

Unintentional Fentanyl Overdoses in New Hampshire: An NDEWS HotSpot Analysis

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Executive Summary

Introduction

Through HotSpot studies, National Drug Early Warning System (NDEWS) Coordinating Center staff can launch rapid, limited onsite investigations of an important drug outbreak in a specific locality. Each HotSpot study includes a 3–5-day site visit by NDEWS scientists to gather additional data and descriptive information that can be used to help interpret the information collected and analyzed by NDEWS staff prior to the site visit. NDEWS also convenes a Planning Committee composed of NDEWS staff and local experts who help to plan the site visit and arrange meetings with persons who can provide the most useful information. The study team is multidisciplinary and may be composed of scientists, public health practitioners, and law enforcement personnel, as the situation requires.

NDEWS identified New Hampshire as a HotSpot location because of the rapid increase in both drug overdose deaths and opioid-related emergency department (ED) visits. Under commission from NDEWS, the University of Maine Rural Drug and Alcohol Research Program completed a rapid report on mortality patterns in mid-2016. Later that same year, we embarked on the current, expanded study. In the preliminary 2016 report, we showed that drug overdose deaths in New Hampshire increased by 1,629% between 2010 and 2015, largely as a result of fentanyl. The county most impacted by these overdose deaths is Hillsborough County in southern New Hampshire, home to 30.6% of the state's population, where 43.6% of the fentanyl deaths occurred.

The Office of the Chief Medical Examiner (OCME) is responsible for determining the cause and manner of death for all drug overdoses statewide. The Chief Medical Examiner (CME) and Deputy Chief Medical Examiners (DCME) perform or oversee all death investigations for the OCME as part of a centralized system of state medical examiners. Assistant Deputy Medical Examiners (ADMEs) are trained death investigators for the OCME system. They respond to death scenes, collect information about the circumstances of death, perform an external examination of the deceased, and document their findings. The system has struggled to address the dramatic increase in case load without sacrificing the quality of toxicological analysis and overall death investigation.

In this analysis, we expanded our preliminary 2016 study to focus on deaths caused by fentanyl and fentanyl analogs. We used medical examiner files, including the death investigation report, the medical examiner report and death certificate information, the autopsy report, and the toxicology findings. By combining these data sources, this report looks beyond the cause and manner of death to the details of these death events, at the decedents' interrelated medical history and social circumstances, as well as at their toxicology and autopsy findings.

Methods

In this study, 541 individuals were identified who died of fentanyl-induced overdose in New Hampshire from January 1, 2015 to September 30, 2016. This dataset was used for the geographic information systems (GIS) location analysis. Cases were included in the final analytical sample if fentanyl, a fentanyl metabolite, or a fentanyl analog were mentioned as a cause of death, but only if the cases were complete (included toxicology and complete medical examiner and death investigator report) and the manner of death was accidental. A sample comprising 505 decedents resulted. These are “occurrent” rather than “resident” deaths, i.e., just those who died in the state of New Hampshire, even if they were legal residents elsewhere. Of the 505 cases, 189 had an autopsy. We sent 136 urine samples originally obtained at autopsy to NDEWS Coordinating Center staff who asked the toxicology lab of the Armed Forces Medical Examiner System (AFMES) to conduct comprehensive drug screening tests.

We also worked with NDEWS collaborator Dr. Kathleen Stewart from the University of Maryland Center for Geospatial Information Science (CGIS) to analyze GIS-based maps exploring the spatial relationships between the location of residence, injury, death, and other sociodemographic characteristics.

Results

Spatial Relationships (n = 541)

New Hampshire is a small, largely rural state with a population of approximately 1.3 million. A substantial concentration of this population is clustered in the southeastern urban hub of Manchester/Nashua in Hillsborough County. Fentanyl deaths are also concentrated in Hillsborough County, which includes 30.6% of the state population. This county was the residence of 39.6% of the decedents who died in New Hampshire from fentanyl, a fentanyl metabolite, or a fentanyl analog in 2015–2016 and the location of where 43.6% of the deaths in the state occurred. Nearly all (96%) of the decedents were New Hampshire residents. Overall, deaths were more likely to occur in an urban rather than in a rural, small town or micropolitan township, and they were significantly more likely to occur in townships with greater population density. Furthermore, 70.3% of fatal overdoses occurred within 5 miles of an interstate highway, and the fatal drug use¹ occurred at the decedent’s residence in 68.6% of deaths.² Relationships between the distribution of decedents’ residences and sociodemographic factors of employment, median income, and percent with college education were not statistically significant.

