PUBLIC HEALTH

Prenatal opioid exposure by likelihood of exposure and risk to prenatal development: Medicaid-covered births in Wisconsin, 2010–2019

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Prenatal opioid exposure is an established public health problem, in particular among Medicaid-covered births. Yet, existing prevalence rates are plausibly underestimated. We leverage extensive linked longitudinal administrative data for all Medicaid-covered live births in Wisconsin from 2010 to 2019 to estimate a range of prevalence rates using an innovative strategy that jointly accounts for both likelihood of exposure and potential risk to prenatal development. We find that 20.8% of infants may have been prenatally exposed to opioids, with 1.7% diagnosed with neonatal abstinence syndrome and an additional 1.2% having a high combined likelihood of exposure and potential risk to prenatal development, 2.6% a moderate combined likelihood and risk, and 15.3% a low or uncertain combined likelihood and risk. We assess improvements in prevalence estimates based on our nuanced classification relative to those of prior studies. Our strategy could be broadly used to quantify the scope of the opioid crisis for pregnant populations, target interventions, and promote child health and development.

INTRODUCTION

The opioid epidemic looms large over US society. High and increasing rates of opioid misuse, dependence, overdose, hospitalization, and death have been well documented, as have their social and economic consequences (*1*–*3*). The resulting national public health crisis has not spared pregnant women and their children (*4*–*7*). Prenatal opioid exposure, as measured by rates of maternal opioid use disorder (OUD) and infant neonatal abstinence syndrome (NAS), is thought to have reached alarming levels, in particular among Medicaid-covered births. National data indicate that approximately one-fifth of Medicaid-enrolled women fill at least one opioid prescription during pregnancy (*4*). Hospital discharge records show an estimated fivefold increase in the prevalence of OUD among mothers who gave birth between 2000 and 2009 and a threefold increase in NAS from 1999 to 2013 (*8*). By 2017, NAS was diagnosed in 7.3 per 1000 infants and maternal OUD in 8.2 per 1000 delivery hospitalizations, up from 4.0 and 3.5 per 1000 in 2010 (*9*). Data from 2019 further indicate that 6.6% of women report opioid prescription use during pregnancy, of which 21% report opioid misuse (*10*). Moreover, most prenatally opioid-exposed births are Medicaid covered, including an estimated 60 to 77% of maternal OUD and 80 to 84% of NAS cases (*8*, *9*, *11*).

Prenatal opioid exposure may have both short- and long-term health implications for mothers and their children. Women with chemical dependencies, including those with OUD, are disproportionately likely to deliver a preterm, low birthweight, or small for gestational age infant, some of whom receive a NAS or neonatal opioid withdrawal syndrome diagnosis (*12*–*15*). They are also at elevated risk for adverse pregnancy outcomes, including severe maternal morbidities (*16*–*18*). However, it is unclear whether associations of prenatal opioid exposure with adverse outcomes for mothers and infants are due to opioid use itself, or to co-occurring risk factors, including socioeconomic adversities and tobacco, alcohol, and other drug use, that pose similar risks to prenatal development, the impact of which is likely to vary by severity and chronicity of exposure (*19*, *20*).

The prevalence of prenatal opioid exposure has most frequently been estimated from hospital discharge records or (public or private) insurance claims records for mothers or infants; however, maternal and child records have not typically been linked to one another. Moreover, existing estimates tend to reflect only a discrete episode of care or a single indicator of potential exposure (maternal OUD diagnosis, NAS diagnosis, any opioid prescription fill during pregnancy) and typically lack contextual information from nonmedical sources, such as sociodemographic characteristics and documentation of substance use–related referrals to child protective services (CPS) shortly after birth. Consequently, diagnoses observed in health records may be subject to substantial selection bias, underascertainment of substance (mis)use and associated prenatal exposure, and sample attrition, such that existing studies may systematically underestimate the prevalence of prenatal opioid exposure, with potential heterogeneity therein by population group and place. Of additional concern, prior studies are largely silent with respect to potential heterogeneity in chronicity (duration) and severity (magnitude) of exposure, which may have important implications for associated risk to prenatal and postnatal development. Failing to identify some mothers and children experiencing chronic and severe prenatal opioid exposure, as well as differentiating those with varying degrees of chronicity and severity of exposure, may result in missed or misstargeted opportunities to provide appropriate substance misuse and/or child development interventions.

Linked multisource administrative data offer opportunities to overcome many of the limitations described above and, thus, to facilitate more accurate and nuanced identification of prenatal opioid exposure by considering both the likelihood that exposure has

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occurred and the potential chronicity and severity of such exposure (*21*). Linked administrative data can also support the construction of cohorts through which to assess prenatal exposure trends longitudinally. In this study, we use longitudinal data from multiple administrative systems to produce a range of estimates of the prevalence of prenatal opioid exposure that consider both the likelihood that exposure has occurred and its potential risk to prenatal development, as approximated by potential chronicity and severity of exposure. Our data include birth certificate records (vital statistics) and Medicaid enrollment and inpatient, outpatient, and pharmaceutical claims records for mothers and their infants spanning the start of pregnancy through 30 days after the birth, as well as CPS agency data that identify mothers who, within 7 days of the birth, were the subject of a screened-in (investigated) referral for alleged maltreatment. Such referrals are predominantly driven by maternal substance use during pregnancy and, under Wisconsin Act 292, prenatal substance exposure constitutes child maltreatment. Our sample includes all Medicaid-covered live births in Wisconsin from 2010 to 2019.

As noted above, prior research has harnessed single indicators of maternal OUD diagnosis, infant NAS diagnosis, or whether a mother filled any opioid prescriptions during pregnancy to approximate prenatal opioid exposure. When used independently, these indicators are implicitly prone to classification error as, for example, infants whose mothers have an OUD diagnosis but who are not diagnosed with NAS may have plausibly been prenatally exposed, albeit likely with a lower risk to prenatal development than implied by a NAS diagnosis. Moreover, none of these indicators convey certainty that an infant was prenatally exposed or that, if exposure did occur, prenatal development was affected. Hence, we draw upon rich administrative records and leverage a range of indicators to construct multiple categories of prenatal exposure that imply varying degrees of certainty regarding the likelihood that prenatal exposure occurred and the potential level of risk that such exposure may have posed to development, as reflected by the implied chronicity and/or severity associated with each, relative to the others. Our approach assumes a dose-response relation between the magnitude of exposure (chronicity and/or severity) and potential risk to prenatal development such that, if prenatal opioid exposure poses a risk to prenatal development, then a greater magnitude of exposure poses greater risk. It implies, for example, that a NAS diagnosis reflects both greater likelihood of exposure and greater risk to prenatal development than a suspected NAS diagnosis, on average, and that both reflect greater likelihood of exposure and greater risk to prenatal development than a single maternal opioid prescription fill during pregnancy.

