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Association of Patient Sex and Pregnancy Status With Naloxone Administration During Emergency Department Visits

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Abstract

Objective: To evaluate the association of sex and pregnancy status with rates of naloxone administration during opioid overdose-related emergency department (ED) visits using the Nationwide Emergency Department Sample (NEDS).

Methods: A retrospective cohort study was conducted using NEDS 2016 and 2017 datasets. Eligible records included men and women, 15–49 years of age, with an opioid overdose-related ED visit; records for women were stratified by pregnancy status (ICD-10 O codes). A multivariable logistic regression model was used to assess the primary outcome of naloxone administration (CPT code: J2310). Secondary outcomes included subsequent admission and mortality. A subgroup analysis compared pregnant women who did versus did not receive naloxone.

Results: Records from 443,714 men, 304,364 non-pregnant women, and 25,056 pregnant women were included. Non-pregnant women had lower odds for naloxone administration (1.70% vs 2.10%; aOR: 0.86(0.83–0.89)) and mortality (2.21% vs 2.99%; aOR: 0.71(0.69–0.73)) but higher odds of subsequent admission (30.22% vs 27.18%; aOR: 1.04(1.03–1.06)) compared with men. Pregnant women had lower odds for naloxone administration (0..27% vs 1.70%; aOR: 0.16(0.13–0.21)) and mortality (0.41% vs 2.21%; aOR: 0.28(0.23–0.35)) but higher odds of subsequent admission (40.50% vs 30.22%; aOR: 2.04(2.00–2.10)) compared with non-pregnant women. Pregnant women who received naloxone had higher odds of mortality (14% vs 0.39%; aOR: 6.30(2.11–18.78)) compared with pregnant women who did not receive naloxone. Pregnant

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women who did not receive naloxone were more likely to have Medicaid as their expected insurance payer, be in the lowest quartile of median household income for residence ZIP code, and have a concurrent mental health diagnosis compared with pregnant women who did receive naloxone.

Conclusion: Reproductive-aged non-pregnant and pregnant women were less likely to receive naloxone during opioid overdose-related ED visits compared to reproductive-aged men. Naloxone administration for reproductive-aged women should be prioritized in the efforts to reduce opioid- and pregnancy-related morbidity and mortality in the United States.

Introduction:

Opioid-related deaths increased annually for two decades prior to 2018.[1–6] The rate of increase in opioid-related deaths in females—particularly women of reproductive age (15–49 years of age)[7]—was greater than the rate of increase for males. Concurrently, reproductive-aged women have the highest rates of drug misuse- or abuse-related emergency department (ED) visits among women.[1] The United States' (US) maternal mortality ratio has also increased, particularly following the implementation of the Pregnancy Mortality Surveillance System.[3,8–12] Maternal mortality review committees have identified drug overdose as a leading cause of pregnancy-related mortality in the US[13], necessitating novel ways to identify risk factors and conduct surveillance to mitigate this significant public health problem.

Guidelines and recommendations from medical societies and public health agencies support administration of naloxone to pregnant women in the setting of suspected opioid overdose.[14–15] However, limited studies have evaluated the effectiveness of emergency departments in administering naloxone specifically to pregnant women; further, few studies have evaluated the effectiveness of naloxone administration based on sex or gender.[16–17]

The Nationwide Emergency Department Sample (NEDS), developed for the Healthcare Cost and Utilization Project (HCUP) with the Agency for Healthcare Research and Quality (AHRQ), is the largest all-payer ED database in the US and estimates about 145 million ED visits each year.[20–21] NEDS—along with other HCUP databases—has been studied to report on opioid-related hospitalizations and ED visits.[22–23] The aim of this study was to compare rates of naloxone administration for reproductive-aged men, non-pregnant women, and pregnant women with opioid overdose-related ED visits using the NEDS. Our null hypothesis is that the rates of naloxone administration will not differ among reproductive-aged men, non-pregnant women, and pregnant women.