¹ The “location of fatal drug use” will also be referred to in this report as the “location of injury.” The latter phrase is used on the death certificate. In overdose cases, it is taken to mean where the fatal drug use occurred.

² By using the broader death certificate dataset of 541, which was used for GIS mapping, the percentage of decedents for whom the location of fatal drug use was the same as the residence location was 68.6%. When the smaller analytical dataset of 505 was used, that percentage was 69.9%.

Decedent Characteristics (n = 505)

The population of decedents is younger and consists of proportionally more males than the census population of the state. The mean age of decedents is 36.2, with males slightly younger than females, and outnumbering them 2 to 1. Mirroring the census population, 95.0% of the study population is White. Compared with the state census population, fewer in this population had a high school diploma or general equivalency diploma (GED; 60.8% vs. 92.3%), and fewer were veterans (3.8% vs. 10.3%). Among the 490 decedents for whom household composition was known, 20.0% lived alone and 4.5% were homeless.

According to death investigator reports, the study population includes a majority (63.4%) with a history of opioid abuse, 9.5% with a history of chronic pain, 12.7% with a history of previous overdose, and 14.9% with an opioid prescription during the previous 12 months. Of those with an opioid abuse history, 89.7% were reported as injection drug users, 81.6% had been using heroin, 7.2% had used a combination of heroin and pills, and only 4.7% had used pills alone.

Female decedents were much more likely to use medical services. They are significantly more likely to have had a prescription for an opioid in the previous 12 months (25.2% vs. 11.9% for males). They are also significantly more likely to have an EMS response (71.2% vs. 59.4%) and significantly more likely to have naloxone present in their toxicology findings (25.2% vs. 15.2%) compared with males.

Decedents 40 years old or older are less likely to be male than those younger than 40 (74.1% vs. 80.1%). They are significantly more likely than those younger than 40 to be living alone (28.7% vs. 14.5%) and significantly more likely to live in a rural area (32.8% vs. 22.7%). Older decedents are significantly less likely to have a history of opioid abuse (50.6% vs. 70.1%) but significantly more likely to have a history of chronic pain (70.8% vs. 29.2%) and significantly more likely to have pharmaceutical opioids present in their toxicology findings (32.2% vs. 17.2%). Older decedents are significantly less likely to have received an EMS response (55.7% versus 65.3%).

Decedents with a known opioid prescription during the previous 12 months numbered 75, 14.9% of the primary study population. Of these, 40.0% had pharmaceutical opioids in their toxicology, which is significantly higher than those with no opioid prescription history, 19.3%. Approximately one third (32.0%) of those with an opioid prescription also had a history of chronic pain, which is significantly more than those lacking an opioid prescription, 5.6%. Having a “rapid” overdose was significantly less common among decedents with a recent opioid prescription, 6.7% compared with 19.8%, but they were no more likely to have naloxone in their toxicology findings.

There are 48 decedents with a reported history of chronic pain. This small subpopulation was significantly different from others only in terms of whether they also had an opioid prescribed within the previous 12 months (50.0% vs. 11.2%) and whether they had a pharmaceutical opioid present in their toxicology findings (41.7% vs. 20.4%).

Most decedents, 63.4%, had a history of opioid abuse. Within this subpopulation, only 8.8% also had a history of chronic pain, 15.9% had a recent prescription for an opioid, and 22.8% had pharmaceutical opioids present in their toxicology. Those with an opioid abuse history were significantly less likely to be alone when they died (53.8% vs. 46.3%), and significantly less likely to have an EMS response (65.6 vs. 34.4%), but they were no more likely to have naloxone present in their toxicology (16.9%). They were, however, significantly more likely to have a history of previous overdose (17.5% vs. 4.3%) and significantly more likely to have been recently released (past two weeks) from jail or substance abuse treatment (6.6% vs. 1.6%). There was no significant difference between those with an opioid abuse history and others in the study population in terms of the percent unemployed, disabled, living alone, or homeless.