Specifically, we leverage 11 indicators of prenatal opioid exposure to construct four exposure categories that reflect two salient dimensions thereof: (i) the likelihood that exposure occurred and (ii) the potential risk of such exposure to prenatal development. To empirically assess the validity of our assumptions regarding the level of likelihood of exposure and potential risk to prenatal development associated with each indicator, we constructed a prenatal exposure index, composed of the sum of the 11 binary indicators of prenatal opioid exposure included in our analyses (range = 0 to 11), and an infant health index, composed of the sum of five indicators representative of poor infant health at birth (range = 0 to 5): low birthweight (<2500 g); preterm birth (<37 weeks); small for gestational age (<10th percentile); low 5-min appearance, pulse, grimace, activity, and respiration (APGAR) score (<7); and admission to the neonatal intensive care unit. We then estimated a bivariate ordinary least squares regression (linear probability model) of each index on each prenatal exposure indicator, such that the resulting coefficient is interpreted as the average difference in score on the index associated with the presence of the indicator. Last, we assigned each indicator to one of four categories taking into account whether the magnitude of its association with each index was above (versus at or below) the median magnitude of association of the full set of indicators with the relevant index. We note, however, that we do not rely solely on the magnitude of these associations in assessing likelihood of exposure and developmental risk given both that they are not causal estimates, but rather unadjusted correlations, and that the indicators themselves are intercorrelated to varying degrees. Hence, we consider the magnitude of these associations in concert with findings from prior research and logical assumptions of opioid-related behaviors vis-à-vis potential exposure and risk (e.g., 90+ days of prescription fills connotes greater potential exposure than fewer days of prescription fills) to inform our categorization of combined likelihood of exposure and risk to prenatal development.

Considering both the likelihood that prenatal opioid exposure has occurred and its potential risk to prenatal development allows us to construct a nuanced classification of in utero opioid exposure that spans both domains, as well as to assess and quantify improvements in prevalence estimates produced using this classification, which leverages 11 indicators of exposure drawn from comprehensive longitudinal administrative data, relative to those produced in prior studies using single-domain, single-indicator measures. We present population-wide estimates of potential prevalence rates of prenatal exposure and trends therein over time, among all Medicaid-covered live births in Wisconsin from 2010 to 2019, for four hierarchically nested categories of exposure defined by their combined likelihood of exposure and potential risk to prenatal development. In addition to providing these estimates for the full population of such births, we also provide them for population subgroups delineated by maternal race/ethnicity, age, education, marital status, birth parity, and urbanicity of residence at the time of the birth. Last, we examine concordance among the 11 indicators of focus to assess whether those that have not been commonly used in prior work provide unique insights into potential prenatal opioid exposure or duplicate information provided by those that have commonly been used to estimate its prevalence (maternal OUD diagnosis, NAS diagnosis, any opioid prescription fill during pregnancy). Our strategy has the potential to be broadly used to quantify the scope of the opioid crisis for pregnant populations, target interventions, and promote child health and development.

RESULTS

Categorization of prenatal opioid exposure by likelihood of exposure and potential risk to child development

Table 1 presents our empirical assessment of the relative likelihood of exposure and potential risk to prenatal development of each indicator (see table S1 for detailed definitions, data sources, and administrative codes used for each indicator). We constructed four categories of combined likelihood of exposure and potential risk to prenatal development. These categories (and the indicators that comprise them) are: NAS diagnosis (infant was diagnosed with NAS within 30 days of birth), high combined likelihood and risk [mother was diagnosed

Table 1. Associations of prenatal exposure indicators and categories with prenatal exposure index and birth health index. A total of 259,723 observations representing all Medicaid-covered live births in Wisconsin from 2010 to 2019. Data are drawn from birth certificate, BadgerCare Plus (Wisconsin's combined Medicaid and State Child Health Insurance Program), and CPS administrative records. The prenatal exposure index is composed of the sum of the 11 indicators of potential prenatal opioid exposure (range = 0 to 11). The birth health index is composed of the sum of five potential indicators of poor infant health at birth (range = 0 to 5): low birthweight (<2500 g), preterm birth (<37 weeks), small for gestational age (<10th percentile), low 5-min APGAR score (<7), and admission to the neonatal intensive care unit. Associations of each indicator/category with the indices were estimated using an ordinary least squares regression of the index on the indicator/category such that they are interpreted as the average difference in the index score associated with the presence of the indicator/category. Other SUD, nonopioid SUD(s).

	Association with prenatal exposure index	Association with birth health index
Median	2.39	0.52
NAS diagnosis		
NAS diagnosis within 30 days of birth	3.37*	0.69*
Category total	3.37*	0.69*
High combined likelihood and risk		
Any OUD diagnosis during pregnancy or delivery hospitalization	3.52*	0.55*
Any MOUD use during pregnancy or delivery hospitalization	3.81*	0.60*
Any OUD treatment during pregnancy or delivery hospitalization	4.40*	0.67*
Category total	3.34*	0.55*
Moderate combined likelihood and risk		
Suspected NAS within 30 days of birth	1.97†	0.52†
CPS investigation within 7 days of the birth	2.39†	0.59*
90+ days of non-MOUD opioid prescription fills during pregnancy	1.63†	0.33†
Category total	2.00†	0.51†
Low or uncertain combined likelihood and risk		
1–29 days of non-MOUD opioid prescription fills during pregnancy	1.03†	0.04†
Other SUD diagnosis during pregnancy or delivery hospitalization	1.99†	0.36†
30–89 days of non-MOUD opioid prescription fills during pregnancy	1.18†	0.14†
OUD in remission during pregnancy or delivery hospitalization	3.85*	0.45†
Category total	1.33†	0.13†

*Above median association with the index. †At or below median association with the index.

with OUD during pregnancy or delivery hospitalization, filled medications for OUD (MOUD) prescription(s) during pregnancy, or was treated for OUD during pregnancy or delivery hospitalization], moderate combined likelihood and risk [infant received a suspected NAS diagnosis within 30 days of birth, mother was the subject of a CPS investigation within 7 days of the birth, and mother filled 90 or more days of non-MOUD opioid prescriptions during pregnancy], and low or uncertain combined likelihood and risk [mother filled 1 to 29 days of non-MOUD opioid prescriptions during pregnancy, was diagnosed with a non-OUD substance use disorder (SUD) during pregnancy or delivery hospitalization, filled 30 to 89 days of non-MOUD opioid prescriptions during pregnancy, or was diagnosed with OUD "in remission" during pregnancy or delivery hospitalization].

