



Descriptive Exploration of Features Among Infants With Prenatal Fentanyl Exposure in a Multisite Cohort of Maternal-Infant Dyads Affected by Opioid Use Disorder

Amanda N. Dorsey, MPH,
Sonja A. Rasmussen, MD, MS,
Janet D. Cragan, MD, MPH,
Shin Y. Kim, MPH,
Pilar M. Sanjuan, PhD,
Tanner Wright, MD,
Claire Williams, MSPH,
Kate Woodworth, MD, MPH,
Marcela C. Smid, MD, MA,
Mishka Terplan, MD, MPH,
Neil S. Seligman, MD, MS,
Shawn A. Thomas, PhD, MPH,
Thomas G. O'Connor, PhD,
Elisha Wachman, MD,
Lawrence M. Leeman, MD, MPH, MS,
Michelle L. Henninger, PhD,
Kristen L. Benninger, MD, MSc,
Kara M. Rood, MD,
Julie H. Shakib, DO, MS, MPH,
Autumn Davidson, MD, MS,
Amy Board, DrPH

National Center on Birth Defects and Developmental Disabilities, CDC, Atlanta, GA (AND, JDC, SYK, CW, KW, MT, SAT, AB); G2S Corporation, Shavano Park, TX (AND, MT); Emory University, Rollins School of Public Health, Atlanta, GA (AND, CW); Johns Hopkins University School of Medicine, Baltimore, MD (SAR); University of New Mexico Health Sciences Center, Albuquerque, New Mexico (PMS, LML); University of South Florida, Tampa, FL (TW); University of Utah Health, Salt Lake City, Utah (MCS, JHS); Friends Research Institute, Baltimore, MD (MT); University of Rochester Medical Center, Rochester, NY (NSS, TGOC); CDC Epidemic Intelligence Service, Atlanta, GA (SAT); Boston Medical Center, Boston, MA (EW); Center for Health Research, Kaiser Permanente Northwest, Portland, OR (MLH, AD); Center for Perinatal Research, Abigail Wexner

Research Institute, Nationwide Children's Hospital, Columbus, OH (KLB); and The Ohio State University College of Medicine, Columbus, OH (KMR)

Abstract

Objectives: A recent case series suggested a possible syndrome associated with prenatal fentanyl exposure. We described, among a cohort of maternal-infant dyads affected by opioid use disorder (OUD), the prevalence of these observed infant features.

Methods: We used data from MAT-LINK, a surveillance system compiling electronic health record (EHR) information from 7 US clinical sites on pregnancies affected by OUD between 2014 and 2021. We described the prevalence of EHR-documented prenatal fentanyl exposure and infant features of interest (cleft palate, corpus callosum abnormality, foot positioning deformities, genital anomalies, microcephaly, micrognathia, toe syndactyly).

Results: Among 5053 maternal-infant dyads affected by OUD, 667 (13.5%; 95% CI: 13.0%–14.0%) had documented prenatal fentanyl exposure, including an over 20-fold increase from 2014 to 2021. Health insurance, prenatal care timing, and nonopioid substance exposures differed between dyads with and without documented prenatal fentanyl exposure. At least one feature of interest was documented for 406 (8.0%) infants, and at least 2 were documented for 0.7%. Among infants with at least one of these features, 18.9% (95% CI: 17.1%–20.8%) had documented prenatal fentanyl exposure, compared with 13.0% (95% CI: 12.5%–13.6%) of infants without any of these features.

Conclusions: In this perinatal OUD cohort, prenatal fentanyl exposure was more commonly documented among infants with at least one compared with none of these infant features. However, features were rare and contextual factors differed among dyads by prenatal fentanyl exposure status. Further analyses examining these infant features, while considering multiple exposures, are needed before substantiating a fetal fentanyl syndrome.

Keywords

fentanyl; pregnancy; infant; opioid-related disorders; electronic health record

Over the past 2 decades, use of prescription and illicit opioids has increased throughout the United States, including among pregnant women.¹ Currently, drug overdose is a leading cause of pregnancy-associated mortality,^{2,3} driven primarily by synthetic opioids such as fentanyl.⁴ Illegallized fentanyl and related analogs have saturated the illicit drug market in the United States over the past 10 years.^{5,6} Data on use of illegalized fentanyl during pregnancy are limited, but one study found that documented fentanyl exposure among infants in a level III neonatal intensive care unit born to mothers receiving methadone or buprenorphine increased from 1.5% in 2018–2019 to 32.3% in 2020–2021.⁷

In 2023, Wadman et al⁸ published a case series of 10 infants with a distinctive set of features, including but not limited to micrognathia, single palmar crease, 2,3 toe syndactyly, adducted thumb, and short nasal tip. The authors determined through birth and other clinical records that these infants all had prenatal polysubstance exposure with some degree of fentanyl exposure. The infants' features were similar to Smith-Lemli-Opitz syndrome

(SLOS), an autosomal recessive condition affecting cholesterol metabolism. However, laboratory testing (ie, chromosome microarray and exome analyses) was not consistent with a genetic etiology.⁹ Wadman et al⁸ proposed that these infants had a syndromic presentation resulting from prenatal fentanyl exposure. They hypothesized and have since demonstrated that pharmaceutical-grade fentanyl might interfere with cholesterol metabolism in vitro,¹⁰ potentially leading to features resembling SLOS. Given the pervasiveness of the US opioid overdose epidemic, which increasingly involves illegalized fentanyl,^{5,6} and the limited information about fentanyl's fetal effects,^{11,12} it is critical that this proposed syndrome is further investigated. More information from larger samples is needed to investigate infant features following prenatal fentanyl exposure, particularly those observed by Wadman et al.⁸ Our objective was to use the MATernaL and Infant clinical Network (MAT-LINK), an electronic health record (EHR) surveillance system of maternal-infant dyads affected by opioid use disorder (OUD),¹³ to conduct the first multi-clinical site analysis describing the prevalence of prenatal fentanyl exposure and infant features proposed by Wadman et al⁸ to be associated with prenatal fentanyl exposure.