Death Event Characteristics (n = 505)

Most (62.6%) victims were reported to be alone when they took the fatal overdose, slightly fewer when they died (57.6%). In 13.9% of cases, there was a witness who was aware of the ingestion. The decedent was found decomposed in 6.3% of cases.

Most victims ingested the drug(s) at their own residence (69.9%). Many others were at another person's residence when they took the drug(s) (17.6%) and died there (13.3%). Seventeen percent of victims died in the emergency department or hospital, regardless of where they ingested the drugs.

911 was called in 92.5% of cases, and EMS responded in 62.0%. In 11.7% of cases, the ADME reported that naloxone was administered. EMS administered 79.7% of the ADME-reported naloxone administrations. A friend, relative, or girlfriend/boyfriend administered it in 0.8% of cases. Within the toxicology data, there were 17.4% cases positive for naloxone, 27 more than reported by the ADME, which means they were probably administered in the emergency department.

Autopsies are routinely done for cases where the likely cause of death is unclear or for potential overdoses where other causes of death cannot be ruled out. Autopsies are also done in cases that may result in a prosecution, which is a decision made by the Attorney General's Overdose Task Force. Within the autopsy study population ($n = 189$), 37.4% of decedents received an autopsy. Surprisingly, autopsies were significantly more likely to be done on cases with female decedents and on decedents who are 40 years old and older. Decedents who received an autopsy were significantly less likely to have a history of opioid abuse.

Toxicology Findings

Polydrug complexity is an important feature of toxicology findings for this population. Within the medical examiner's toxicology findings (most are blood specimens), there are 114 drugs and metabolites identified. Individual toxicology tests ranged widely from just one substance reported (9.7%) to 19 substances in one decedent. Fentanyl was found in 98.4% and fentanyl

analogs in 11.7% of cases; these cases overlap. The mean number of parent³ drugs was 6.23. Key co-intoxicant and potentially synergistic drugs present include heroin/morphine (20.6%), non-fentanyl opioids (34.5%), benzodiazepines (27.5%), cocaine (31.1%), and alcohol (32.9%).

Postmortem levels of fentanyl confirmed in our sample range widely from 0.75 to 113.00 ng/mL, with a mean of 9.96. We compared the distributions of fentanyl levels for cases where fentanyl was the only drug found with cases with key co-intoxicants (opioids, benzodiazepines, or alcohol); the distributions were not statistically different. The distribution of fentanyl levels among the subgroup of decedents who reportedly had a “rapid” overdose was not statistically different from other decedents.

We collaborated with NDEWS to submit 136 urine specimens from the autopsy subpopulation to the Armed Forces Medical Examiner System (AFMES) to screen quickly for a wide range of drugs. Their analysis also reflected polydrug complexity, with an average of 2.88 drug categories present per specimen. Among all urine tests, 98% tested positive for any form of fentanyl, 52% for non-fentanyl opioids, 28% for benzodiazepines, and 37% for cocaine.

Discussion and Conclusions

Compared with the New Hampshire census population, the fentanyl overdose study population proportionally over-represents males approximately 2:1 and over-represents males and females in their 20s and 30s as well as, to a slightly lesser extent, those in their 40s and early 50s. Compared with the population of living fentanyl users, it is likely that the study population of those who died contains older, more physically and/or more medically vulnerable individuals. Thus, our findings should not be generalized to this population without elucidating the potential differences.

The GIS analytical support provided by NDEWS helped to elucidate spatial distribution relationships. Although fentanyl-associated mortality has reached most communities in the state, it is disproportionately located in urban centers in the southeast quadrant of the state, especially Hillsborough County. We ruled out statistically significant relationships between decedent residence location and township-level socioeconomic factors of employment, income, and educational level. The concentration of deaths is, however, related to population density, urban status of the area, and proximity to major highways.

Despite the ubiquitous presence of multiple drugs in these decedents, the effects of fentanyl were evidently so strong that there were no statistical differences in the fentanyl level (mean and standard deviation) with or without the presence of these co-intoxicants. The range of fentanyl levels was wide, from 0.75 to 113.00 ng/mL, with an average of 9.96 ng/mL.