The median associations of the 11 indicators with the prenatal exposure index and infant health index are shown in the second and third columns of Table 1. The indicators that make up the NAS diagnosis and high combined likelihood and risk categories each have above median magnitudes of association with each index. All of the indicators that make up the moderate combined likelihood and risk category have below median magnitudes of association with the prenatal exposure index and all but one have below-median magnitudes of association with the infant health index. The one exception, CPS investigation within 7 days of birth, has a magnitude of association with the infant health index that is slightly above the median. We argue, however, that this indicator is most appropriately categorized in the moderate rather than high combined likelihood and risk category both because it is only moderately associated with the exposure index and because its association with infant health may be driven by other factors that are correlated with both CPS involvement and adverse birth outcomes, such as concerns with parental supervision, mental health, incarceration, or other factors that compromise parental care.

All of the indicators that make up the low or uncertain combined likelihood and risk category have below median magnitudes of association with the infant health index and all but one have below median magnitudes of association with the prenatal exposure index. The exception, OUD in remission during pregnancy or delivery hospitalization, has a strong association with the prenatal exposure index which, as discussed below with respect to our analyses of concordance among the indicators, largely reflects overlap among OUD in remission during pregnancy, OUD diagnosis during pregnancy, and receiving MOUD during pregnancy (and, to a lesser extent, NAS diagnosis). We argue that this indicator is best categorized as low or uncertain combined likelihood and risk given both its weak association with the infant health index and that its strong association with the prenatal exposure index reflects the presence of other indicators that frequently co-occur with OUD in remission, rather than reflecting the influence of OUD in remission itself. That is, we argue that, just as a nonopioid SUD diagnosis during pregnancy conveys reasonable uncertainty that prenatal exposure to opioids has occurred, so too does a diagnosis of OUD in remission. Notably, the ordering of the combined likelihood and risk categories follow expected patterns of magnitude of association with respect to both the exposure index and infant health index, with magnitudes of association, respectively, of 3.37 and 0.69 for NAS diagnosis, 3.34 and 0.55 for high combined likelihood and risk, 2.00 and 0.51 for moderate likelihood and risk, and 1.33 and 0.13 for low or uncertain likelihood and risk.

Prevalence of potential prenatal opioid exposure among Medicaid-covered births in Wisconsin, 2010–2019

Table 2 presents independent and cumulative prevalence estimates for each indicator and category of potential exposure over the 2010 to 2019 period. Note that the cumulative prevalence estimates are hierarchical in nature such that the magnitude of increase in each step reflects the ordering in which the indicators are added. Within each category, we added indicators in descending order by raw (independent) prevalence rate. The NAS diagnosis rate, representing the proportion of infants diagnosed with NAS within 30 days of birth, was 1.7% over the period. The high combined likelihood and risk rate, which encompasses maternal OUD diagnosis and/or treatment, including MOUD fills, during the pregnancy or birth

Table 2. Estimated prevalence of prenatal opioid exposure, indicators and categories of likelihood of exposure and potential risk to prenatal development among Medicaid-covered births in Wisconsin, 2010–2019. A total of 259,723 observations representing all Medicaid-covered live births in Wisconsin from 2010 to 2019. Data are drawn from birth certificate, BadgerCare Plus (Wisconsin's combined Medicaid and State Child Health Insurance Program), and CPS administrative records. Other SUD, nonopioid SUD(s). Percent of births presented. The independent percent reflects the proportion of all births for which the indicator is present regardless of the presence of any other indicators. The cumulative percent reflects the total percent of births with potential prenatal opioid exposure when the indicator is added to all previously included indicators. Indicators were added in hierarchical fashion in the order presented in the table (from top to bottom).

	Independent (%)	Cumulative (%)
NAS diagnosis		
NAS diagnosis within 30 days of birth	1.7	1.7
Category total	1.7	1.7
High combined likelihood and risk		
OUD diagnosis during pregnancy or delivery hospitalization	2.1	2.7
MOUD use during pregnancy or delivery hospitalization	1.5	2.9
OUD treatment during pregnancy or delivery hospitalization	0.8	2.9
Category total	2.4	2.9
Moderate combined likelihood and risk		
Suspected NAS within 30 days of birth	1.7	4.3
CPS investigation within 7 days of the birth	1.4	5.0
90+ days of non-MOUD opioid prescription fills during pregnancy	0.8	5.5
Category total	3.6	5.5
Low or uncertain combined likelihood and risk		
1–29 days of non-MOUD opioid prescription fills during pregnancy	13.2	17.8
Other SUD diagnosis during pregnancy or delivery hospitalization	4.7	19.9
30–89 days of non-MOUD opioid prescription fills during pregnancy	1.1	20.7
OUD in remission during pregnancy or delivery hospitalization	0.4	20.8
Category total	18.2	20.8

hospitalization, identifies an additional 1.2% of births, bringing the cumulative rate to 2.9%, with the largest increase from inclusion of OUD diagnosis during pregnancy or delivery hospitalization. The moderate combined likelihood and risk rate, which is composed of suspected NAS diagnosis within 30 days of birth, CPS investigation within 7 days of the birth, and 90 or more days of non-MOUD opioid prescription fills by the mother during pregnancy (excluding birth hospitalization), identifies an additional 2.6% of births, increasing the cumulative rate to 5.5%, with the largest increase coming from suspected NAS diagnosis. Last, the low or uncertain combined likelihood and risk rate, our most inclusive indicator, identifies 15.3% of additional births such that the total cumulative rate suggests that 20.8% of infants whose delivery was covered by Medicaid may have had some level of opioid exposure in utero, with the primary additional driver being 1 to 29 days of non-MOUD prescriptions during pregnancy (13.2%).

Trends in the prevalence of potential prenatal opioid exposure among Medicaid-covered births in Wisconsin, 2010–2019

The estimates presented in Table 2 represent prevalence rates for each indicator and category of potential prenatal opioid exposure among Medicaid-covered births in Wisconsin, pooled over the analytic period. This may mask substantial variation in prevalence rates of the indicators or categories over time. This assertion is corroborated by the results presented in Fig. 1 (see also table S2A), which presents time trends for each category. The NAS diagnosis rate, for example, is at a low of 0.9% in 2010 before increasing annually to a high of 2.1% in 2016 and 2017, then decreasing modestly to 1.8% in 2019. In short, NAS diagnoses roughly doubled over the 10-year period despite decreasing modestly in the final 2 years. We find a similar pattern for the high combined likelihood and risk and moderate combined likelihood and risk rates. For example, the cumulative rate when the high combined likelihood and risk category is added to the NAS category rises from 1.6% in 2010 to a high of 3.8% in 2017 and 2018, before falling to 3.5% in 2019. The cumulative rate when the moderate combined likelihood and risk category is included rises from 3.3% in 2010 to a high of 7.2% in 2018 before declining to 5.8% in 2019.