METHODS

Data Source

We utilized data from MAT-LINK, a sentinel surveillance system comprised of mother-infant dyads according to exposures of interest from 7 geographically diverse clinical sites across the United States.¹³ MAT-LINK encompasses all pregnancies at these clinical sites with a known outcome between January 2014 and August 2021, where the mother had an OUD. Clinical sites contributed information from EHRs on the mother-infant dyads. Information readily extractable through automated processes from the EHR was provided for all MAT-LINK dyads. For variables indicated below as requiring manual abstraction, clinical sites provided data on a census of pregnancies where MOUD was documented, but had the option to manually abstract information on either all or a random sample of pregnancies affected by OUD where MOUD was not documented. Sampling weights were subsequently applied to account for the sampling of manually abstracted information at some clinical sites. Further information about MAT-LINK is published elsewhere.¹³ Mother-infant dyads were included in this analysis if (1) procedural and diagnostic code information (ie, ICD-9/10-CM codes and CPT codes) was available for the dyad; (2) the infant was live born; (3) the infant did not have an SLOS diagnosis; and (4) an estimated gestational age between 20 and 46 weeks was reported.

Fentanyl Exposure

Multiple sources of information in MAT-LINK were used to assess if nonpharmaceutical fentanyl exposure occurred prenatally. All screening and confirmatory urine, umbilical cord, and meconium fentanyl laboratory testing results (including testing for norfentanyl and acetyl fentanyl analogs) during pregnancy or infancy were captured for mother-infant dyads if performed and documented. Positive tests between the mother's last menstrual period and 2 days after delivery, or any positive test on infant samples during the first 2 weeks of life, were considered indicative of prenatal fentanyl exposure. We also searched for ICD-10-CM

codes for poisoning by fentanyl or fentanyl analogs (T40.411-T40.414), implemented in October 2020.¹⁴

In addition, clinical sites abstracted whether fentanyl was documented by maternal self-report during pregnancy (1) before initiation of OUD treatment; (2) during any prenatal care visit or contact with health care; or (3) in an overdose. If fentanyl was reported through any extracted or abstracted source described above, then the infant was classified as likely prenatally exposed to fentanyl. The remaining infants were classified as having no evidence of prenatal fentanyl exposure.

Infant Features and Additional Outcomes

Included infant features were selected based on the features described by Wadman et al⁸ and data availability in MAT-LINK: corpus callosum abnormalities, cleft palate with or without cleft lip, foot positioning deformities, genital anomalies, microcephaly, micrognathia, and toe syndactyly (Supplemental Table 1, Supplemental Digital Content 1, <http://links.lww.com/JAM/A754>). Included infant features were defined by procedural and diagnostic codes and free text searches of health care encounter verbatim descriptions and descriptions of birth defects noted during delivery and/or at child follow-up encounters, when available (Supplemental Table 2, Supplemental Digital Content 1, <http://links.lww.com/JAM/A754>). For microcephaly, we added a separate definition using INTERGROWTH-21st standardized head circumference.¹⁵ Infants with a head circumference equal to or below the third percentile were defined as having microcephaly. Additional infant outcomes included in this analysis were gestational age, INTERGROWTH-21st standardized birth length and birth weight percentiles, and feeding difficulties, as these outcomes were also described by Wadman and colleagues. They were informed by procedural and diagnostic codes and an indicator abstracted by clinical sites of whether the infant experienced poor feeding at any time within 28 days of birth.

Demographic and Contextual Characteristics

Our data included maternal age, race, ethnicity, health insurance status, urbanicity, and number of prior pregnancies, which we reported as consistent with prior MAT-LINK analyses.¹³ We further categorized prenatal care initiation into trimesters based on timing in relation to the estimated date of delivery. Procedural and diagnostic codes documented between the estimated last menstrual period and the infant's date of birth were used to identify nonopioid substance exposures during pregnancy (Supplemental Table 3, Supplemental Digital Content 1, <http://links.lww.com/JAM/A754>).

Statistical Analysis

We described contextual characteristics of the analytic sample stratified by documented prenatal fentanyl exposure. These proportions were standardized by the clinical site distribution among our overall analytic sample with direct standardization techniques to account for clinical site heterogeneity in contextual characteristics and fentanyl testing and detection practices.¹⁶ We then calculated the percentage of mother-infant dyads with any documented fentanyl test, any documented fentanyl test with a positive result, and any documented prenatal fentanyl exposure overall, stratified by infant birth year. All descriptive

statistics involving prenatal fentanyl exposure were weighted to account for MAT-LINK sampling techniques, as manually abstracted information was available for all pregnancies with documented MOUD at each clinical site, but only available for a simple random sample of pregnancies affected by OUD with no documented MOUD.¹³ We incorporated clustering of pregnancies belonging to the same person using survey procedures in SAS v9.4.