³ “Parent” drugs refer to the original drug taken by the decedent before the body metabolizes it and changes its chemistry slightly. The term for drugs that have been metabolized is “metabolite.”

Nevertheless, the mean and range of fentanyl levels when fentanyl was the only drug found in toxicology were statistically the same as the mean and range for the cases where fentanyl was only one of several synergistic co-intoxicants. This suggests that fentanyl presence alone seems to be sufficient to cause death.

Most decedents in the study population received some type of medical intervention: EMS response, naloxone administration, emergency room visit, or hospital admission. Certain subpopulations were, however, significantly less likely to receive any of these interventions: decedents 40 years or older; decedents we categorized as “opioid-naïve” (those who lacked any history of opioid abuse, recent opioid prescription, or previous overdose); and decedents residing in rural or micropolitan townships. Age plays an important role in these patterns because older decedents are significantly more likely to be living alone, to reside in a rural township, or to be categorized as “opioid naïve.”

In conclusion, the findings of our research shed new light on the population of decedents who died in 2015 and 2016 as a result of unintentional fentanyl poisoning. They focus attention on a mixture of rural and urban decedents from a primarily White population who died in New Hampshire. Victims who were older, lived in more rural areas, and lacked an opioid-related history had significantly less access to care. Although most decedents were found to use multiple drugs, fentanyl levels ranged broadly among them, with no significant relationship to the presence of other co-intoxicants, or to decedents’ opioid-related history.

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Introduction

Through HotSpot studies, National Drug Early Warning System (NDEWS) Coordinating Center staff can launch rapid, limited onsite investigations of an important drug outbreak in a specific locality. Each HotSpot study includes a 3–5-day site visit by NDEWS scientists to gather additional data and descriptive information that can be used to help interpret the information collected and analyzed by NDEWS staff prior to the site visit. An integral component of the HotSpot approach is that the NDEWS convenes a Planning Committee composed of NDEWS staff and local experts who help to plan the site visit and arrange meetings with persons who can provide the most useful information. The study team is multidisciplinary and may be composed of scientists, public health practitioners, and law enforcement personnel, as the situation requires.

NDEWS identified New Hampshire as a HotSpot location because of the rapid increase in both drug overdose deaths and opioid-related emergency department (ED) visits. Under commission from NDEWS, we completed a rapid report on mortality patterns in mid-2016. Later that same year, we embarked on the current, expanded study. In the preliminary 2016 report (Sorg and Wren, 2016), we showed that drug overdose deaths in New Hampshire nearly tripled from 163 in 2012 to 431 in 2015, primarily as a result of fentanyl. Fentanyl-related deaths nearly doubled from 2014 to 2015 (145 to 283) and accounted for almost two-thirds of all New Hampshire drug deaths. Between 2010 and 2015, fentanyl deaths increased by 1,629%. The county most impacted by these overdose deaths was Hillsborough County in southern New Hampshire, which is home to 30.6% of the state's population, where 43.6% of the fentanyl deaths occurred.

New Hampshire is a small, largely rural state with a substantial concentration of population clustered in the southerly hub of Manchester/Nashua, in Hillsborough County (**Figure 1**). The state medical examiner system has struggled to address this dramatic increase in its case load without sacrificing the quality of toxicological analysis and overall death investigation (Andrew and Duval, 2017). They have reduced the proportion of cases that are transported to Concord for autopsy, while increasing the number that receive a more comprehensive toxicology. That includes pharmaceutical drugs (instead of just illicit drugs).

The Office of the Chief Medical Examiner (OCME) is responsible for determining the cause and manner of sudden, unexpected, or unnatural deaths falling under its jurisdiction. The Chief Medical Examiner (CME) and Deputy Chief Medical Examiners (DCME) are licensed physicians certified by the American Board of Pathology in forensic pathology. They perform or oversee all death investigations for the OCME as part of a centralized system of state medical examiners. Assistant Deputy Medical Examiners (ADMEs) are investigators for the OCME. They respond to death scenes, collect information about the circumstances of death, perform an external examination of the deceased, and relay their findings to the CME or DCME. ADMEs must be trained in forensic death investigation and have background or training in medical issues that

impact such investigations. Qualified persons are appointed by and serve under the supervision of the Chief Medical Examiner.