In contrast, we see a large decline over time in prenatal opioid exposure when considering the low or uncertain likelihood and risk category. Here, the exposure rate declines from 23.2% in 2010 to 21.0% in 2015, reaching a low of 16.1% in 2019. Notably, Wisconsin implemented its prescription drug monitoring program (PDMP) in June of 2013 and these declines may, in part, reflect the effect of PDMP and other changes in opioid-related health care policy and practice, including the Centers for Disease Control and Prevention (CDC) opioid prescribing guidelines that occurred during the latter half of the observation period (*22*–*24*). Critically, while this trend broadly suggests that opioid prescribing decreased in the latter half of the period, we do not see declines in higher-risk opioid exposure categories. On the whole, we find that, from 2010 to 2019, the NAS diagnosis rate doubled, the (cumulative) high combined likelihood and risk rate increased by 1.9 percentage points (119%), and the moderate combined likelihood and risk rate increased by 2.5 percentage points (76%), whereas the low or uncertain combined likelihood and risk rate declined by 7.1 percentage points (31%).

The results presented in Fig. 2 (see also table S2B) provide a more nuanced depiction of these trends for the individual indicators that comprise the likelihood and risk categories. The NAS diagnosis category consists of a single indicator (infant NAS diagnosis within 30 days of birth). Hence, we take the opportunity, here, to compare the time trend in our NAS measure to that of the NAS rate found in Wisconsin hospital discharge data from the Healthcare Cost and Utilization Project (HCUP) (*25*). Specifically, we compare the NAS diagnosis rate during delivery hospitalization for all Wisconsin live

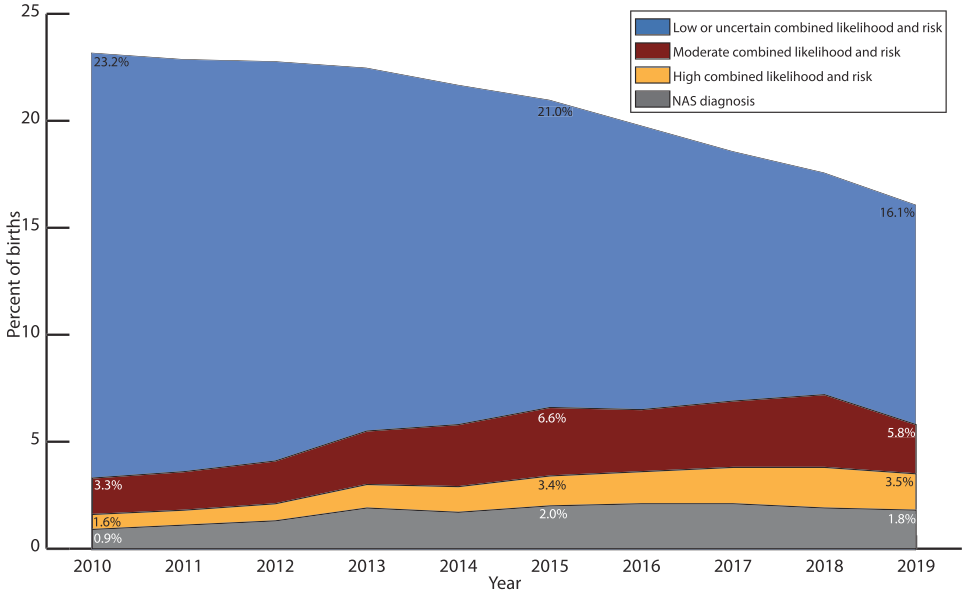

Fig. 1. Time trends in the estimated annual prevalence of prenatal opioid exposure by categories of combined likelihood of exposure and potential risk to prenatal development among Medicaid-covered births in Wisconsin, 2010–2019. 259,723 observations representing all Medicaid-covered live births in Wisconsin from 2010 to 2019. Data are drawn from birth certificate, BadgerCare Plus (Wisconsin's combined Medicaid and State Child Health Insurance Program), and child protective services administrative records. NAS, neonatal abstinence syndrome.