We calculated the prevalence of each included infant feature among the overall analytic sample and the count of features documented for each infant. We compared the prevalence of documented prenatal fentanyl exposure among infants with compared with without at least one of these features of interest and generated an odds ratio using logistic regression and survey procedures in SAS v9.4 to incorporate sampling weights and clustering. The prevalence of these features was then analyzed specifically among infants with prenatal fentanyl exposure. Three subject matter experts (S.R., J.C., and K.W.) reviewed all birth defect-related ICD codes among infants with at least one feature of interest to see whether any other features were commonly observed. We then compared the weighted prevalence of feeding difficulties between infants with and without prenatal fentanyl exposure, in addition to gestational age and standardized birth weights and lengths.

Counts smaller than 5 were suppressed to conform with Assurance of Confidentiality standards under which MAT-LINK data are protected.¹⁷ This activity was reviewed by the Centers for Disease Control and Prevention (CDC), deemed as surveillance and not research, and was conducted consistent with applicable federal law and CDC policy. All MAT-LINK clinical sites underwent IRB review and received approval or exemption before data collection. Analyses were conducted in June 2025.

RESULTS

Prenatal Fentanyl Exposure

Among 5053 included mother-infant dyads, 667 had documented prenatal fentanyl exposure (13.5% [95% CI: 13.0–14.0]), among whom 224 were indicated exclusively via abstracted information, 210 were indicated exclusively via laboratory testing data, and 233 were indicated by both sources of information (Table 1; Figure 1; Supplemental Table 4, Supplemental Digital Content 1, <http://links.lww.com/JAM/A754>). Thirty individuals had a fentanyl poisoning ICD code documented, but all codes were documented during the postpartum period, thus not contributing to our definition of prenatal fentanyl exposure. The distributions of maternal age, ethnicity, and number of prior pregnancies were similar across documented prenatal fentanyl exposure status (Table 1). However, compared with those without exposure, dyads with prenatal fentanyl exposure more frequently had public insurance (90.0%; 95% CI: 88.8–91.2 vs. 80.9%; 95% CI: 79.9–82.0), their first prenatal care appointment documented during the third trimester (28.3%; 95% CI: 24.5–32.1 vs. 15.4%; 95% CI: 14.8–16.0), and EHR-documented MOUD during pregnancy (81.2%; 95% CI: 77.5–85.0 vs. 73.1%; 95% CI: 72.4–73.9) (data not shown). Prenatal cannabis, sedative, stimulant, nicotine, and other nonopioid substance exposures were more commonly documented among those with versus without prenatal fentanyl exposure. Dyads without prenatal fentanyl exposure more frequently resided in rural areas than dyads with prenatal fentanyl exposure (7.8%; 95% CI: 7.4–8.2 vs. 5.3%; 95% CI: 4.5–6.1).

The percentage of infants with any documented prenatal fentanyl exposure increased from 1.6% (95% CI: 1.2–2.0) in 2014 to 34.3% (95% CI: 30.3–38.4) in 2021, with the largest increase from 2020 (18.8%; 95% CI: 17.1–20.6) to 2021 (Fig. 2). The frequency of fentanyl testing and documented positive tests was also considerably higher in 2021 (tested: 40.7%; positive test: 21.3%) compared with 2014 (tested: < 5 infants; positive test: 0.0%) (Fig. 2).

Infant Features

Among the 5053 infants, 406 (8.0%) had at least one of the included infant features. The most common features were microcephaly, defined by head circumference $\leq$ 3rd percentile (8.4%) or diagnostic and procedural codes (3.3%), male genital anomalies (6.3% of males), and foot positioning deformities (1.0%) (Table 2). Thirty-six infants (0.7%) had at least 2 included features, with 3 being the maximum observed for any infant ($n < 5$) (Table 3). Among infants with at least one included feature, 18.9% (95% CI: 17.1–20.8) had documented prenatal fentanyl exposure, compared with 13.0% (95% CI: 12.5–13.6) of those without any of these features (odds ratio: 1.6, 95% CI: 1.4–1.8). When stratified by documented prenatal fentanyl exposure, many feature counts were sparse, but no substantial differences in prevalence estimates were detected (data not shown).

Subject matter experts examined all birth defect-related ICD-9/10-CM codes documented among infants with at least one of the included features. No notable patterns emerged for additional birth defects occurring among these infants. Feeding difficulties were more common among infants with, versus without, documented prenatal fentanyl exposure, but gestational age, birth weight and length were all similar across groups (Supplemental Table 5, Supplemental Digital Content 1, <http://links.lww.com/JAM/A754>).

DISCUSSION

Among 5053 mother-infant dyads affected by OUD, > 1 in 8 had documented prenatal fentanyl exposure. Though some contextual characteristics were similar between those with and without prenatal fentanyl exposure, those with documented exposure were more likely to be publicly insured, have their first prenatal care appointment in the third trimester, and have documented prenatal exposures to cannabis, sedatives, stimulants, nicotine and/or other nonopioid substances. Documented prenatal fentanyl testing and exposure increased over 20fold from 2014 to 2021. Overall, ~1 in 12 infants in the cohort had at least 1 of the 7 included infant features, most commonly microcephaly, male genital anomalies, and foot positioning deformities. Of these infants, the vast majority had only one feature documented, in contrast to the constellation of features observed among the 10 infants in the Wadman et al⁸ case series.