By statute, all suspected fatal overdoses are investigated by the OCME to determine cause and manner of death. Only a few decedents in recent years received an autopsy, compared with the early 2000s, when approximately 90% received an autopsy. Currently, autopsies are ordered for cases in which an overdose cause may be uncertain, where other causes of death must be ruled out (frequently those younger than 40 years of age), in much younger decedents (e.g., teenaged), or in cases that may be prosecuted.

In this report, we have expanded the effort initiated in our preliminary study to conduct a more detailed study of the deaths caused by fentanyl and fentanyl analogs. We review information from medical examiner files, including the death investigation report, the medical examiner report and death certificate information, the autopsy report, and the toxicology findings. We explore the utility of expanded toxicology testing of urine specimens. And we seek to increase the understanding of fentanyl/fentanyl analog-associated deaths, including decedents' medical history, social circumstances, and the associated cause and manner of death.

Methods

Study Populations and Data Sources

Overview of Sample Selection

In this study, 541 individuals were examined who died of unintentional fentanyl-induced overdose in New Hampshire from January 1, 2015 to September 30, 2016. Decedents were identified by using the cause of death generated by the Office of the Chief Medical Examiner. Cases were included in our definition of “fentanyl-induced” if fentanyl, a fentanyl metabolite, or a fentanyl analog were mentioned in the cause of death. This dataset of 541 was used for spatial analysis.

We selected 505 cases for more detailed analysis (decedent characteristics, death event, and toxicology). Cases were accepted only if full documentation was available at the time of data collection. Documentation required for the analytical sample included Medical Examiner Final Cause of Death Report; Assistant Deputy Medical Examiner (ADME) Death Investigation Report; Toxicology Report; and Autopsy Report (when an autopsy was performed). Our final analytical sample of cases with full documentation included 258 cases from 2015 and 247 from 2016.

Autopsies were performed on 189 individuals within our sample of 505. In these cases, we used any additional findings of medical conditions that were found. Some of the autopsied cases had urine samples retained, $n = 136$. These were used for the expanded toxicology analysis performed by AFMES.

Spatial Analysis (n = 541)

We collaborated with National Drug Early Warning System colleague Prof. Kathleen Stewart, director of the Center for Geospatial Information Science (CGIS) at the University of Maryland, who used geographic information systems (GIS) to produce maps displaying the spatial relationships of the location of residence, injury, and decedent fatal drug use, and death variables to each other and to other sociodemographic characteristics. We provided a database of 541 cases for which we had location data. This dataset was extracted prior to removing cases with incomplete ADME or toxicology data, which was done to produce the dataset to be used for the bulk of this study.

Occurrent Ratios (n = 773)

The fentanyl-included deaths in this study are “occurrent” rather than “resident” deaths. That is, this population consists of those who died in the state of New Hampshire, even if they were legal residents elsewhere. Likewise, it does not include those New Hampshire residents who died elsewhere as a result of fentanyl. To provide an overview of trends for the state, we calculated the occurrent death ratio per 100,000 population by using the number of unintentional fentanyl-induced deaths from 2013 through 2016, updated 4/17/17, divided by the New Hampshire estimated population for 2015, according to the U.S. Census.

Medical Examiner Report (n = 505)

The Medical Examiner Final Cause of Death Report provided the cause and manner of death, which is sent to vital records to populate the death certificate. We did not examine the Death Certificates directly.

The cause of death includes two parts. Part I lists the immediate cause of death that can be preceded by up to three separate conditions that led to the immediate cause. Part II is used to report other significant conditions that may have contributed to death. When multiple, potentially synergistic drugs (such as opioids, benzodiazepines, or alcohol) are present in the toxicology, it becomes difficult to separate their effects. The National Association of Medical Examiners' guidelines recommend that all potentially synergistic co-intoxicants be mentioned (Davis, 2014); nevertheless, some pathologists still prefer to select a primary causal drug. Because pathologists' practices vary, we examined the literal cause of death they provided for the death certificate along with their toxicology findings.

Autopsy Report (n = 189)

Of the 505 cases in our final sample, 189 cases had an autopsy. For those cases, we examined the autopsy findings to identify comorbid diseases of the lung, heart, or liver that were identified in addition to drug toxicity.