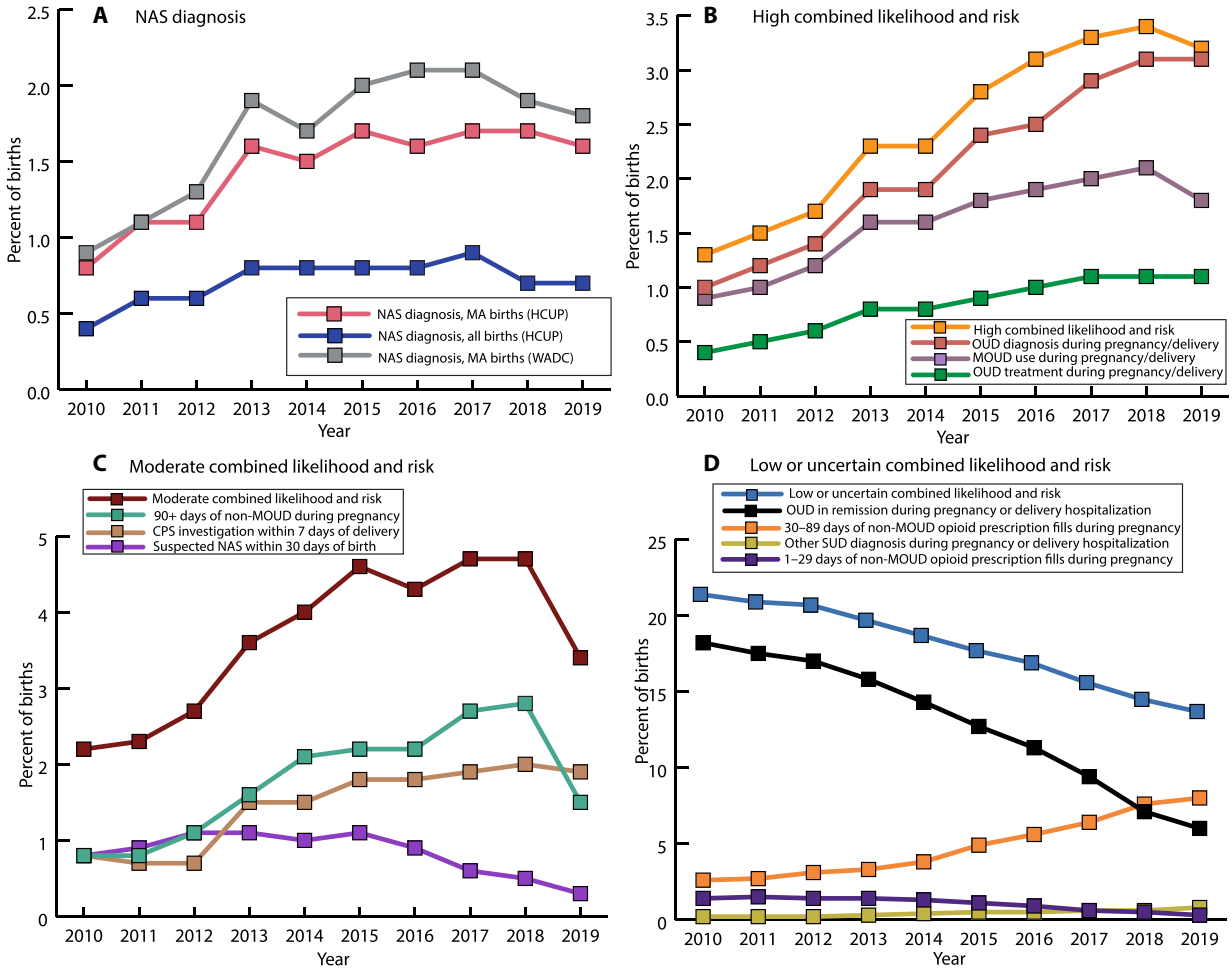

Fig. 2. Time trends in estimated annual prevalence of prenatal opioid exposure by indicators and combined categories of likelihood of exposure and potential risk to prenatal development among Medicaid-covered births in Wisconsin, 2010–2019, indicator components. 259,723 observations representing all Medicaid-covered live births in Wisconsin from 2010 to 2019. (**A**) presents time trends in NAS diagnosis rates using (i) Medicaid-covered births in HCUP data, (ii) Medicaid-covered births in WADC data, and (iii) all births in HCUP data. (**B**) presents time trends in the rate of the high combined likelihood and risk of prenatal exposure category and the indicators that comprise this category. (**C**) presents time trends in the rate of the moderate combined likelihood and risk of prenatal exposure category and the indicators that comprise this category. (**D**) presents time trends in the rate of the low or uncertain combined likelihood and risk of prenatal exposure category and the indicators that comprise this category. Data are drawn from birth certificate, BadgerCare Plus (Wisconsin's combined Medicaid and State Child Health Insurance Program), and child protective services administrative records and, in (A), hospital discharge data from HCUP. Categories are not mutually exclusive. HCUP, Healthcare Cost and Utilization Project; WADC, Wisconsin Administrative Data Core; NAS, neonatal abstinence syndrome; OUD, opioid use disorder; MOUD, medications for opioid use disorder; CPS, child protective services; Other SUD, non-opioid substance use disorder(s).

births (HCUP data), that for Medicaid-covered live births (HCUP data), and the NAS diagnosis rate within 30 days of birth among Medicaid-covered live births [our measure using Wisconsin Administrative Data Core (WADC) data] during the same period. As expected, these trends follow a generally similar pattern, albeit with a steeper increase in NAS between 2010 and 2017 among Medicaid-covered births relative to all births. Also, consistent with prior research, the overall NAS rate is considerably higher among Medicaid-covered births than among all births (*26*). Notably, the NAS rate within 30 days of birth found in our data is modestly higher in most years than the corresponding HCUP estimate among Medicaid-covered births, which is based on NAS diagnoses during the delivery hospitalization, with magnitudes of difference on the order of 0.1 to 0.5 percentage points (13 to 31%). This indicates that a nonnegligible portion of NAS cases are diagnosed following birth hospitalization discharge such that hospital discharge data may substantially underestimate the "true" infant NAS rate. Overall, between 2010 and 2019, we find a 0.9 percentage point (100%) increase in NAS diagnoses within 30 days of birth among Medicaid-covered deliveries (WADC data), 0.8 percentage point (100%) increase in NAS diagnoses during the delivery hospitalization among Medicaid-covered deliveries (HCUP data), and 0.3 percentage point (75%) increase in NAS diagnosis for all births (HCUP data) in Wisconsin.

Turning to the high combined likelihood and risk category, we find an upward trend among each of the three indicators, albeit of varying degree. Considering the difference in the prevalence of each between 2010 and 2019, we find increases of 2.1, 0.9, and 0.7 percentage points (210, 100, and 175%), respectively, for OUD diagnosis,

MOUD prescription fills, and OUD treatment during pregnancy or delivery hospitalization. For the moderate category, the data show diverging trends among the indicators. Whereas we find increases in suspected NAS and CPS investigations, on the order of 0.7 and 1.1 percentage points (88% and 138%), we see a large decline in 90 or more days of non-MOUD opioid prescriptions filled during pregnancy, on the order of 0.5 percentage points (63%), with the steepest decline occurring after 2015. Last, for the low or uncertain combined likelihood and risk category, we see increases in OUD in remission, which rose by 0.6 percentage points (300%) over the period, and nonopioid SUD diagnosis, which rose by 5.4 percentage points (208%). At the same time, we find substantial declines in prescription fills during pregnancy, at 12.2 percentage points (67%) for 1 to 29 days and 1.1 percentage points (79%) for 30 to 89 days. Again, the steepest declines in prescription fills coincide with the timing of Wisconsin's PDMP implementation and changes in opioid prescription guidelines and associated practices (*22*–*24*). In short, despite that non-MOUD opioid prescription fills declined considerably over, and in particular during the latter half of, the observation period, we find little evidence of declines in other, higher likelihood and higher risk, measures of prenatal opioid exposure, suggesting that prescription rates are unlikely to have been the predominant driver of prenatal opioid exposure since 2013 and that this has, increasingly, become the case over time.

Concordance of indicators

Table 3 presents estimates of concordance between each pair of indicators (bivariate correlations between each pair of indicators are presented in table S3). Specifically, we assess how frequently each is present conditional on the other being present. Each estimate represents the proportion of cases for which the row indicator is present, conditional on the column marker being present. Considering the concordance of NAS and OUD diagnosis, for example, the estimate in the NAS row and OUD diagnosis column indicates that 61% of mothers who had an infant who was diagnosed with NAS (and 39% of those who did not) had an OUD diagnosis during pregnancy or delivery hospitalization, whereas the estimate in the OUD diagnosis row and NAS column indicates that 48% of mothers who had an OUD diagnosis during pregnancy or delivery hospitalization (and 52% of those who did not) had an infant who was diagnosed with NAS. Throughout the table, instances of greater than 50% concordance are bolded and instances of 25 to 50% concordance are italicized.

