratory symptoms, SGA, and extended maternal length of hospitalization.

Consistency was also identified regarding prenatal buprenorphine exposure during both gestational periods, which related to a decreased risk of preterm birth when compared with untreated pregnancies.

4 Discussion

This study comprehensively evaluated the use of OAT during pregnancy and incorporated the time-varying nature of exposure. Our findings suggest that prenatal methadone exposure late (alone) or both early and late in pregnancy was associated with a higher risk of multiple adverse neonatal and pregnancy outcomes, including preterm birth, low birth weight, NAS, NICUa, respiratory symptoms, and extended length of maternal hospital stay (> 7 days) compared with untreated pregnancies in pregnant women with OUD. In comparison, prenatal buprenorphine exposure in both early and late pregnancy was associated with a lower risk of preterm birth, when compared with untreated OUD pregnancies. Additionally, when compared with prenatal buprenorphine exposure, methadone was associated with a higher risk of adverse neonatal outcomes and extended maternal hospitalization. Some estimates were based on the small counts, thus resulting in high variability, wide CIs, and potential chance findings.

Although methadone and buprenorphine have long been recommended as the standard of care for the treatment of OUD in pregnancy [2, 27], NAS is a common adverse consequence in neonates with in-utero exposure to prescription opioids. In our cohort, 55% and 60% of infants prenatally exposed to buprenorphine and methadone, in particular during late pregnancy, experienced NAS, which aligns with the reported prevalence (40–90%) of NAS among neonates with prenatal opioid exposure [9]. Subsequently, clinical correlates of NAS are also likely to present in neonates. A substantial increase in the rate of NICUa has been found that directly correlates to the necessary care infants receive with NAS [28–30]. Similarly, respiratory symptoms and feeding difficulties are frequently observed among neonates with NAS [29, 31–33]. Therefore, further investigations into adverse neonatal outcomes among neonates with and without NAS are necessary to determine the potential pathway between prenatal OAT exposure and adverse infant outcomes.

Compared to OAT-untreated pregnancies, pregnancies exposed to either buprenorphine or methadone during pregnancy were similar in regard to pre-eclampsia, postpartum hemorrhage, and caesarean delivery, apart from an OAT-associated increase in extended maternal hospitalization (> 7 days). A few randomized clinical trials and a retrospective cohort study with 62 subjects reported no difference in caesarean delivery among buprenorphine (alone or combined with naloxone) exposure compared with methadone exposure without a confounding adjustment [11, 34, 35].

In our analysis, we found that over one-third of pregnancies with a known diagnosis of OUD were not prescribed any OATs. This might be due in part to the fact that Medicaid-insured women likely encounter poorer access to OAT because of limited insurance coverage, in addition to insufficient treatment programs, social stigma, and misconceived attitudes about OAT [36–40]. Moreover, disparities in the receipt of pharmacotherapy remained in younger women and African-American women compared with older white women. Recent studies based on Pennsylvania Medicaid enrollees and a state-level dataset of pregnant women in Massachusetts have also identified younger individuals and individuals of color as "higher risk" for not utilizing pharmacotherapy for OUD [19, 36]. These findings highlight the need to improve access to care for this subgroup of patients. Disparities in the receipt of care for OUD may be alleviated by addressing social stigma, improving the diversity of healthcare providers, and providing systematic care [41].

Although our results demonstrated that OAT untreated pregnancies were not associated with significantly inferior neonatal outcomes when compared to the methadone treatment group, findings must be interpreted cautiously as the untreated group likely has unmeasured confounding variables influencing the observed patterns and results. Furthermore, the effectiveness of OATs in minimizing symptoms of withdrawal, relapse rate, and illicit drug use was not examined in our study. Recent publications have suggested that use of medium-high dose ranges of methadone and buprenorphine reduces illicit opioid use compared with placebo [10, 42, 43], aligned with the observed lower prevalence of the use of opioid analgesics and illicit drugs among OAT-treated pregnancies versus untreated pregnancies (Table 1).

Additionally, our findings favored OAT using buprenorphine with a lower prevalence of low birthweight, preterm birth, and NICUa as compared with methadone, in accordance with previously published evidence [8–10, 30, 31, 40]. However, findings from the previous literature were controversial on infant birth weight, body length, malformations, or withdrawal syndromes, which may be due in part to a varying sample size and confounding adjustment [7, 9, 13]. Opioid agonist treatments using buprenorphine or methadone for OUD are accessible for RI Medicaid beneficiaries, in alignment with many other states in the USA. However, strict regulations on prescribing buprenorphine and methadone are applied [46]. Healthcare providers who undergo specific training are authorized to prescribe buprenorphine as the treatment for OUD; in contrast, methadone can only be provided through individualized treatment programs requiring daily travel for patients [46, 47]. As a result, commitment to

Table 5 Crude and adjusted (inverse probability-weighted) ORs of adverse neonatal and pregnancy outcomes associated with prenatal exposure to methadone early (alone) or late (alone) in pregnancy compared with buprenorphine