Methods:

A retrospective cohort study was conducted using NEDS, a sample from the State Inpatient Databases and State Emergency Department Databases to create national and regional estimates of ED care for patients initially seen in the ED and then admitted to the same hospital, as well as patients with ED visits that do not result in admission.[20] This research was qualified as exempt research under the Department of Health and Human Services regulations by the Johns Hopkins Medicine Institutional Review Board. No identifiable data

were available to the researchers.. Eligible records of contemporaneous data from the 2016 and 2017 datasets included men and women with an opioid overdose-related ED visit defined using the following 10th revision of the *International Statistical Classification of Diseases and Related Health Problems* (ICD-10) codes: T40.0–40.4, T40.6, F11, F19, O99.32, R41.82, or I46.9 (Appendix 1, available online at http://links.lww.com/xxx). These codes were selected based on previous research[1,22–24], guidance for researchers from public health agencies[25], and the recognition that ED coding for opioid overdose-related exposures and symptoms is not uniform[26]. The exposure variable was defined as being female. The unexposed comparison cohort was age-matched men. Men and women not of reproductive age as defined by the World Health Organization (15–49 years of age)[7] or records where age was missing were excluded. Women of reproductive age with opioid overdose-related ED visits were stratified by pregnancy status (ICD-10 O codes including those associated with the postpartum period). In our cohort, less than 2% of records with ICD-O codes had codes associated with the postpartum period and a subgroup analysis was not performed. Women who did not have a diagnosis of pregnancy are further referred to as non-pregnant women. The recommendations of the Strengthening the Reporting on Observational Studies in Epidemiology (STROBE) and REporting of studies Conducted using Observational Routinely-collected Data (RECORD) statements for undertaking observational research were used to perform this research.

Demographic details were described at the patient and ED facility level. Patient level characteristics included age, expected insurance payer, median household income for residence ZIP code, urban-rural designation of residence[27], and concurrent diagnosis of depression, anxiety or other mental health disorder (ICD-10 F codes) (Appendix 1 [http://links.lww.com/xxx]). ED facility level characteristics included geographical region in the US, trauma center level, urban-rural designation[27], and teaching status. The primary outcome was administration of naloxone (*Current Procedural Terminology* (CPT) code: J2310). Secondary outcomes included subsequent admission from ED to ED facility (further referred to as subsequent admission), and mortality in ED or after admission to ED facility (further referred to as mortality).

Comparisons were made between all reproductive-aged non-pregnant women and similarly aged men, and between reproductive-aged pregnant women and all reproductive-aged non-pregnant women. A subgroup analysis was also performed comparing pregnant women who received naloxone versus pregnant women who did not receive naloxone.

Stata 14.2 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.) was used for statistical analyses. Descriptive statistics (analysis of variance) were used to compare the demographics of the groups. Two-tailed P-values were reported and a P-value of 0.05 was used to define statistical significance. Univariate logistic regression was used to determine the probability of occurrence of the primary and secondary outcomes within the groups, and to calculate crude odds ratios (ORs). Potential confounding factors were adjusted for in a multivariable logistic regression model. The factors included age, expected insurance payer, quartile of median household income for residence ZIP code, rural designation of residence, concurrent diagnosis of depression or anxiety, any concurrent mental health diagnosis, ED facility region, ED facility trauma center level, ED facility

urban-rural designation, and ED facility teaching status. As we had a small number of outcome events and the adjusted model included many covariates, a propensity score matching analysis was performed for the primary outcome. The results were consistent with those from our multivariable logistic regression model (Appendix 2 [http://links.lww.com/xxx]). Records with missing data (other than age) were not excluded from the analysis. Both unadjusted and adjusted odds ratios (aORs) were calculated along with 95% confidence intervals.

Results:

Overall, there were 659,330 records of women and 794,923 records of men with opioid overdose-related ED visits. After application of exclusion criteria, 329,420 records of reproductive-aged women and 443,714 records of similarly aged men with opioid-overdose related visits were included (Figure 1). Among reproductive-aged women, 304,364 were non-pregnant and 25,056 were pregnant.

