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Fentanyl related overdose in Indianapolis: Estimating trends using multilevel Bayesian models

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HIGHLIGHTS

- Dataset was every lethal overdose observed by Marion County Coroner from 2010 to 2017.
- We estimated demographic, spatial, and time trends in positive fentanyl tox screens.
- Rate of fentanyl-related OD rose exponentially from < 15% of ODs before 2014 to ~50%.
- Rates among blacks were lower than whites at beginning of study, but higher than whites by 2017.
- Bayesian models were used for these analyses with R script provided as a supplement.

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ABSTRACT

Introduction: The opioid epidemic has been largely attributed to changes in prescribing practices over the past 20 years. Although current overdose trends appear driven by the opioid fentanyl, heroin has remained the focus of overdose fatality assessments. We obtained full toxicology screens on lethal overdose cases in a major US city, allowing more accurate assessment of the time-course of fentanyl-related deaths.

Methods: We used coroner data from Marion County, Indiana comprising 1583 overdose deaths recorded between January 1, 2010 and April 30, 2017. Bayesian multilevel models were fitted to predict likelihood of lethal fentanyl-related overdose using information about the victim's age, race, sex, zip code, and date of death.

Results: Three hundred and seventy-seven (23.8%) overdose deaths contained fentanyl across the seven-year period. Rates rose exponentially over time, beginning well below 15% from 2010 through 2013 before rising to approximately 50% by 2017. At the beginning of the study period, rates of fentanyl overdose were lowest among Black persons but increased more rapidly, eventually surpassing Whites. Currently, White females are at particularly low risk of fentanyl overdose whereas Black females are at high risk. Rates were highest for younger and middle-aged groups. Over time, fentanyl was more likely detected without the presence of other opioids.

Conclusions: Fentanyl has increasingly been detected in fatal overdose deaths in Marion County. Policy and program responses must focus on education for those at highest risk of fentanyl exposure and death. These responses should also be tailored to meet the unique needs of high-risk demographics.

1. Introduction

The United States is experiencing a massive increase in the rate of fatal opioid[1] overdose, with deaths having quadrupled over the past 16 years (Rudd, 2016). This trend is largely attributed to the sharp increase in opioid prescribing that occurred over the past two decades (Alpert, Powell, & Pacula, 2017; Banta-Green, Beletsky, Schoeppe, Coffin, & Kuszler, 2013; CDC, 2011; Dart et al., 2015), and much of the public health response to this crisis has been aimed at curbing problematic prescribing (Wickramatilake et al., 2017). However, to a large extent, the recent rise in overdose deaths is the result of illicit opioids (Rudd, 2016; Rudd et al., 2014), and research suggests that this

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[1] In this paper we use "opioid" to refer to the entire family of natural, synthetic, and semi-synthetic opiates.

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increase has been exacerbated by the dwindling availability of their prescriptions counterparts (Cerdá, Santaella, Marshall, Kim, & Martins, 2015; Cicero, Ellis, Surratt, & Kurtz, 2014; Mars, Bourgois, Karandinos, Montero, & Ciccarone, 2014; Ray, Quinet, Dickinson, Watson, & Ballew, 2017).

Previous research demonstrates heroin overdose death rates have more than tripled from 2010 to 2014 (Rudd, 2016), but what is often less addressed in the literature are deaths associated with fentanyl. The additional arrival of fentanyl—a synthetic opioid 50 times more potent than heroin (National Center for Injury Prevention and Control, 2016)—within the U.S. illicit drug market has further increased the risk of fatal opioid overdose (Frank & Pollack, 2017; Ray et al., 2017). Despite fentanyl's prevalence in the illicit drug market, heroin has remained the focus of overdose fatality assessments. This is because the International Classification of Diseases (ICD), the standard diagnostic tool used by the Centers for Disease Control and Prevention (CDC) to examine mortality trends, codes fentanyl and many other loosely related drugs together under the same umbrella category "synthetic opioids" (T40.4), with no unique diagnostic code for fentanyl specifically (Wysowski, 2007; Fernandez, Hackman, McKeown, Anderson, & Hume, 2006; Ossiander, 2014). For example, from 2014 to 2015 heroin death rates increased by 20.6%, yet deaths from synthetic opioids increased by 72.2%. The CDC notes this increase is most likely attributable to illicitly manufactured fentanyl; however, ICD codes are not able to assess trends by a specific substance. This is problematic, as policy and program responses to the opioid epidemic require accurate information regarding the drugs driving overdose trends to maximize their effectiveness.