Prenatal fentanyl exposure was documented more commonly among infants with at least one of the included features compared with infants with none of these features. However, several unmeasured contextual factors limited our ability to causally attribute these features to fentanyl. First is the unknown drug purity. Adulterants are common in illicit drugs, including illegalized fentanyl,^{5,18} though they are not systematically tested for or knowingly consumed.¹⁹ The potential role of unknown adulterants among infants with any of these features of interest remains unknown. Second, the need to consider potential effects of

other prenatal substances and medication exposures is paramount when considering the association between fentanyl exposure and these infant features, which are hypothesized to be related to aberration in cholesterol metabolism.^{8,10} It is unknown whether other opioid types can have similar effects on cholesterol biosynthesis.¹⁰ Antipsychotic medications may interrupt fetal cholesterol metabolism,^{8,20} and OUD and mental health disorders frequently co-occur,²¹ so future analyses should include these medications. In this analysis, we also observed a higher prevalence of other prenatal substance exposures among dyads with, versus without, prenatal fentanyl exposure. Given the known association between substances like alcohol²² and nicotine²³ and birth defects, and fentanyl's increasing role as an adulterant in some nonopioid illicit substances,²⁴ future studies may consider the role of other substance exposures. Third, other contextual factors²⁵ including environmental exposures, disproportionately affect people affected by OUD and have been linked to several features in this study, including cleft palate and limb defects.^{26,27} Taken together, the fundamental question of whether fentanyl is driving the observed infant features in Wadman et al (2023),⁸ or if those infant features may be the result of other exposures, separately or in combination with fentanyl, remains unanswered.

The more than 20-fold increase in fentanyl exposure over time in our analysis of dyads affected by OUD emphasizes the importance of further understanding its impacts. From 2014–2021, fentanyl use geographically expanded in the United States,²⁴ potentially exacerbated by the COVID-19 pandemic,²⁸ but data-related considerations also likely influenced our observed increase. Awareness of fentanyl in the illicit drug supply increased during this timeframe, in part due to harm reduction efforts,²⁹ meaning mothers affected by OUD later in the surveillance period may have been more likely to know they were using fentanyl or a drug adulterated by fentanyl, report it to their provider, and have medical record documentation. This time period also saw significant increases in the availability of laboratory testing for fentanyl in clinical settings,³⁰ potentially increasing the number of pregnancies with fentanyl exposure identified across time. However, MAT-LINK clinical sites qualitatively reported heterogeneous fentanyl testing protocols, even in recent years, where some clinical sites conducted routine urine drug tests, including fentanyl tests, among all pregnant women with a substance use disorder, whereas others did not conduct in-house fentanyl toxicology tests and decreased toxicology testing over time. Therefore, prenatal fentanyl exposure might be underestimated at some clinical sites. In addition, before October 2020, no ICD-10-CM code to document fentanyl exposure was available; therefore, some instances of prenatal fentanyl exposure might be missed by our exposure definition, as health care providers were limited to coding different or broader synthetic opioid classes.³¹ Manually abstracted indicators of prenatal fentanyl use are additionally subject to underreporting, as manual abstractors relied on information documented in the EHR to determine whether prenatal fentanyl exposure occurred for each infant. Thus, MAT-LINK data likely contains many misclassified³² and unreported instances of prenatal fentanyl exposure. However, our ability to leverage abstracted medical information in addition to laboratory testing facilitated the identification of 667 infants with documented prenatal fentanyl exposure, 224 of whom were identified exclusively through abstracted medical information.

Some infant features in this analysis might be more prevalent than general US estimates; however, direct comparison is difficult due to different ascertainment methodologies, feature definitions, and random error from smaller counts. We observed 0.5% of infants having any cleft palate with or without cleft lip, whereas the National Birth Defect Prevention Network (NBDPN) estimated that from 2016 to 2020, 0.06% of live births had cleft palate only and 0.1% had cleft lip with or without cleft palate.³³ Our observed prevalence of talipes equinovarus was also 3 times NBDPN's estimate of 0.2%.³³ When we defined microcephaly using a standardized head circumference $\leq 3\%$, we identified almost three times the number of infants that we would expect. Among both infants with and without documented prenatal fentanyl exposure, the median birth weight was lower than average. Further research is needed to understand whether the prevalence of these features is elevated among infants with prenatal opioid, specifically fentanyl, exposure, while considering the additional potential impacts of maternal health, prenatal care, prescription medications, polysubstance use, and environmental and other exposures. Further research is also needed to understand why feeding difficulties were more common among infants with prenatal fentanyl exposure, compared with those without, in this analytic sample. It is possible that severity of NOWS presentation could explain at least part of this relationship, and warrants further consideration using data that can capture severity of NOWS and feeding difficulties with a standardized approach.³⁴