Pregnant women were younger than non-pregnant women and men (Table 1). The majority of each group was insured by Medicaid, with the highest frequency among pregnant women. More pregnant women were in the first quartile of median household income for residence ZIP code, whereas more men had a metropolitan residence. The majority of each group had a concurrent mental health diagnosis, but the frequency was highest for pregnant women and the diagnosis was less likely to be depression or anxiety. Non-trauma centers, metropolitan teaching hospitals, and ED facilities in the South (Appendix 3, available online at http://links.lww.com/xxx) had the largest percentage of opioid overdose-related ED visits based on ED facility characteristic.

Primary and secondary outcome results are summarized in Table 2. Non-pregnant women had lower odds for ED naloxone administration (1.70% vs 2.10%; aOR: 0.86 (0.83–0.89)) and mortality (2.21% vs 2.99%; aOR: 0.71 (0.69–0.73);) but higher odds of subsequent facility admission (30.22% vs 27.18%; aOR: 1.04 (1.03–1.06)) compared with men. Pregnant women had lower odds for ED naloxone administration (0.27% vs 1.70%); aOR: 0.16 (0.13–0.21)) and mortality (0.41% vs 2.21%; aOR: 0.28 (0.23–0.35);) but higher odds of subsequent facility admission (40.50% vs 30.22%; aOR: 2.04 (2.00–2.10)) compared with non-pregnant women.

Comparisons between pregnant women who received naloxone and pregnant women who did *not* receive naloxone are summarized in Tables 3 and 4. Pregnant women who did not receive naloxone were statistically more likely to have Medicaid as their expected insurance payer, be in the lowest quartile of median household income for residence ZIP code, and have a concurrent mental health diagnosis compared to pregnant women who did receive naloxone. The distribution of records differed based on region of the US. There were no other differences in ED facility characteristics (Table 3).

None of the pregnant women who received naloxone in the ED were subsequently admitted compared with 40.6% of those who did not receive naloxone. Pregnant women who received

naloxone had higher odds of mortality (14% vs 0.39%; aOR: 6.30 (2.11–18.78)) compared with those who did not receive naloxone (Table 4).

Discussion:

Sex and pregnancy status were associated with disparities in naloxone administration in the ED, subsequent admission, and mortality. Compared with men, pregnant and non-pregnant women were less likely to receive naloxone and more likely to be admitted to the ED facility; but had lower mortality with opioid-overdose related ED visits. Pregnant women had strikingly lower odds of receiving naloxone and higher odds of admission compared to non-pregnant reproductive-aged women.

We further identified specific patient characteristics and demographic information contributing to disparities in naloxone use during pregnancy. Pregnant women with Medicaid insurance, in the lowest quartile of median household income for residence ZIP code, and with any concurrent mental health diagnosis were less likely to receive naloxone compared to other pregnant women after adjusting for all other available patient and ED facility characteristics.

Research addressing sex-based disparities in naloxone administration is sparse and reports mixed results.[16–17] Faul et al. found that odds of pre-hospital naloxone administration by emergency medical services (EMS) personnel for males were less than females.[16] In contrast, another study reported male sex and comorbid disease as predictors for naloxone administration in inpatient and postoperative settings.[17] However, sex was significant when adjusting only for patient and hospital characteristics—similar to the methodology of this study. Differences in setting (ED versus pre-hospital versus inpatient and postoperative) likely contribute to differences in detected associations as each setting is comprised of unique health care professionals with varying levels of confidence administering naloxone. Further studies stratifying data based on setting could identify priority areas for education and intervention.