In an effort to better examine trends in fentanyl overdose some researchers have looked directly at the medical examiner and coroner data (see Somerville et al., 2017; Warner, Trinidad, Bastian, Miniño, & Hedegaard, 2016), and others have used computer software to code the actual text written by the certifier (Ossiander, 2014); however, analyzing the text of the certifier can be challenging when there are multiple opioid substances detected. Another method for examining the presence of fentanyl is to look at the results from the toxicology analysis. In using toxicology data, researchers are not assessing fentanyl as a "cause of death" but rather as a substance detected as part of a drug overdose investigation. The present study uses this latter method by examining data from toxicology reports to assess trends in the presence of fentanyl in drug overdoses in Marion County, Indiana, from January 1, 2010, through April 30, 2017. In doing so, we document the dramatic increases in fentanyl-related deaths, examine sociodemographic characteristics among these fatalities, and also explore polydrug combinations. We use Bayesian models to examine trends in rates of a positive fentanyl toxicology screen among people who lethally overdosed and provide estimates of the course of the epidemic.

2. Materials and methods

The data used in this study come from the Marion County Coroner's Office. This Office serves Marion County, which is the largest county in Indiana (2015 population estimated at 939,020) and the location of the state capitol of Indianapolis. The Marion County Coroner's Office has jurisdiction over all drug overdose fatalities within the county, and, as part of an ongoing collaboration with Indiana University researchers, maintains a database with information from death certificates and toxicology reports on all drug overdose fatalities. The data used in this study consist of every lethal overdose reported by the coroner's office from January 1, 2010, through April 30, 2017, and consist of 1698 cases. Of these, 107 cases were dropped because the overdose occurred outside of Marion County, four cases were dropped because the place of overdose was unknown, and four cases were dropped because the person was a child under 5 years of age (the next youngest death was 16 years old), for a final sample of 1583 individuals. We captured sociodemographic variables such as age, race/ethnicity, and gender from the death certificates and the presence of opioids from toxicology reports. For the toxicology report there is a detection threshold established by the testing agency and when a substance exceeds that threshold it is included in the toxicology report and coded into the database. The opioids we were able to consistently code for during this time period included fentanyl (with analogues such as norfentanyl, acetylfentanyl), 6-monoacetylmorphine (heroin), morphine, codeine, oxycodone, hydrocodone, oxymorphone, and hydromorphone. It should be noted that one of the limitations of using toxicology data is the inability to accurately determine morphine and codeine. Specifically, because some illicit manufactured opioids, such as heroin, undergo a rapid transformation into natural opioids of morphine and codeine (Avella, Katz, & Lehrer, 2007), we follow previous work looking at polydrug interactions (Harruff, Couper, & Banta-Green, 2015) and did not include morphine or codeine though did include these substances in our overall detection of opioids.

2.1. Analytic approach

Our analysis begins by looking at raw numbers of drug overdoses over time and the presence of fentanyl among these cases; however, our primary goal is to build a statistical model of changes over time in the probability of a positive fentanyl toxicology screen among people who lethally overdose. This allows for a more complete demographic picture of the epidemic and estimates of its course over time. All data preparation and analysis were performed using R and the Stan probabilistic programming software, which allowed us to fit fully Bayesian models and specify priors (R package rethinking v 1.59). Lethal overdoses are modeled using the following information: location of overdose by zip code, exact date of death, age at death, and race/gender categories. We guard against overfitting in three ways: (1) by using weakly informative priors on all parameters (e.g., Normal [0,5] on the slope parameter for z-scored date of death, suggesting mild skepticism that any two-year interval would see rates of positive Fentanyl toxicology screens move from $< 0.001\%$ to $> 99.99\%$ of all lethal overdoses); (2) by using graphical checks and WAIC estimates to guide the decision of whether to include a given covariate in the final model (Watanabe, 2010); and (3) by fitting hierarchical models for relevant parameters to partially pool estimates toward the population mean where appropriate, such as for subgroups with small numbers of observations.