Attributing fentanyl as a cause for the observed features has real-world consequences for mothers with substance use disorders, so it is important that evidence justifying any attribution is strong. These implications include stigma from health care providers,³⁵ inadequate prenatal care access,³⁵ and other punitive consequences,³⁶ particularly among under-resourced communities.³⁷ While efforts continue to investigate potential causal mechanisms of the observed features in the Wadman et al⁸ case series, providers can take steps to support dyads exposed to fentanyl and other opioids. MOUD is the standard of care for treating OUD during pregnancy, including those who use fentanyl.³⁸ In our data, we observed MOUD was documented more frequently during pregnancy among dyads with versus without prenatal fentanyl exposure. This might be because receiving MOUD might result in more health care system interactions, leading to more opportunities for documentation of fentanyl exposure. Though fentanyl use often warrants additional MOUD prescribing considerations due to risk of buprenorphine-precipitated withdrawal from fentanyl, particularly during pregnancy,³⁹ MOUD is still associated with reductions in adverse pregnancy and infant features compared with no or shorter treatment and is an important prenatal care provision for dyads affected by OUD.³⁸

This analysis is subject to several limitations. Because we leveraged an existing data source, rather than standardized physical examinations of each infant, not all features documented in the Wadman et al⁸ case series, including cholesterol metabolism, facial features, adducted thumbs, and single palmar creases, could be examined in MAT-LINK data. Infant features that are included are subject to misclassification. For example, micrognathia maps imperfectly to ICD codes, and rocker bottom feet do not have an ICD-9-CM specific code. Thus, we expect that these infant features will be documented less reliably than others, such as cleft palate, in the EHR. In addition, some included features might not have been recognized by a physician or documented using ICD codes. Several limitations in the

ascertainment of prenatal fentanyl exposure using EHRs are also described above. While we could not verify that all fentanyl exposures ascertained were nonpharmaceutical, including epidural medications,⁴⁰ we did not include prescribed fentanyl in our exposure definition and relied on sources of information likely to indicate nonpharmaceutical use. This applies to other types of prenatal substance exposures captured in our analysis as well, such as cannabis, stimulants, and benzodiazepines. Due to limited fetal information on stillborn infants in MAT-LINK, we restricted our analysis to live-born infants. Our results might underestimate the impact of these infant features, particularly among those with prenatal fentanyl exposure, if these features contribute to stillbirth, especially in the presence of prenatal fentanyl exposure. Our results are not generalizable to the entire US population of maternal-infant dyads affected by OUD, as MAT-LINK only encompasses 7 clinical sites. These data do not fully represent the spectrum of maternal characteristics, substance use patterns, and genetic profiles of all women accessing perinatal OUD services in the United States. As a secondary analysis of sentinel surveillance data designed to broadly capture dyad features, this report does not equip us to definitively substantiate a syndrome attributed to prenatal fentanyl exposure. Strengths of our analysis include a large sample of infants among whom fentanyl exposure was relatively common. This helped us contextualize the extent to which signals of infant features reported in the Wadman et al⁸ case series are observed in a population of susceptible infants across 7 clinical sites, including cases where only some features of interest are expressed, even if we are not yet equipped with this data source alone to substantiate the plausibility of a fetal fentanyl syndrome.