	Exposure to OAT in early pregnancy only		Exposure to OAT in late pregnancy only	
	Crude OR (95% CI)	Weighted OR (95% CI)	Crude OR (95% CI)	Weighted OR (95% CI)
Neonatal outcomes				
Preterm birth (< 37 weeks)				
Buprenorphine	Ref.	Ref.	Ref.	Ref.
Methadone	1.52 (0.38–6.03)	1.87 (0.33–10.67)	5.11 (1.14–22.90)	7.74 (1.26–47.41)
Low birthweight (< 2500 g)				
Buprenorphine	Ref.	Ref.	Ref.	Ref.
Methadone	2.51 (0.48–13.17)	0.80 (0.09–6.93)	2.69 (0.40–18.18)	9.15 (0.88–95.46)
Neonatal intensive care unit admission				
Buprenorphine	Ref.	Ref.	Ref.	Ref.
Methadone	2.38 (0.70–8.13)	1.98 (0.43–9.17)	1.35 (0.39–4.65)	1.42 (0.31–6.53)
Neonatal abstinence syndrome				
Buprenorphine	Ref.	Ref.	Ref.	Ref.
Methadone	0.66 (0.17–2.66)	0.42 (0.08–2.28)	1.91 (0.49–7.41)	2.61 (0.51–13.36)
Respiratory symptoms				
Buprenorphine	Ref.	Ref.	Ref.	Ref.
Methadone	1.70 (0.36–8.06)	1.28 (0.22–7.52)	0.93 (0.19–4.50)	1.18 (0.19–7.32)
Feeding difficulties				
Buprenorphine	Ref.	Ref.	Ref.	Ref.
Methadone	0.32 (0.08–1.28)	0.14 (0.03–0.58)	1.26 (0.33–4.88)	2.76 (0.68–11.27)
Small for gestational age				
Buprenorphine	Ref.	Ref.	Ref.	Ref.
Methadone	5.11 (1.70–15.40)	4.86 (1.39– 17.01)	0.21 (0.07–0.67)	0.23 (0.06–0.87)
Maternal and obstetrical complications				
Length of maternal hospital stay (> 7 days)[c]				
Buprenorphine	Ref.	Ref.	Ref.	Ref.
Methadone	2.63 (0.74–9.39)	2.66 (0.55–12.90)	1.31 (0.37–4.66)	1.42 (0.30–6.71)
Caesarean delivery				
Buprenorphine	Ref.	Ref.	Ref.	Ref.
Methadone	3.04 (0.86–10.70)	2.69 (0.62–11.78)	0.19 (0.05–0.66)	0.27 (0.07–1.15)

CI confidence interval, *OAT* opioid agonist treatment, *OR* odds ratio, *Ref.* reference

[a]Counts and percentages of events were not reported because of the small numbers (<11) for most of the outcomes of interest

[b]Stabilized inverse probability of treatment weightings of early and late exposure were computed with the numerator model adjusting for baseline covariates (i.e., maternal age, race, year of birth, multiple gestation, pre-existing comorbid conditions, and healthcare resource utilization at baseline), and the denominator model adjusting for additional time-varying comedication use, substance use, and markers of opioid use disorder severity. Previous exposure history was included in the models for late exposure. Infant sex was included for adverse neonatal outcomes. A product of stabilized inverse probability of treatment weighting for early and late exposure was used in the outcome models

[c]Missing values were ≤ 0.5% and only complete cases were analyzed

maintaining methadone treatment may affect patients' access to the general healthcare system. It is hypothesized, however, that the affected patterns of accessing general healthcare systems could reside in the pathway between OATs and pregnancy outcomes. Future research may further decompose total exposure effects into direct and indirect effects of OAT on pregnancy outcomes passing through the resulting changes in healthcare-seeking behaviors during pregnancy.

In an aim to expand upon existing research, we applied MSMs with time-varying exposure and covariates, which is advantageous in multiple ways. First, MSM with time-varying exposure and covariates is designated to address covariates that simultaneously confound and mediate the exposure-outcome association [24, 48]. Adjusting for such confounding variables with multivariable regression models might still result in biases [48]. In this study, illicit drug/tobacco/alcohol use or concomitant use of medications has been described as a predictor of adverse neonatal outcomes [29, 49–51], and may impact the use of OAT. Further, OAT treatment may influence subsequent illicit drug use or

concomitant medication use by assisting the management of illicit drug use and encouraging patient engagement in antenatal care. Successful incorporation of MSMs has improved the assessment of treatment effects with the presence of time-varying confounding despite this approach being less frequently applied in pregnancy studies.