The relationship between date of death and rate of positive fentanyl toxicology screen was modeled using linear, quadratic and cubic parameters. Higher-order polynomials did not improve WAIC scores and so were not included in the final model. Age at death was entered into the model with linear and quadratic parameters (higher-order polynomials did not improve fit). Ethnicity (Black, White, or Other) and sex (Male, Female) combinations were introduced as varying intercepts ($J = 1,2, \ldots, 6$) to allow partial pooling to constrain estimates for groups with small numbers (e.g., only 5 people were categorized as Other Female). Zip code was introduced into the model as a varying intercept as well, which improved fit and suggested that there may be geographic "hot" and "cool" spots that cannot be better accounted for by measured demographic patterns in lethal overdoses.

To allow for the possibility that different groups have experienced different trajectories in rates of lethal fentanyl-related overdose over time, we varied the slope parameters for date of death by each gender/ethnicity combination, improving model fit considerably as estimated by WAIC and graphical checks. We also included an interaction term between age and date of death, as risk of fentanyl-related overdose appears to have increased at slightly faster rates for younger than for older people. Varying time slopes by zip code yielded worse WAIC scores and were therefore not included in the final model, suggesting little evidence that different zip codes have experienced different trajectories in rates of fentanyl-related overdose over time. Code for data preparation, model fitting, and figures are included as a supplement.

Our use of multilevel modeling also allows for the inclusion of

covariates at the zip code-level. Therefore, we included the following geographic covariates with data derived from the U.S. Census: median household income for each zip code, percent in poverty, percent urban, and percent of residents holding a bachelors degree or higher. However, none of these variables showed substantive predictive power (for all coefficient estimates, 75% credible intervals included zero). Therefore, we did not include these predictors in our final models.

3. Results

We analyzed 1583 overdoses occurring in Marion county during the study period (January 1, 2010 through April 30, 2017), with ages at death ranging from 16 years to 77 years old. Of these, 377 (23.8%) contained fentanyl. The average age of the total drug overdose population was 40.2 years; 64.1% were male; and 81.1% were coded as White, 17.3% Black, 1% Hispanic/Latino, and 1.3% were unknown or other (given the small group size, we analyzed ethnic groups as White, Black, or Other). Compared with the overall sample of lethal drug overdoses, the sociodemographic characteristics of those who died while testing positive for fentanyl suggest they were on average more likely to be younger (37.6 years) and more likely to be male (66.8%) and Black (20.4%).

Fig. 1a illustrates the number of drug overdose deaths during the study period (with 2017 representing January 1, 2017 through April 30, 2017) with lines representing the percent of deaths where any opioid is present and the percent of deaths where fentanyl is present. The number of drug related overdose deaths has increased in Marion County during the study period, from 121 in 2010 to 325 in 2016. The percent of overdose deaths containing any of the opioids coded for in this study (i.e. fentanyl, 6-monoacetylmorphine, morphine, codeine, oxycodone, hydrocodone, oxymorphone, and hydromorphone) also increased from 64.5% in 2010 to 81.2% in 2016. Similarly, the detection of fentanyl has shown dramatic increases. In 2014 the presence of fentanyl in drug overdose deaths increased nearly five-fold from 7% in 2013 to 29% in 2014. In 2016 fentanyl was detected in 44.9% of all drug overdose and so far in 2017 has been detected in 44.7% of cases, outstripping heroin (37.4%).