Our data also showed that 81% of pregnant women with opioid overdose-related ED visits had a concurrent mental health diagnosis. Bagley et al. found that 86% of pregnant women in the third trimester with opioid use disorders retrospectively self-reported a mental health diagnosis. However, this cohort was taken from an urban, academic outpatient setting in Massachusetts specializing in caring for pregnant women with substance use disorder.[28] These data are supported by Weiss' report of HCUP data demonstrating that the percent of inpatient stays with a concurrent mental health disorder was twice as high for opioid-related stays than non-opioid-related stays.[22] Bagley's findings—while limited—in combination with our nationally representative data provide further evidence for a high prevalence of mental health disorders in pregnant women who use opioids and a high burden of morbidity for people with mental health disorders.[29–30]

We also found that pregnant women who received naloxone were more likely to experience mortality in the ED or after admission to the ED facility. We propose explanations for this finding based on clinical experience and previous research. First, pregnant women who need

naloxone may be less likely to receive it in the hospital setting. This could result from physician-based differences in assessing the risk-to-benefit ratio of administering naloxone or predilection for including pregnancy-related etiologies in their differential diagnoses. Second, women with fatal opioid overdoses may have had a delay in receiving naloxone until cardiac or respiratory arrest. As such, the decision point to administer naloxone in pregnancy may favor the severe spectrum of disease in which mortality is a more likely sequela. Lastly, previous research found women were less likely to receive life-saving interventions such as cardiopulmonary resuscitation during cardiac arrest when compared to men.[31–32]

This study has many strengths. The primary and secondary outcomes of reproductive-aged individuals with opioid overdose-related ED visits were stratified by sex and pregnancy status and confounding factors such as patient and ED facility characteristics were included in the analysis to isolate the effects of the defined exposures. NEDS allowed for mortality to be assessed in the ED and during subsequent admission to the facility to reduce information bias due to misclassification. As the use of a CPT code to evaluate naloxone administration is not validated, we confirmed the ICD-10 inclusion criteria for opioid overdose-related ED visits captured the majority of records with a CPT code for naloxone administration. Furthermore, this analysis specifically focused on a time period with current ICD-10 coding practices to reduce any misclassification of cases during the ICD-9 to ICD-10 transition. Overall, the use of the largest all-payer ED database in the US had distinct advantages. It allowed for identification of risk factors for not receiving naloxone in the ED, and evaluation of the health care system's adherence to clinical guidelines that support the administration of naloxone to pregnant women in the setting of suspected opioid overdose.

Despite the strengths of this study, there are unknowns within the cohort. These findings should be interpreted as hypothesis-generating and in the context of the potential limitations, which may vary by sex or pregnancy status. First, NEDS relies on ED health care professional documentation and likely represents an underestimate of opioid overdose-related ED visits and, particularly, naloxone administration. In tandem, these estimates of ED-based naloxone administration underestimate the health system's effectiveness as they do not capture pre-hospital community- or EMS-administered naloxone. Second, NEDS only captures ED visits and is not specific to a particular patient. Thus, it is possible that one patient could have had multiple opioid overdose-related ED visits. Third, limited clinical data are available in NEDS, precluding the ability to assess for severity in presentation which contributes to the clinical decision to administer naloxone or not. We were also unable to identify or control for the type of opioid associated with the ED visit. We cannot rule out the effect of Simpson's paradox if clinical presentation severity or opioid type is unequally distributed among groups and contributes to differing rates of naloxone administration. Severity in presentation also contributes to the clinical decision on hospital admission. As such, performance bias, or the systematic difference in care provided among study groups, may differentially affect the hospital admission rate for pregnant women. Additionally, this study was performed using data that were not created or collected to answer the specific research question.

Lastly, a clear limitation of this study was the inability to assess for disparities based on race or ethnicity. NEDS does not disaggregate data to allow for this analysis. This perpetuates health inequities with the lack of research, representation, and targeted public and clinical health interventions for racial and ethnic minorities. Self-reported race and ethnicity are essential for studying perinatal outcomes as severe maternal morbidity, pregnancy-associated mortality, and pregnancy-related mortality disproportionally affect African American, Hispanic, and American Indian/Alaska Native women.[3,8–13]

This study found that reproductive-aged non-pregnant and pregnant women were less likely to receive naloxone during opioid overdose-related ED visits compared to reproductive-aged men. The findings contribute new evidence to a robust body of literature demonstrating disparities in clinical and perinatal outcomes for vulnerable populations, including pregnant women who use opioids. Administration of naloxone for suspected opioid overdose among reproductive-aged women should be prioritized in the efforts to reduce opioid- and pregnancy-related morbidity and mortality in the United States.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Précis:

Reproductive-aged non-pregnant and pregnant women were less likely to receive naloxone during opioid overdose-related emergency department visits compared with reproductive-aged men.