CONCLUSIONS

The paucity of data about fentanyl's fetal effects is concerning amid an ongoing fentanyl use crisis. The case series published by Wadman et al⁸ proposed a fetal syndrome associated with prenatal fentanyl exposure, accompanied by a plausible biological mechanism^{8,10}; however, considering alternative or interaction mechanisms is prudent given the contextual differences we observed between those with and without documented prenatal fentanyl exposure. Several features of interest to this proposed syndrome were present but rare in our sample, and < 1% of infants had at least 2 of these features documented. Further investigation incorporating multilevel factors is needed to examine all potential factors that may be driving the features observed in Wadman et al⁸ before substantiating a fetal fentanyl syndrome.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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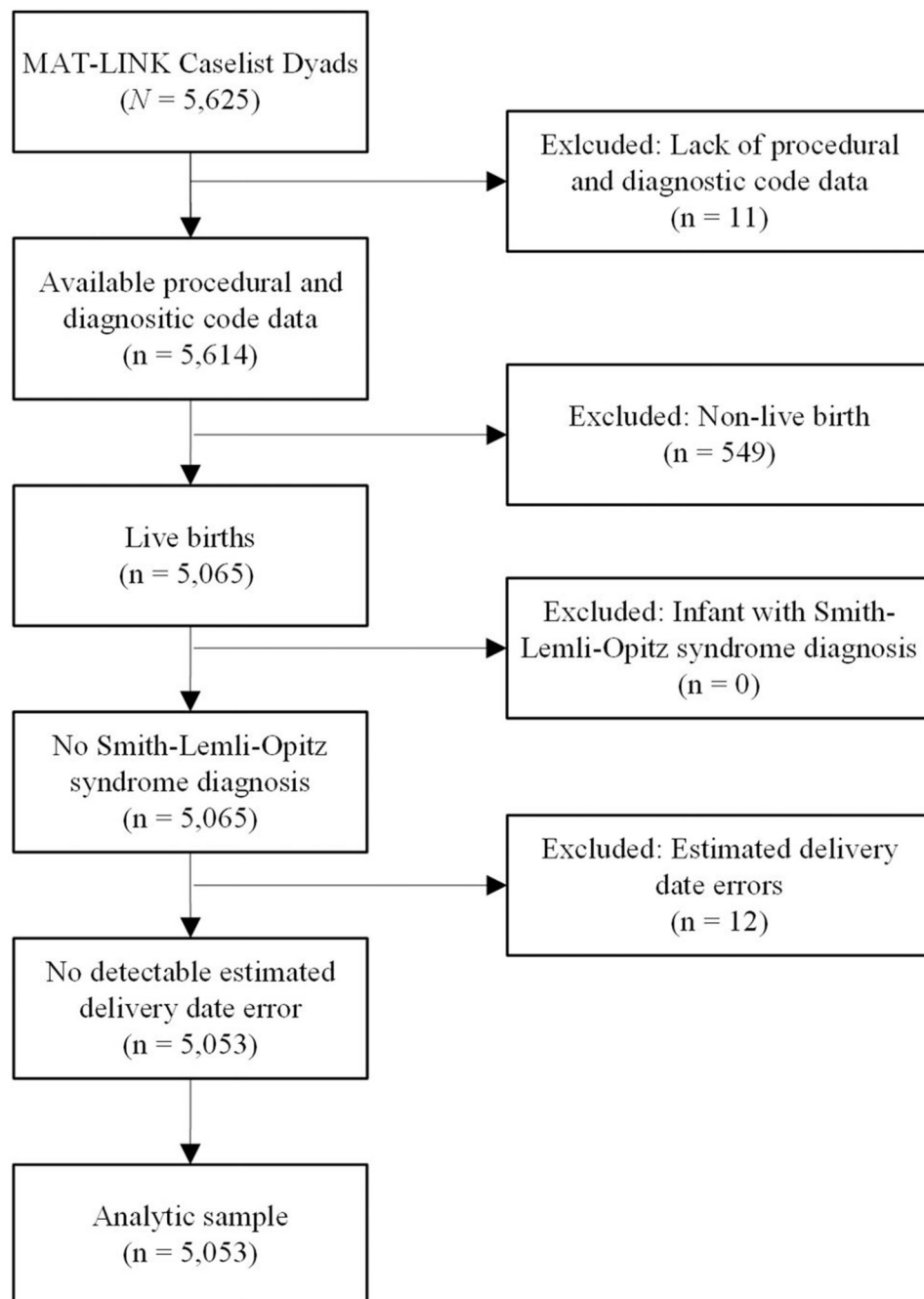


FIGURE 1.
Analytic sample flowchart.