We also looked at polydrug interactions with fentanyl and other opioids for which data were available (heroin, oxycodone, hydrocodone, oxymorphone, and hydromorphone). In 2010 and 2011 there were no cases of fentanyl mixed with heroin; however, in 2010 oxycodone, hydromorphone, and oxymorphone occurred in 40% of fentanyl detections and hydrocodone in 27% of cases. By 2013 heroin was detected in 29% of fentanyl cases and peaked in 2015 with detections in

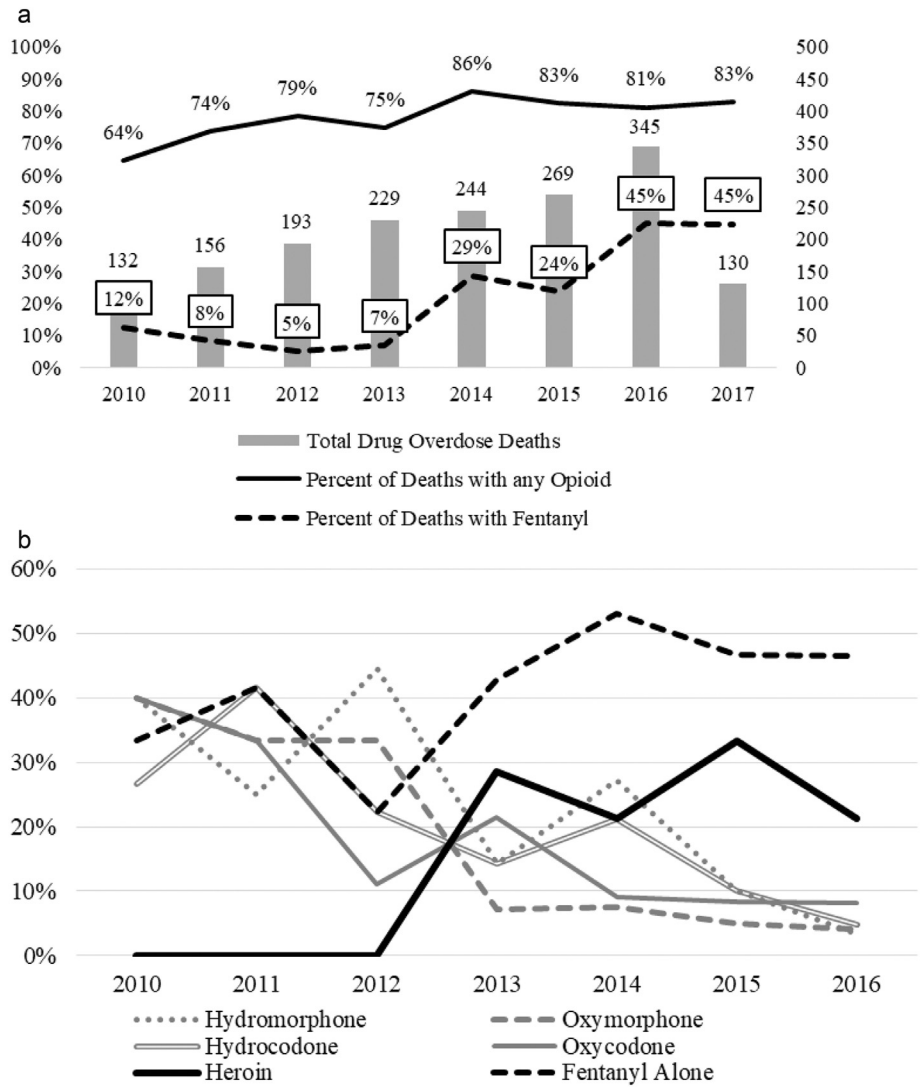

Fig. 1. a) Detection of opioids and fentanyl among drug overdose deaths. Note that the bars and lines are on different scales, with bars giving all-cause overdose counts and lines giving the proportion of all-cause overdose deaths involving any opioid (solid) versus deaths involving fentanyl (dotted). b) Proportion of fentanyl-related deaths that involve other opioids.