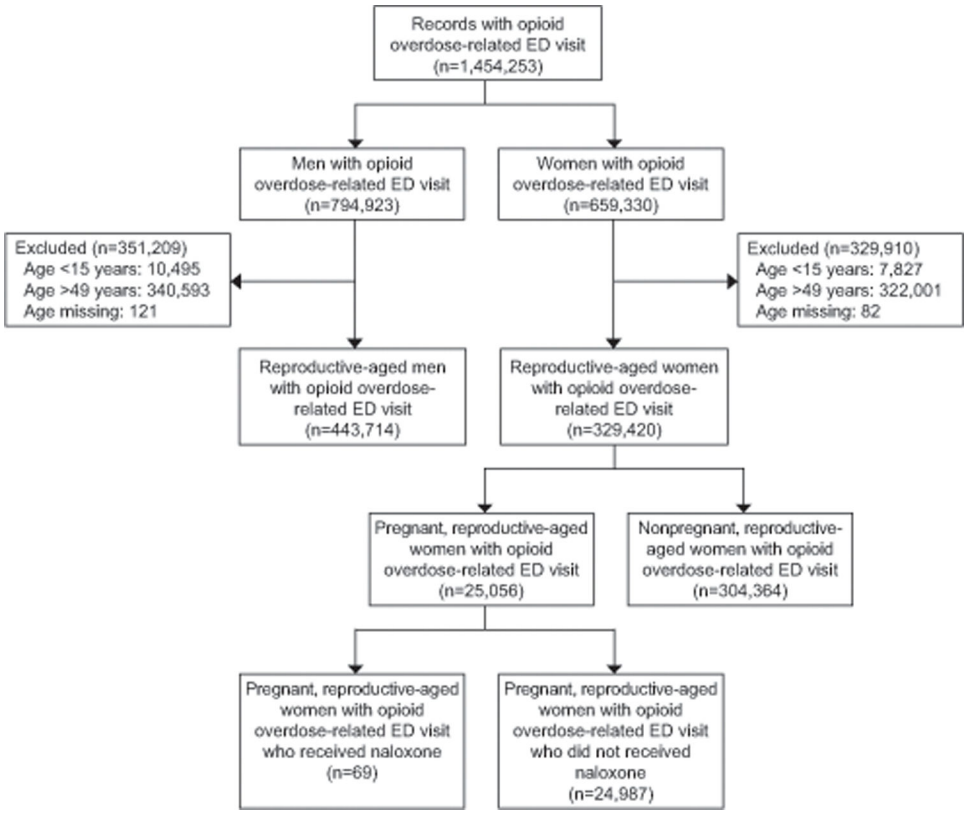

Figure 1.

CONSORT (Consolidated Standards of Reporting Trials) flow diagram for inclusion and exclusion of records in Nationwide Emergency Department Sample database. Opioid overdose-related International Classification of Diseases, Tenth Revision (ICD-10) codes: T40.0–40.4, T40.6 F11, F19, O99.32 R41.82, I46.9. Centers for Disease Control and Prevention ICD-10 codes for pregnancy: O00–9A. CPT code for naloxone administration: J2310. World Health Organization defined women of reproductive age: 15–49 years. ED, emergency department.

Table 1.