Second, MSM with time-varying exposure enables the estimation of exposure and exploration into the etiological window regarding perinatal outcomes. We did observe a dynamic treatment pattern in our cohort, including treatment discontinuation and late initiation in this study (eFigs. 1 and 2 of the ESM). Notably, a significant difference in newborn outcomes was observed among infants prenatally exposed to methadone during late pregnancy (>20 gestational weeks) versus untreated infants. Conversely, early pregnancy exposures alone were broadly similar in newborn outcomes. Previous evidence suggested late pregnancy opioid use imparts a higher risk of NAS compared with early use after controlling for additional risk factors [56]. Additionally, an increase in methadone dosages is typical in late pregnancy, which might be linked to worse infant outcomes [57].

5 Limitations

Several limitations are present in this study. As with many administrative databases, we did not have information on some confounding factors, such as socioeconomic status and a lack of access to buprenorphine, because of the insurance coverage or geographic location. Residual confounding by indication might also exist as more challenging patients are likely to be directed to methadone clinics. To address the severity of OUD, we accounted for three conditions (i.e., opioid-related overdose, hepatitis C virus infection, and injection drug use-related infection) that have been assessed as markers of severity of OUD or addiction based on the previous literature [23]. Furthermore, we accounted for the use of non-opioid illicit substances and benzodiazepines at baseline and in pregnancy, which were also identified as indicators of severe addiction [58]. In addition, we computed an E-value to evaluate the sensitivity of our findings in relation to residual confounding [26]. For adverse pregnancy and neonatal outcomes, E-value point estimates (i.e., ORs) ranged from 2.55 to 8.04 (eTables 5 and 6 of the ESM) [59], indicating a moderate-to-strong association that unmeasured confounding needs to have with both exposure and outcome to hypothetically explain away the observed exposure-outcome association. Nevertheless, our findings do not have a causal interpretation. Additional concern remains regarding exposure misclassification as buprenorphine was defined upon prescription dispensing. To address such bias, we required patients to have two or more dispensations of buprenorphine or two or more clinical visits indicating OAT with methadone, and the results remained consistent. Additionally, it is plausible for pregnant women to receive OAT with methadone through RI programs outside of Medicaid. However, this exposure misclassification likely leads to more conservative findings. Outcome misclassifications are also likely to exist. Therefore, we adopted validated operational algorithms that have been widely used in the literature. Nevertheless, a claims database has limited data to identify the severity of outcomes (e.g., NAS). Additionally, primary caesarean delivery cannot be distinguished from repeated caesarean delivery using claims data on the basis of ICD-9/10 diagnostic and procedural codes, although from a safety point of view, primary and unplanned caesarean delivery could be more relevant given that repeated caesarean delivery is highly likely to result from a previous caesarean delivery [60]. For any caesarean delivery, maternal complications and malpresentation appear to be more influential, as opposed to a history of caesarean [60]. Surveillance bias might occur given the reported perinatal risks associated with prenatal opioid exposure [5–10]. However, we believe such a bias would not be substantial as all pregnant women were diagnosed with OUD at baseline or during pregnancy regardless of the receipt of OATs. Identification of tobacco, alcohol, and substance use based on diagnostic codes might be underestimated; therefore, we cannot exclude the use of other illicit substances during the study timeframe consumed by the studied population. Furthermore, changes in access to general healthcare systems might vary among patients who received different treatments, as patients who received OAT with methadone are required to visit a specific methadone program daily, which might result in changes in their healthcare-seeking behaviors. Correction for a *p*-value was not performed; therefore, the stated confidence level applies only to each interval individually. Last, but not least, our study was subject to a small sample size likely resulting in limited power, wide CIs, and potential chance findings. Therefore, inference should not merely rely on CIs but also consider the strength of associations. Further investigation with larger cohorts and more recent data is warranted to fully reveal the relationship between OATs in pregnancy and pregnancy and neonatal outcomes.

6 Conclusions

Our findings suggest that buprenorphine and methadone prescribed for OAT are associated with varying perinatal risks. Yet, buprenorphine use may be preferred to methadone in the setting of pregnancy OAT. The public health system and clinicians alike need to weigh the potentially undesired consequences of OAT for OUD in pregnancy against the effectiveness of OAT in suppressing opiate withdrawal and fatal overdose.

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Declarations

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Ethics Approval This study was approved and granted a waiver of informed consents by the Institutional Review Board of The University of Rhode Island (IRB 1289357-4) and Rhode Island Department of Health (IRB#: 2019-11).

Consent to Participate Not applicable.

Consent for Publication Not applicable.

Availability of Data and Material We thank the Rhode Island Department of Health and the Executive Office of Health and Human Services for providing the data access. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the Rhode Island Department of Health upon appropriate application (https://health.ri.gov/records/).

Code Availability The codes used in this study are available upon request.

Authors' Contributions SW and XW have full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: XW, SW, KJM. Acquisition, analysis, or interpretation of data: SW, XW. Drafting of the manuscript: SW, XW, KJM. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: SW. Clinical, technical, or material support: JP, AKL, KEW, TNB, AH, BJQ. Supervision: Wen, KJM. All authors read and approved the final version.

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