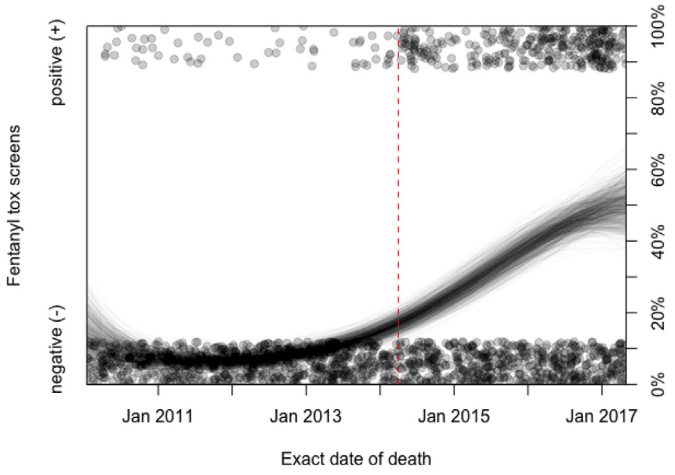

Fig. 2. City-wide estimates for lethal overdoses over time. Observed data are plotted as vertically jittered points. Model-based estimates are shown as one thousand regression lines sampled from the posterior distribution to display uncertainty in the regression relationship between time and lethal overdose. The vertical dotted line marks April 2014.

32% of fentanyl cases. As shown in Fig. 1b, fentanyl is increasingly being detected with heroin while decreasingly being detected with prescription opioids. However, it is also important to note that fentanyl is often detected alone; that is, without other opioids. As illustrated in Fig. 1b, the proportion has fluctuated during the study period, yet when we consider that in 2010 there were only 15 fentanyl detections, with 33% (n = 5) detected alone, and in 2016 there were 146 detections with 47% (n = 68) detected alone, it is clear that much of the recent spike in fentanyl-related deaths are associated with fentanyl alone.

3.1. Model estimates

Next we turn to our Bayesian model of changes over time in the probability of a positive fentanyl toxicology screen among people who lethally overdose. Fig. 2 shows the trajectory over time for the city as a whole, with one thousand regression lines sampled from the posterior distribution to display uncertainty in the regression relationship between time and lethal fentanyl-related overdose rates. Fentanyl-related deaths were very rare (mostly < 10%) until mid-2014 when the county began to see exponential increases. In 2017, for the first time, rates of fentanyl-related overdose are likely to break 50%, far higher than other common drugs such as heroin.

Fig. 3 shows Bayesian estimates across the lifespan, broken down by race/ethnicity, sex, and time, with dark lines indicating risk of fentanyl-related overdose for these demographic categories at different ages. Grey shaded regions give 95% credible intervals for these estimates, widened via model-based simulation to account for variation due to geography.

Rates of lethal fentanyl-related overdose appear to be highest for young and middle-aged people, with a steep drop-off around age 50–60. Although the model allowed for the possibility that time trajectories would differ by race, sex, and age (e.g., model estimates show rates for younger people increasing slightly more quickly than rates for older people), our estimates suggest that all groups experienced exponential increases in fentanyl-related overdose over time with particularly large spikes in 2014–2015.

There were important differences in trajectories by demographic groups. Relative to Whites, Blacks began the decade with very low rates of fentanyl-related overdose; however, risk of fentanyl-related overdose increased more rapidly among Blacks in the past 2–3 years and is now higher than the risk for Whites. For example, in January 2011, Blacks had an estimated 3% rate of fentanyl-related overdose as compared to 9% rates for Whites. By 2017 that pattern had reversed dramatically, with Blacks at 61% risk versus 46% for Whites.

Our model suggests White Females may be at particularly low risk and Black Females at particularly high risk. Sampling from the posterior allows us to assign a probability to these comparisons between demographic groups and gives us a sense of the uncertainty in our estimates. As of January 2017, the average White female had an estimated 40% rate of fentanyl-related overdose—there was a 98% probability that their true rates were lower than Black Females, a 99% probability that they were lower than Black Males, and a 94% probability that they were lower than White Males. The average Black female, on the contrary, had estimated rates of 62%, putting them at higher risk than White Females (98% probability) and White Males (89% probability). Although rates for Black Females were also higher than the 59% rates we estimate for Black Males in the same month, uncertainty in the credible intervals for these subgroups is relatively large and the probability that true rates for Black Females were higher than rates for Black Males is only 60%.