Baseline characteristics of study population

	Men	Non-pregnant women	Pregnant women	P
Patient Characteristic	***(n=443,714 unless specified)***	***(n=304,364 unless specified)***	***(n=25,056 unless specified)***	
Age in years, mean (SD)	32.96 (8.72)	33.28 (8.90)	27.38 (5.49)	<0.01
Expected insurance, n (%)	(n=442,767)		(n=25,010)	<0.01
Medicaid	184,172 (41.6) *	144,312 (47.5)	18,071 (72.3)	
Private	86,717 (19.6)	60,738 (20.0)	3,262 (13.0)	
Self-pay	118,383 (26.7)	56,765 (18.7)	2,270 (9.1)	
Other	53,495 (12.1)	41,833 (13.8)	1,407 (5.6)	
Quartile of median household income for ZIP code, n (%)	(n=425,677)	(n=295,634)	(n=24,528)	<0.01
Q1	146,872 (34.5)	104,502 (35.4)	10,987 (44.8)	
Q2	106,600 (25.0)	78,864 (26.7)	6,548 (26.7)	
Q3	91,710 (21.5)	63,185 (21.4)	4,409 (18.0)	
Q4	80,495 (18.9)	49,083 (16.6)	2,584 (10.5)	
Urban-rural designation of residence, n (%)	(n=432,439)	(n=299,656)	(n=24,789)	<0.01
Metropolitan	380,769 (88.1)	256,399 (85.6)	21,678 (87.5)	
Non-metropolitan	51,670 (12.0)	43,257 (14.4)	3,111 (12.6)	
Concurrent diagnosis, n (%)				
Depression or anxiety	65,968 (14.9)	68,948 (22.7)	2,987 (11.9)	<0.01
Any mental health	348,996 (78.7)	236,125 (77.6)	20,319 (81.1)	<0.01
ED Facility Characteristic				
Region, n (%)				<0.01
Northeast	108,967 (24.6)	63,600 (20.9)	3,794 (15.1)	
Midwest	83,786 (18.9)	62,193 (20.4)	4,992 (19.9)	
South	166,300 (37.5)	122,136 (40.1)	11,479 (45.8)	
West	84,661 (19.1)	56,435 (18.5)	4,791 (19.1)	
Trauma center level, n (%)	(n=436,311)	(n=299,234)	(n=24,692)	<0.01
Not a trauma center	205,987 (47.2)	150,540 (50.3)	10,556 (42.8)	
Level I	103,747 (23.8)	60,189 (20.1)	7,133 (28.9)	
Level II	72,505 (16.6)	48,801 (16.3)	3,896 (15.8)	
Level III	54,072 (12.4)	39,704 (13.3)	3,107 (12.6)	
Urban-rural designation, n (%)				<0.01
Metropolitan	401,380 (90.5)	268,542 (88.2)	22,670 (90.5)	
Non-metropolitan	42,334 (9.5)	35,822 (11.8)	2,386 (9.5)	

	Men	Non-pregnant women	Pregnant women	P
Patient Characteristic	***(n=443,714 unless specified)***	***(n=304,364 unless specified)***	***(n=25,056 unless specified)***	
Teaching status, n (%)				<0.01
Metropolitan non-teaching	115,692 (26.1)	84,366 (27.7)	5,999 (23.9)	
Metropolitan teaching	285,688 (64.4)	184,176 (60.5)	16,671 (66.5)	
Non-metropolitan	42,334 (9.5)	35,822 (11.8)	2,386 (9.5)	

* Percentages may not compute to 100% due to rounding.

Table 2.

Primary and secondary outcomes for reproductive-aged non-pregnant women versus men, and pregnant women versus non-pregnant women with opioid overdose-related emergency department visit

	Men	Non-pregnant women	Pregnant women	Non-pregnant women versus men		Pregnant women versus non-pregnant women	
	(n=443,714)	(n=304,364)	(n=25,056)	Un-adjusted OR (95% CI)	Adjusted OR (95% CI)†	Un-adjusted OR (95% CI)	Adjusted OR (95% CI)†
Naloxone Administration, n (%)	9,303 (2.10)	5,186 (1.70)	69 (0.27)	0.81 (0.78–0.84)	0.86 (0.83–0.89)	0.16 (0.13–0.20)	0.16 (0.13–0.21)
Subsequent facility admission, n (%)	120,611 (27.18)	91,972 (30.22)	10,136 (40.5)	1.16 (1.15–1.17)	1.04 (1.03–1.06)	1.57 (1.53–1.61)	2.04 (2.00–2.10)
Mortality, n (%)	13,289 (2.99)	6,734 (2.21)	102 (0.41)	0.73 (0.71–0.75)	0.71 (0.69–0.73)	0.18 (0.15–0.22)	0.28 (0.23–0.35)