Table 3. Concordance of prenatal opioid exposure indicators among Medicaid-covered births in Wisconsin, 2010–2019. A total of 259,723 observations representing all Medicaid-covered live births in Wisconsin from 2010 to 2019. Data are drawn from birth certificate, BadgerCare Plus (Wisconsin's combined Medicaid and State Child Health Insurance Program), and CPS administrative records. Each estimate represents the proportion of cases for which the column measure is indicated, conditional on the row measure being indicated. Bold indicates greater than 50% concordance and italic indicates 25 to 50% concordance. NAS, infant received a NAS diagnosis within 30 days of birth; OUD diag., mother diagnosed with OUD during pregnancy or delivery hospitalization; MOUD, mother filled any MOUD prescriptions during pregnancy; OUD tmt., mother received OUD treatment during pregnancy or delivery hospitalization; suspected NAS, infant received a diagnosis of suspected NAS within 30 days of birth; CPS investigation, mother was subject of a CPS investigation within 7 days of the birth; 90+ days non-MOUD, mother filled 90 or more days of non-MOUD opioid prescriptions during pregnancy; 1–29 days non-MOUD, mother filled 1–29 days of non-MOUD opioid prescriptions during pregnancy; other SUD, mother diagnosed with nonopioid SUD during pregnancy or delivery hospitalization; 30–89 days non-MOUD, mother filled 30–89 days of non-MOUD opioid prescriptions during pregnancy; OUD in remission, mother diagnosed with "OUD in remission" during pregnancy or delivery hospitalization.

	NAS	OUD diag.	MOUD	OUD tmt.	Susp. NAS	CPS invest.	90+ days non-MOUD	1–29 days non-MOUD	Other SUD	30–89 days non-MOUD	OUD in remiss.
NAS	–	**0.61**	**0.57**	*0.31*	0.00	*0.25*	0.10	0.18	*0.43*	0.05	0.11
OUD diagnosis	*0.48*	–	**0.57**	*0.38*	0.15	0.17	0.09	0.16	**0.55**	0.05	0.14
MOUD	**0.61**	**0.77**	–	*0.45*	0.15	0.16	0.05	0.18	*0.47*	0.04	0.16
OUD treatment	**0.63**	**0.96**	**0.85**	–	0.13	0.17	0.02	0.18	**0.52**	0.03	0.17
Suspected NAS	0.00	0.18	0.13	0.06	–	0.15	0.05	0.18	*0.41*	0.04	0.03
CPS investigation	*0.28*	*0.25*	0.18	0.10	0.19	–	0.04	0.17	*0.39*	0.03	0.03
90+ days of non-MOUD	0.20	0.23	0.09	0.02	0.10	0.07	–	0.00	0.19	0.00	0.01
1–29 days of non-MOUD	0.02	0.03	0.02	0.01	0.02	0.02	0.00	–	0.06	0.00	0.01
Other SUD	0.15	0.24	0.16	0.09	0.15	0.12	0.03	0.17	–	0.03	0.05
30–89 days of non-MOUD	0.08	0.09	0.05	0.02	0.06	0.04	0.00	0.00	0.11	–	0.01
OUD in remission	*0.43*	**0.71**	**0.62**	*0.34*	0.14	0.10	0.02	0.17	**0.59**	0.02	–

It is notable that relatively few indicators demonstrate high (>50%) or moderate (25 to 50%) concordance with one another, with most pairs demonstrating quite low concordance (<25%). This underscores the potential contribution of considering a wider range of indicators than have typically been included in estimating prenatal exposure rates (most frequently, only NAS and OUD diagnosis), as we do here. We find greatest concordance (>0.75) among indicators of MOUD, OUD diagnosis, and OUD treatment during pregnancy. This makes sense given that an OUD diagnosis should be necessary for OUD treatment, including MOUD. For example, 96% of those who received OUD treatment during pregnancy had an OUD diagnosis during pregnancy or delivery hospitalization and 85% had MOUD prescription fills (63% had an infant who was diagnosed with NAS). Of those with MOUD fills during pregnancy, 77% had an OUD diagnosis during pregnancy or delivery hospitalization (61% had an infant who was diagnosed with NAS). We also find relatively high levels of concordance (>0.50) of OUD in remission with OUD diagnosis, MOUD fills, and nonopioid SUD diagnosis during pregnancy and, to a lesser extent, of nonopioid SUD diagnosis during pregnancy with OUD diagnosis, MOUD, and nonopioid SUD during pregnancy. Last, it is notable that 92% of infants diagnosed with NAS had at least one other prenatal exposure indicator present, whereas 8% of infants diagnosed with NAS had no other indicator present, and that only 9% of infants with at least one other indicator present also had a NAS diagnosis, whereas 91% were not diagnosed with NAS (not shown in Table 3). On the whole, these results suggest that those indicators that have not typically been used to produce estimates of the prevalence of prenatal opioid exposure contribute additional, rather than redundant, information about potential exposure.

Heterogeneity by maternal characteristics

Figure 3 depicts prevalence rates for each combined likelihood and risk category by maternal characteristics at birth (see table S4 for results from tests for statistically significant differences). These results indicate that, on the whole, infants born to white and Black mothers have considerably higher rates of prenatal exposure than infants born to mothers in other racial and ethnic groups, and that rates of NAS and high combined likelihood and risk of prenatal opioid exposure are particularly high for infants born to white mothers, whereas rates of moderate combined likelihood and risk and, to a lesser extent, of low or uncertain combined likelihood and risk, are particularly high for those born to Black mothers. We also find that prenatal exposure tends to increase with age, in particular when considering higher levels of combined likelihood and risk (NAS diagnosis and high combined likelihood and risk categories). In addition, prenatal exposure is disproportionately common among mothers with less than a high school education (on all but the high combined likelihood and risk category), unmarried mothers, and those having a higher-order (rather than first) birth. Last, we find that the infant NAS rate is higher for urban mothers than suburban and rural mothers; the high combined likelihood and risk rate is higher for rural mothers than suburban and, to a lesser extent, urban mothers; the moderate combined likelihood and risk rate is higher for urban than suburban and rural mothers; and the low or uncertain likelihood and risk rate is higher for rural than suburban