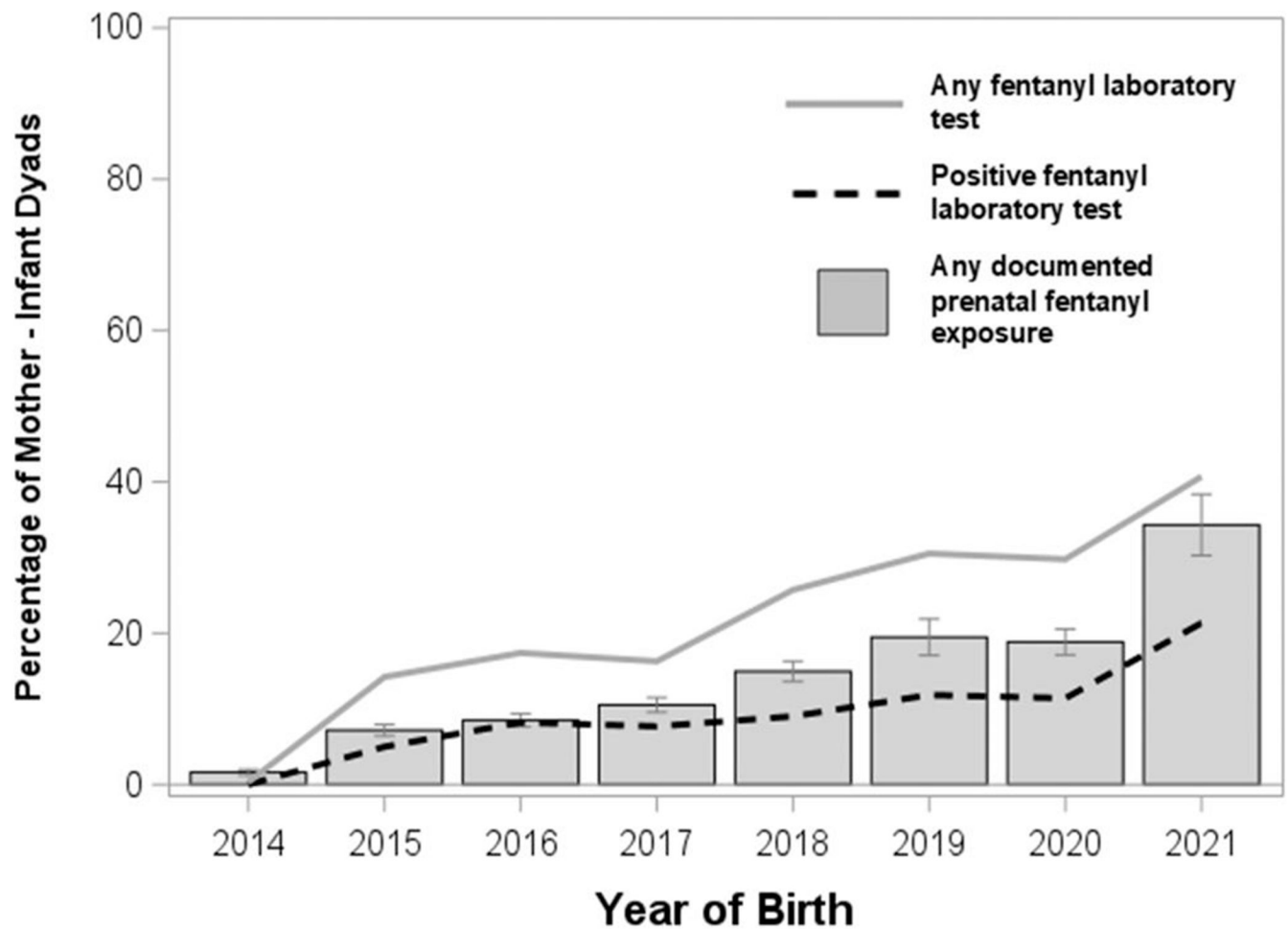


FIGURE 2.

Percentage of mother-infant dyads with any documented prenatal fentanyl exposure, a positive fentanyl laboratory test, or any fentanyl laboratory testing according to infant year of birth. The “Any fentanyl laboratory test” line depicts the percentage of mother-infant dyads with a documented fentanyl test, irrespective of the test result. The “Positive fentanyl laboratory test” line only depicts those with a positive fentanyl laboratory test. Fentanyl tests were only included if performed (1) among infants, or (2) among the mother between the last menstrual period through 2 days after delivery. The “Any documented prenatal fentanyl exposure” bars depict the percentage of mother-infant dyads that had (1) a positive fentanyl test with the criteria described above, or (2) data abstracted from the medical record indicative of likely prenatal fentanyl exposure. Abstracted information includes documented reports of fentanyl before initiation of opioid use disorder (OUD) treatment, during any prenatal care visit or contact with health care, or during an overdose, if applicable, during the respective pregnancy. These percentages are weighted to account for MAT-LINK sampling procedures. Error bars represent 95% CIs.

TABLE 1.
Characteristics of Mothers With and Without Documented Prenatal Fentanyl Exposure

Maternal Characteristics	With Documented Prenatal Fentanyl Exposure (n = 667;13.5% [95% CI:13.0–14.0])	Without Documented Prenatal Fentanyl Exposure (n = 4386;86.5% [95% CI:86.0– 87.0%])
	Standardized Weighted Percentage, 95% CI ^{*†}	Standardized Weighted Percentage, 95% CI ^{*†}
Age at time of birth, years		
≤ 24	17.1 (12.1, 22.0)	20.4 (19.3, 21.5)
25–29	33.5 (30.5, 36.4)	35.6 (34.5, 36.6)
30–34	33.0 (27.9, 38.2)	29.1 (28.1, 30.0)
≥ 35	16.4 (14.1, 18.8)	15.0 (14.2, 15.8)
Race		
American Indian or Alaska Native	0.7 (0.4, 1.1)	2.9 (2.5, 3.3)
Black or African American	6.9 (6.1, 7.7)	5.2 (4.5, 5.8)
White	85.9 (84.5, 87.2)	84.4 (83.5, 85.4)
Other race [‡]	3.0 (2.4, 3.5)	4.2 (3.9, 4.6)
Not reported	3.6 (2.6, 4.5)	3.2 (2.6, 3.9)
Ethnicity [§]		
Hispanic or Latina	24.5 (23.4, 25.6)	24.5 (23.7, 25.3)
Not Hispanic or Latina	72.8 (71.5, 74.2)	72.9 (72.1, 73.8)
Not reported	2.7 (1.7, 3.6)	2.6 (2.2, 3.0)
Health insurance		
Public	90.0 (88.8, 91.2)	80.9 (79.9, 82.0)
Private	7.5 (6.3, 8.7)	15.8 (14.8, 16.9)
No insurance	1.2 (0.9, 1.5)	2.1 (1.9, 2.4)
Other/not reported	1.3 (0.9, 1.7)	1.1 (1.0, 1.2)
Maternal urbanicity [¶]		
Urban core	84.2 (82.2, 86.2)	82.6 (81.9, 83.2)
Urban other	9.2 (7.3, 11.0)	8.4 (7.9, 9.0)
Rural	5.3 (4.5, 6.1)	7.8 (7.4, 8.2)
Not reported	1.3 (1.0, 1.7)	1.2 (1.1, 1.3)
No. prior pregnancies		
Nulliparous: 0	21.8 (18.9, 24.7)	23.0 (21.9, 24.1)
Multiparous: 1–2	47.0 (43.9, 50.1)	46.6 (45.5, 47.7)
Multiparous: ≥ 3	21.4 (19.1, 23.7)	21.6 (20.8, 22.4)
Not reported	9.9 (8.7, 11.0)	8.8 (8.4, 9.3)
Trimester of first reported prenatal care		
First trimester	28.2 (25.8, 30.5)	40.1 (39.0, 41.1)
Second trimester	28.6 (25.4, 31.8)	30.1 (29.2, 31.1)
Third trimester	28.3 (24.5, 32.1)	15.4 (14.8, 16.0)
Not reported	15.0 (13.6, 16.3)	14.4 (13.9, 14.9)