Zip code of lethal overdose also provided some information about risk of fentanyl-related overdose unaccounted for by the other information we had available. Fig. 4 shows a map of the relative risk of fentanyl-related overdose by zip code after accounting for time and demographic variables. As shown, risk varies substantially by geography, with some zip codes yielding about 8% greater risk of fentanyl-related overdose assuming all other factors are held constant (e.g., race, age). This suggests the possibility of geographic “hot” and “cool” spots with respect to fentanyl. This could have purely spatial causes (e.g., a particularly potent batch of fentanyl is distributed by someone dealing within a specific neighborhood), or could be due to latent variables we did not measure such as neighborhood disorder (Epstein et al., 2014) or relative neighborhood disadvantage experienced by overdose victims (see Mennis et al., 2016), or all of the above. We further explored this using available data from the U.S. Census and tested for effects of median household income, percent of the zip code residents in poverty, percent holding a bachelors degree or higher, and percent urban. However, none of these measures were significant predictors.

4. Discussion

The present study used toxicology and death certificate data from the Marion County (Indianapolis) Coroner's Office to examine changes in fentanyl-related overdoses from January 1, 2010, through April 2017. Our analysis assessed changes in the detection of fentanyl alongside other opioids in overdose deaths and also provided us with sociodemographic and geographic measures that we used in multilevel Bayesian models to estimate past and present trends in fentanyl-related overdose. Our findings suggest drug overdoses have continued to increase since 2010 and opioids are consistently detected among the majority of these deaths. However, fentanyl has increasingly been detected in fatal drug overdose deaths since 2014 and now comprises nearly half of all lethal overdose deaths. We also explored polydrug interactions in an effort to better understand what fentanyl is being mixed with. This analysis illustrates that, during the study period, fentanyl is decreasingly being detected alongside prescription opioids and is increasingly detected with heroin, but more often fentanyl-related deaths are from fentanyl alone. Finally, our model suggests different demographic groups have experienced distinctive trajectories in fentanyl-related overdoses. Specifically, risk of fentanyl-related overdose has risen more rapidly for Blacks than for Whites, with Blacks beginning the decade with the lowest rates of fentanyl-related overdose but ending the study period with higher rates than Whites. White females may now be at particularly low risk and Black females at particularly high risk. In the media the opioid epidemic has largely been framed as a White problem. Our findings suggest that, in Indianapolis at least, this may have been partially true in the past but is no longer the case.