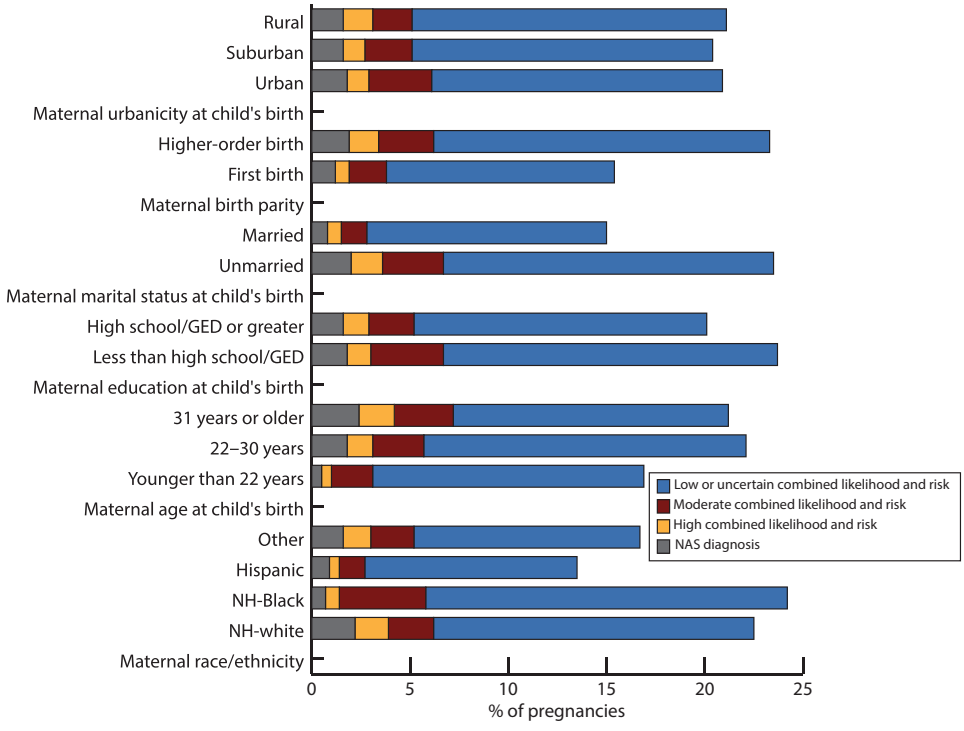

Fig. 3. Estimated prevalence of prenatal opioid exposure, by likelihood of exposure and potential risk to prenatal development among Medicaid-covered births in Wisconsin, 2010–2019, heterogeneity by population subgroups. 257,189 observations representing all Medicaid-covered live births in Wisconsin from 2010 to 2019 with non-missing data on the population subgroup characteristics. Data are drawn from birth certificate, BadgerCare Plus (Wisconsin's combined Medicaid and State Child Health Insurance Program), and child protective services administrative records. GED, General Educational Diploma; NH, non-Hispanic.

and, to a lesser extent, suburban mothers. Together, these patterns highlight potential differences in prenatal exposure behaviors and/or their detection vis-à-vis existing indicators thereof in Medicaid diagnosis, claims, and prescription fills data, as well as in CPS administrative data.

DISCUSSION

This study leverages extensive linked longitudinal administrative data for all Medicaid-covered live births in the State of Wisconsin from 2010 to 2019 to estimate the prevalence of prenatal opioid exposure when both likelihood of exposure and potential risk to prenatal development, as approximated by magnitude (chronicity and severity) of exposure, are jointly considered. These dimensions have typically been examined independently of one another, despite that their joint consideration is particularly salient to classifying risk associated with opioid use during pregnancy. Our data, spanning pregnancy through 30 days after a birth, include vital statistics (birth certificates), BadgerCare Plus (Wisconsin's joint Medicaid and State Children's Health Insurance Program) enrollment and claims (inpatient, outpatient, diagnoses, treatments, and pharmacy prescription fills), and CPS investigations within 7 days of the birth.

Our findings suggest four general conclusions. First, we find that approximately 1.7% of all Medicaid-covered live births in Wisconsin have a NAS diagnosis within 30 days of birth. Notably, this estimate is roughly 21% higher than is found in hospital discharge (HCUP) records for the same population of Wisconsin Medicaid–covered births, suggesting that accounting for NAS diagnoses beyond the delivery-related hospital stay is imperative to accurate surveillance.

Second, we find an additional 1.2% of Medicaid-covered live births in Wisconsin to have a high combined likelihood of prenatal opioid exposure and risk to prenatal development such that, cumulatively, approximately 2.9% of such births are characterized by high likelihood and risk vis-à-vis prenatal opioid exposure, inclusive of those with a NAS diagnosis. Another 2.6% of such births are characterized by a moderate combined likelihood and risk level, raising the cumulative total to 5.5%, and an additional 15.3% are characterized by a low or uncertain combined likelihood and risk level such that, on the whole, up to 20.8% of all Medicaid-covered infants born in Wisconsin may have experienced some degree of prenatal opioid exposure.

These findings suggest that rates derived from hospital discharge and other, less comprehensive, data considerably underestimate the prevalence of developmentally salient prenatal opioid exposure, and that actual rates may be two to six times higher. For example, Hirai *et al.* (*9*), using national HCUP data, estimate NAS and maternal opioid–related diagnoses rates among Medicaid-covered live births from 2010 to 2017 to be approximately 1%. By comparison, we estimate rates of NAS and maternal OUD diagnosis in Wisconsin during those years to be 60 to 90% higher, at 1.6 and 1.9%, respectively. Our more inclusive categories for the 2010–2017 period are 2.3% (high likelihood and risk), 3.5% (moderate likelihood and risk), and 19.0% (low or uncertain likelihood and risk) (noncumulative estimates presented, see table S2). This underscores the efficacy of considering a wider range of indicators than are typically used to estimate prenatal opioid exposure prevalence rates. Notably, however, because our sample is drawn only from Wisconsin, we cannot be certain that these differences in estimates reflect only differences in exposure measures used and not also differences between the national and Wisconsin Medicaid populations.

In addition, that we find relatively low concordance between most indicators of potential exposure and, in particular, of those that are unique to our study with those that have been used in prior studies (NAS diagnosis, maternal OUD diagnosis during pregnancy, and, in some cases, any opioid prescription fills during pregnancy), highlights that the additional indicators provide independent rather than duplicative evidence of potential prenatal exposure and, thus, may identify it among mothers and children for which it is not identified by standard indicators. Moreover, in the absence of prescription opioid fills resulting from either a lack of data tracking prescription fills or, in the presence of such data, no observed opioid prescription fills, indicators such as OUD diagnosis or OUD treatment, including MOUD, during pregnancy or delivery hospitalization, may proxy for illicit or treatment-related exposure during pregnancy.