†Adjusted for age, expected insurance payer, national quartile of median household income for residence ZIP code, rural designation of residence, concurrent diagnosis of depression or anxiety, any concurrent mental health diagnosis, ED facility region, ED facility trauma center level, ED facility urban-rural designation, and ED facility teaching status.

Table 3.

Baseline characteristics for pregnant women who received versus did *not* receive naloxone

	Pregnant women who did not receive naloxone	Pregnant women who received naloxone	*P*
Patient Characteristic	***(n=24,987 unless specified)***	***(n=69)***	
Age in years, mean (SD)	27.38 (5.49)	28.67 (5.84)	0.053
Expected insurance payer, n (%)	(n=24,941)		<0.01
Medicaid	18,036 (72.3) *	35 (50)	
Private	3,250 (13.0)	12 (17)	
Self-pay or no charge	2,252 (9.03)	18 (26)	
Other	1,403 (5.63)	4 (6)	
Quartile of median household income for residence ZIP code, n (%)	(n=24,459)		<0.01
Q1	10,967 (44.8)	20 (29)	
Q2	6,527 (26.7)	21 (30)	
Q3	4,396 (18.0)	13 (19)	
Q4	2,569 (10.5)	15 (22)	
Urban-rural designation of residence, n (%)			0.159
Metropolitan	22,611 (90.5)	59 (86)	
Non-metropolitan	2,376 (9.5)	10 (15)	
Concurrent diagnosis, n (%)			
Depression or anxiety	2,984 (11.9)	3 (4)	0.052
Any mental health	20,288 (81.2)	31 (45)	<0.01
ED Facility Characteristic			
Region (%)			<0.01
Northeast	3,781 (15.1)	13 (19)	
Midwest	4,968 (19.9)	24 (35)	
South	11,451 (45.8)	28 (41)	
West	4,787 (19.2)	4 (6)	
Trauma center level (%)	(n=24,623)		0.311
Not a trauma center	10,525 (42.7)	31 (45)	
Level I	7,125 (28.9)	8 (12)	
Level II	3,881 (15.8)	15 (22)	
Level III	3,092 (12.6)	15 (22)	
Urban-rural designation (%)			0.159
Metropolitan	22,611 (90.5)	59 (86)	
Non-metropolitan	2,376 (9.5)	10 (15)	
Teaching status (%)			0.193

	Pregnant women who did not receive naloxone	Pregnant women who received naloxone	*P*
Patient Characteristic	***(n=24,987 unless specified)***	***(n=69)***	
Metropolitan non-teaching	5,973 (23.9)	26 (38)	
Metropolitan teaching	16,638 (66.6)	33 (48)	
Non-metropolitan	2,376 (9.51)	10 (15)	

* Percentages may not compute to 100% due to rounding.

Table 4.

Secondary outcomes for pregnant women who received versus did *not* receive naloxone with an opioid overdose-related ED visit

	Pregnant women who did not receive naloxone	**Pregnant women who received naloxone**	**Pregnant women who received naloxone vs pregnant women who did *not* receive naloxone**	
	(n=24,987)	**(n=69)**	**Un-adjusted OR (95% CI)**	**Adjusted OR (95% CI)[†]**
Subsequent facility admission, n (%)	10,137 (40.6)	0 (0)	--	--
Mortality, n (%)	98 (0.39)	4 (14)	15.53 (5.59–43.74)	6.30 (2.11–18.78)

[†]Adjusted for age, expected insurance payer, national quartile of median household income for residence ZIP code, rural designation of residence, concurrent diagnosis of depression or anxiety, any concurrent mental health diagnosis, ED facility region, ED facility trauma center level, ED facility urban-rural designation, and ED facility teaching status.