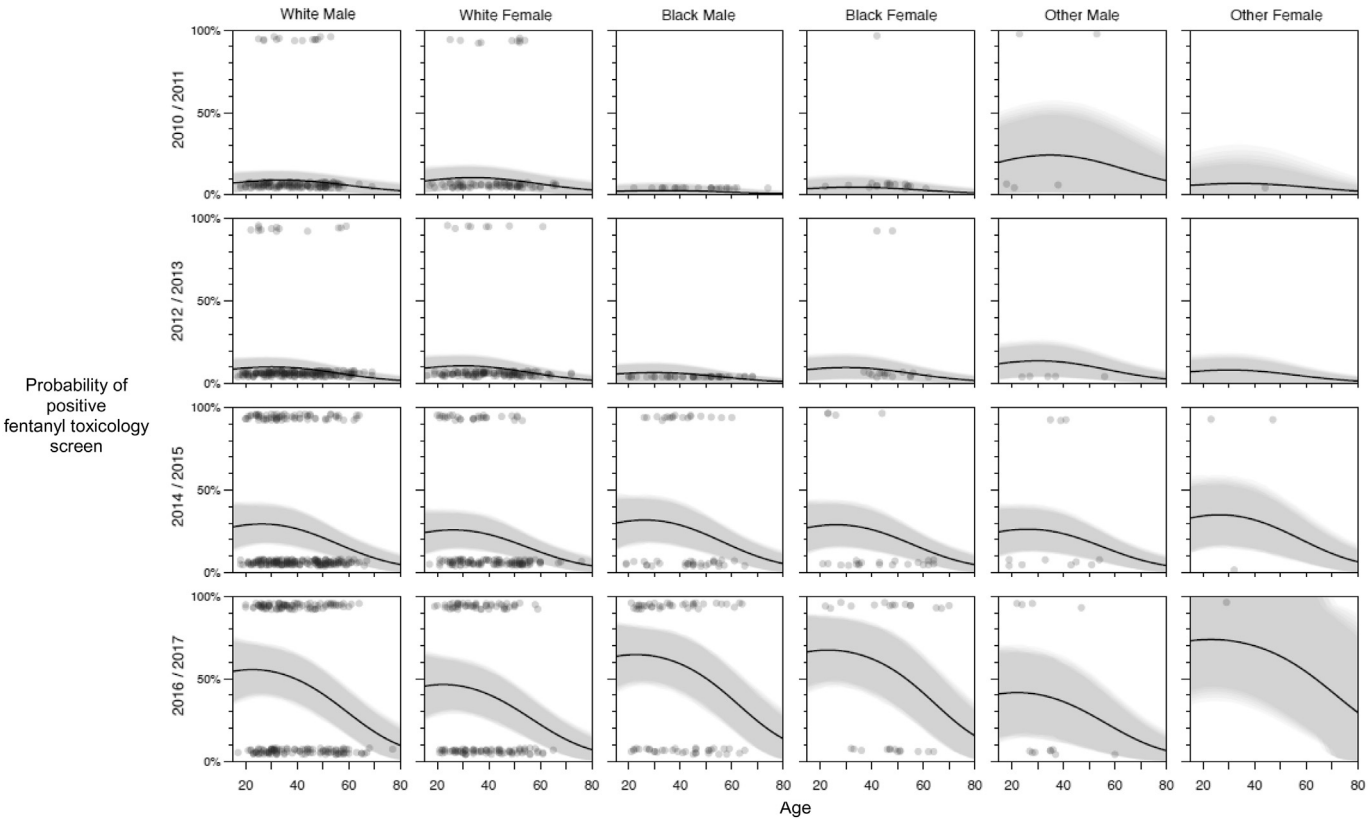

Fig. 3. Rates of positive fentanyl toxicology screens at overdose by age at death, race, sex, and time. Observed data are plotted as vertically jittered points with lines giving model-based estimates (solid) and 95% credible intervals (shaded) halfway through each plotted 2-year interval. Residual error due to geography was added to model estimates by simulating zip code-level variation from model parameters. In 2014, all demographic groups experienced dramatic increases in rates of lethal fentanyl-related overdose. Prior to 2014, black people were at particularly low risk of lethal fentanyl-related overdose. However, they experienced relatively fast rate increases and by 2017 their risk had surpassed that of white people.

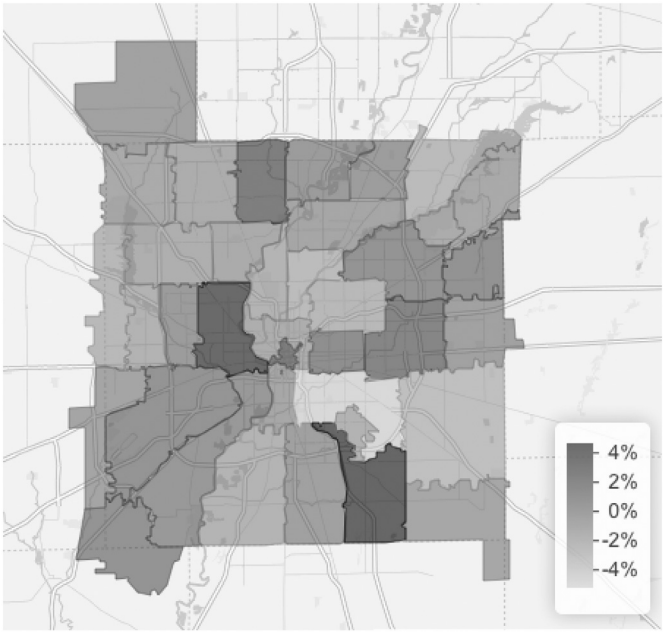

Fig. 4. Risk of lethal Fentanyl-related overdose attributable to zip code of overdose, after accounting for date of death, age at death, race, and sex.