Third, whereas we find that opioid prescription fills among pregnant women in our sample decreased precipitously between 2010 and 2019, in particular in the period after opioid prescribing guidelines and practices changed nationally and PDMP was implemented in Wisconsin (in 2013), this decline did not lead to lower rates of the most developmentally salient categories of prenatal opioid exposure. Rather, we observe increases in all categories of prenatal opioid exposure (NAS diagnosis, high combined likelihood and risk, and moderate combined likelihood and risk) during this period, except for the low or uncertain combined likelihood and risk category. The rate of Medicaid-covered live births in Wisconsin resulting in a NAS diagnosis roughly doubled (from 0.9 to 1.8%), that for those characterized as high combined likelihood and risk increased by 146% (from 1.3 to 3.2%), and that for those characterized as moderate combined likelihood and risk increased by 55% (from 2.2 to 3.4%). These increases were primarily driven by increases in diagnosed or suspected NAS within 30 days of birth, OUD diagnosis and treatment during pregnancy and delivery hospitalization, MOUD prescription fills, and CPS referrals shortly after birth. Some of these indicators (MOUD prescription fills and OUD treatment and diagnoses) may capture information about illicit opioid exposure (illicitly obtained prescription opioids or nonprescribed opioids, such as heroin, that are not observed in Medicaid prescription fill data), which may have contributed to increased rates of NAS between 2010 and 2019, despite reductions in non-MOUD prescriptions over the period. As prescription opioids became harder to obtain via licit means, after changes in prescribing guidelines and practices, PDMP implementation, and other supply-side interventions (e.g., the reformulation of oxycontin in 2010) were implemented, research has documented shifts in opioid consumption from licit to illicit markets (*27*, *28*). Notably, however, we cannot determine whether increases in NAS and suspected NAS rates over the period were predominantly driven by increases in infants presenting with NAS-related symptoms, as opposed to reflecting a greater awareness of potential maternal exposure by health care providers and heightened recommendations for screening and management that may have led to more consistent surveillance of newborns (*29*, *30*).

In contrast, when considering all 11 indicators (the cumulative rate, inclusive of the low or uncertain combined likelihood and risk category), we detect a substantial decline of 36% (from 21.4 to 13.7%) in the overall prevalence of potential prenatal opioid exposure, reflecting a sizable decline in opioid prescription fills during pregnancy, in particular over the latter half of the period. Together, these findings indicate that, whereas PDMP implementation and

shifting norms among prescribers may have led to large reductions in maternal opioid prescriptions during pregnancy, they do not appear to have led to reductions in high-risk prenatal opioid exposure (*24*). Moreover, whereas prescription fills during pregnancy closely track prenatal exposure rates for each of the categories considered here during the 2010–2012 period, they diverge thereafter. Thus, while non-MOUD prescription opioid use among pregnant women whose births were covered by Medicaid may have played a large role in prenatal opioid exposure in the early years of the last decade, other forms of opioid access, including MOUD prescriptions for OUD and illicit opioids, likely drove prenatal exposure rates in more recent years.

Fourth, our subgroup analyses suggest considerable heterogeneity in the prevalence of potentially developmentally salient prenatal opioid exposure among Medicaid-covered births by maternal characteristics and geography. Of note, for the most developmentally salient categories (all but low or uncertain combined likelihood and risk), white non-Hispanic, older, less educated, and unmarried mothers are at highest risk of delivering a prenatally opioid-exposed infant, as are mothers delivering a higher-order (rather than first) birth, and those living in urban and rural (rather than suburban) areas. This variation should be considered for targeting and tailoring screening and intervention initiatives.

There are several important limitations that should be taken into account when interpreting our findings. First, not all mothers in our sample were enrolled in Medicaid for the full period spanning all of pregnancy through 30 days after the birth. Exclusion of some portion of this period from our data, due to Medicaid nonenrollment, may downwardly bias our estimates. Second, our conceptualization of risk to prenatal development rests on the (dose response) assumption that greater chronicity and/or severity of exposure will result in greater risk to prenatal development. Although we empirically tested this assumption by estimating bivariate associations of our exposure indicators and combined likelihood and risk categories with an index composed of key measures of infant health at birth, future research is needed to establish the extent to which this assumption holds, that is, whether our "higher-risk" categories are more strongly associated with infant and child outcomes than our "lower-risk" categories, after taking into account other confounding factors. Third, NAS diagnoses are based on an index of symptoms that is completed by clinicians and may reflect the clinician's knowledge of a mother's behaviors and/or medical history, in addition to their observations of the infant. This may, at least in part, account for the high level of concordance of NAS diagnosis with OUD diagnosis and treatment, including MOUD, that we observe in our data. It is also important to recognize that NAS diagnoses may reflect exposure to substances other than opioids and that some NAS diagnoses made subsequent to the delivery hospitalization may reflect the effects of opioids administered to the infant during the hospitalization. Last, given that our data are drawn from Medicaid-covered live births in Wisconsin, we cannot be sure our results generalize to non–Medicaid-covered births in Wisconsin or to births in other states.

Despite these caveats, our results have implications for future research and for practice. This study demonstrates that administrative data can be used to provide a range of estimates of potential prenatal exposure to opioids based on the likelihood that exposure occurred and the potential risk to prenatal development implied by a given indicator. Whereas we demonstrate that the categories are associated, at the bivariate level, with an index of infant health at birth, future research examining the extent to which specific categories may be causally linked to maternal and child outcomes and at what orders of magnitude, is warranted. In addition, our approach to identifying categories of prenatal opioid exposure that incorporate both likelihood of exposure and potential risk to prenatal development may be useful for identifying mothers and children who could benefit from interventions to treat OUD and promote healthy child development, and for effectively targeting such interventions. Although our analyses leverage health care data drawn only from Medicaid administrative records, these same measures should be widely available in all-payor claims and detailed health records, regardless of payor type. Nonetheless, future research would be well served by testing their validity in non-Medicaid samples. Further, creating an integrated medical record that reaches across health care systems may lead to improved clinical care. For example, ensuring that prenatal care providers have access to medical records from health care received before pregnancy may facilitate earlier identification of potential opioid exposure and prompt changes in treatment approaches, including transitions to recommended MOUD and engagement in counseling. Pediatrician access to mothers' medical records may also help ensure early identification and optimal management of infants at risk of NAS or developmental challenges associated with prenatal opioid exposure. Future research identifying specific health and developmental risk factors associated with each of the categories we consider will also help inform practice in these areas.

MATERIALS AND METHODS

Our sample includes 259,723 observations representing all Medicaid-covered live births in Wisconsin from 2010 to 2019. Data are drawn from birth certificate, BadgerCare Plus (Wisconsin's combined Medicaid and State Children's Health Insurance Program), and CPS administrative records. See the Supplementary Materials for details on our data, measures, and methods. The study was approved by the Institutional Review Board at the University of Wisconsin-Madison (#2015-1583).

Supplementary Materials

This PDF file includes:

Materials and Methods
Tables S1 to S4
References

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