Maternal Characteristics	With Documented Prenatal Fentanyl Exposure (n = 667; 13.5% [95% CI: 13.0–14.0])	Without Documented Prenatal Fentanyl Exposure (n = 4386; 86.5% [95% CI: 86.0–87.0%])
	Standardized Weighted Percentage, 95% CI ^{*†}	Standardized Weighted Percentage, 95% CI ^{*†}
Any reported nonopioid substance [#]		
Cannabis		
Yes	28.9 (25.8, 32.1)	21.2 (20.3, 22.1)
No	71.1 (67.9, 74.2)	78.8 (77.9, 79.7)
Sedative		
Yes	9.6 (8.0, 11.2)	5.5 (5.2, 5.8)
No	90.4 (88.8, 92.0)	94.5 (94.2, 94.8)
Stimulant		
Yes	42.3 (39.0, 45.5)	23.1 (22.3, 23.8)
No	57.7 (54.5, 61.0)	76.9 (76.2, 77.7)
Alcohol		
Yes	4.5 (3.5, 5.5)	3.9 (3.7, 4.2)
No	95.5 (94.5, 96.5)	96.1 (95.8, 96.3)
Nicotine		
Yes	72.5 (70.2, 74.8)	52.8 (51.7, 54.0)
No	27.5 (25.2, 29.8)	47.2 (46.0, 48.3)
Other nonopioid substances		
Yes	46.7 (43.7, 49.8)	41.4 (40.5, 42.3)
No	53.3 (50.2, 56.3)	58.6 (57.7, 59.5)

^{*} Bolded values indicate non-overlapping CIs.

[†] Percentages are standardized by the analytic sample's clinical site distribution, account for MAT-LINK sampling strategies, and incorporate clustering at the mother level.

[‡] Other race includes Asian, Native Hawaiian or other Pacific Islander, multiracial individuals, and unspecified other race.

[§] All women with a reported ethnicity of Hispanic or Latina are grouped as Hispanic or Latina, regardless of race.

^{||} Other insurance includes unspecified health insurance types.

[¶] Urbanicity status was determined based on the rural-urban commuting area designation. Subgroup descriptions are detailed in the Supplementary Table of the prior study.¹³

[#] Refer to Supplemental Table 3, <http://links.lww.com/JAM/A754>, for ICD-9/10-CM codes.

TABLE 2.

Frequency of Infant Features of Interest Among Entire Analytic Sample (N = 5053) of Infants Born to Mothers With Opioid Use Disorder ^{*,†‡}

Feature	Analytic Sample (N = 5,053) N (%)
Cleft palate with or without cleft lip [§]	24/5,053 (0.5)
Micrognathia	46/5053 (0.9)
Toe syndactyly	8/5053 (0.2)
Foot positioning deformities	
Rocker bottom feet	< 5
Talipes equinovarus	30/5053 (0.6)
Foot positional deformities (broadly)	53/5053 (1.0)
Corpus callosum abnormalities	< 5
Microcephaly	
Diagnostic and procedural codes	169/5053 (3.3)
Head circumference ≤ 3rd percentile [¶]	358/4275 (8.4)
Genital anomalies	
Males [#]	142/2267 (6.3)
Females [#]	10/2130 (0.5)

^{*} The table is not restricted to infants with prenatal fentanyl exposure due to small feature counts. Prenatal fentanyl exposure is documented among 13.5% (95% CI: 13.0%–14.0%) of these infants and is expected to be an underestimate.

[†] Frequencies < 5 are suppressed to maintain confidentiality.

[‡] See Supplemental Table 2, <http://links.lww.com/JAM/A754>, for more information on the ascertainment methodology and feature definitions.

[§] < 5 infants had cleft lip (+/- cleft palate).

^{||} Includes rocker bottom feet, talipes equinovarus, and other foot position deformities such as congenital talipes calcaneovalgus.

[¶] Seven hundred sixty-eight infants were missing infant sex or head circumference at birth, and 10 infants had gestational age out of range for INTER GROWTH-21st standards (≥ 43 wk or ≤ 24 wk).

[#] Infant sex was not reported for 656 infants.

TABLE 3.

Number of Features of Interest Observed Among Infants Within the Analytic Sample *

No. Features of Interest ^{†‡§¶}	Prevalence Among MAT-LINK LiveBorn Infants
0	4647/5053 (92.0%)
1	370/5053 (7.3%)
≥ 2 [#]	36/5053 (0.7%)

* The table is not restricted to infants with prenatal fentanyl exposure due to small feature counts. Prenatal fentanyl exposure is documented among 13.5% (95% CI: 13.0%–14.0%) of these infants and is expected to be an underestimate.

[†] Features include cleft palate with or without cleft lip, corpus callosum abnormalities, foot positioning deformities, male genital anomalies, microcephaly, micrognathia, and toe syndactyly.

[‡] Microcephaly is defined using procedural and diagnostic codes.

[§] Cleft palate with and without cleft lip is included.

[¶] Includes rocker bottom feet, talipes equinovarus, and other foot position deformities such as congenital talipes calcaneovalgus.

[#] Only 2267 infants had “male sex” documented and were eligible to be classified as having a male genital anomaly.

[#] The maximum number of features among any infant was 3.