By using toxicology data instead of ICD codes we were better able to detect changes in specific substances and more accurately determine when fentanyl entered the illicit drug market in Marion County, providing convergent evidence with national studies that show illicit opioids, particularly fentanyl, are driving the increases in fatal drug overdose (Rudd, 2016; Rudd et al., 2014). Our findings also add substantially to understandings of racial differences in the opioid epidemic. Prior research has documented that prescription rates of opioids are lower among Blacks compared to Whites (Meghani, Byun, & Gallagher, 2012). It is possible that Black people were more likely than Whites to encounter fentanyl as the drug entered the illicit market in the middle of the decade. Unlike earlier authors who theorized that differences in mortality were the result of differential use behaviors by race (see Chen et al., 2005; McCabe, Teter, Boyd, Knight, & Wechsler, 2005 and Meghani et al., 2012), recent mixed-methods studies with active opioid users (Carroll, Marshall, Rich, & Green, 2017; Macmadu, Carroll, Hadland, Green, & Marshall, 2017) suggest exposure to fentanyl is largely driven by product supply. It is also important to note that these studies and others (see Amlani et al., 2015; Hempstead & Yildirim, 2014) show opioid users prefer to avoid fentanyl for fear of unpredicted effects. Thus, our findings regarding race might suggest changes in overall product supplies (e.g., fentanyl rather than heroin), increased availability, or potentially that there are other socioeconomic factors contributing to fatal rather non-fatal overdose among disadvantaged populations.

It is worth highlighting some strengths and weaknesses of the current paper. The use of multilevel Bayesian models has substantial advantages over classical methods. Uncertainty is clearly displayed in our estimates, with wider credible intervals for groups and time points for which we have less information, such as very young ages and very late time points. Partial pooling is also clearly visible, with estimates for groups with few observations pulled toward the population mean. This represents a mathematically rigorous compromise between overfitting to small groups and under-fitting by ignoring observed variation. For

example, varying intercepts and slopes for all race/sex subgroups allowed estimates for the Other Female category to follow a distinct but not wild trajectory, appropriate given the small number of observations in this group (n = 5, see Fig. 3). Finally, estimating population distributions for groups allows us to simulate unobserved data. For example, risk of fentanyl-related overdose in three zip codes with no observations were simulated for Fig. 4 using the model's estimated variation between zip codes. Point estimates for these zip codes will appear “average” but the simulation allows us to add a measure of uncertainty to these point estimates (see Gelman & Hill, 2007).

There were significant limitations to this study. Data were only available for a single Midwestern geographic area and may not be generalizable to other urban or rural areas in the United States. Similarly, this study was constrained by our reliance on multiple sources of administrative data and we were limited in the years for which electronic death certificates were available as well as the substances that we could reliably code for over this period. For example, we were unable to reliably code for methadone or benzodiazepines for this time period. Moreover, we are not able to further disentangle the contributing factors to these deaths to better assess other elements that might explain our findings. Finally, our use of zip code as the level of geographic analysis has drawbacks, as zip codes are not clearly theoretically meaningful units. The results of the current study indicate that rates of fentanyl-related overdose do depend on location in Indianapolis; however, even after exploring household income, percent in poverty, percent urban, and percent holding a bachelors degree or higher, we were still unable to answer the question of why which limits the generalizability of the study and calls for further research.

Given our findings and those from extant research, the policy implications of increased fentanyl-related deaths suggest a need to better educate potential fentanyl users so they understand how to protect themselves and people who they use with from exposure and overdose. This education should focus on the potential for fatal overdose from fentanyl when using illicit opioids, the use of test kits to enable users to detect fentanyl, and the benefits of both agonist and antagonist medication assisted treatment. Finally, our demographic findings indicate the need for culturally appropriate education efforts that take into consideration the unique experiences those at groups whose risk exposure is rapidly rising (e.g., Blacks and Black females).

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Contributors

PP, BR, DW designed the study. PP conducted the Bayesian analysis and wrote the first draft of the manuscript and BR conducted the descriptive analysis. PH collected the data and MG contributed to writing and edits. All authors contributed to writing on additional drafts and have approved the final manuscript.

Conflict of interest

None of the authors have competing interests to declare.

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