Death Investigation Report (n = 505)

An Assistant Deputy Medical Examiner Report is produced for all cases. It is the major source of information regarding the decedent's social and medical background and details about the death event. Background information is obtained through interviews with the decedent's friends and family, as well as through scene investigation. Although many of the data elements (e.g., age, sex, location of injury, and location of death) are collected for every death, most of the information on the ADME Report is narrative and qualitative. We examined the details of these reports to identify those subpopulations with an explicitly reported history of opioid abuse, chronic pain, previous overdose, and EMS response. Data were only coded present/positive if it was explicitly mentioned in the ADME report.

Toxicology Report (n = 505)

The Toxicology Report includes both screening and quantitative data on the specimens collected by the ADME or collected by the forensic pathologist at autopsy.⁴ The screening tests

⁴ Note that two tests are required by forensic pathologists to confirm the involvement of a drug in death, the screening presence, and the confirmatory concentration amount. The toxicology concentration is needed to evaluate the relative toxicity of the drug in a given decedent and to make a decision about its role in their death. This decision takes into account the age and physical condition of the decedent, including their medical problems. It also requires an assessment of the potential impact of postmortem interval and chemical changes on the drugs in their system. The decision can be complex. Hence, differences between the frequencies of substances seen on death certificates and the frequency seen among the toxicology tests does not necessarily indicate a gap in reporting on the death certificate.

are done by using urine specimens (when an autopsy was done) or blood. Most quantitative toxicology tests are performed by using peripheral blood specimens, usually femoral. Other sources, such as heart blood or vitreous, are used when peripheral blood samples are unavailable or as a second confirmatory test. Most toxicology specimens are postmortem specimens; nevertheless, in those few cases in which death is delayed in the hospital, antemortem admission blood may be used.

Toxicology specimens are sent by the OCME to one of two laboratories. The New Hampshire State Police Forensic Lab (NHFL) does the majority of testing for cases that do not receive an autopsy and performs presumptive and confirmatory testing on a wide range of commonly misused and abused drugs. NMS Labs provides testing for all autopsies as well as for nonautopsied cases that require further testing.

Confirmatory quantitative levels for fentanyl and norfentanyl were analyzed. For fentanyl analogs, other opioids, benzodiazepines, and alcohol, we coded only presence or absence. Three subsets of cases were identified: 1) cases with only fentanyl or the metabolite norfentanyl identified in the toxicology; 2) cases with fentanyl or norfentanyl with or without other drugs but without major co-intoxicants (other opioids, benzodiazepines, or alcohol); and 3) cases with fentanyl or norfentanyl, with at least one major co-intoxicant present. *t* tests were run to compare the mean levels of fentanyl among the groups.

Cases in which fentanyl and other major co-intoxicants were present were examined to quantify the types and number of drugs present as an indicator of polydrug use. Additionally, the toxicology report was used to identify whether naloxone had been administered to the decedent to treat the overdose. To rule out that the naloxone was present because the decedent had taken Suboxone®, those cases that also had buprenorphine present in the toxicology were removed.

Expanded Toxicology Testing by AFMES (n = 136)

As part of this study, we also sent 136 urine samples, which had been obtained at autopsy and had been frozen, to the toxicology laboratory of the Armed Forces Medical Examiner System (AFMES) for screening tests, which provided a partial cross-validation of the NMS results. They tested each specimen for more than 150 drugs using LC/MS/MS.

We used the AFMES toxicology report to identify the presence or absence of fentanyl or fentanyl analogs, as well as the presence of various co-intoxicants, including other opioids, any benzodiazepine, and alcohol. The toxicology findings serve as an indicator of the number of co-intoxicant drugs that are present in the decedent, whether or not they contributed directly to the death. Reporting both toxicology findings and death certificate drug mentions paints a fuller picture of the underlying range of drugs present in this population of decedents. Many of these drugs may be there because of legitimate therapeutic reasons. The co-occurring therapeutic drugs and the overlying drugs being misused or abused may interact in ways that are not well understood. Certain co-occurring drugs may contribute synergistically to the death. For example, any drug that can depress respiratory function, such as alcohol, may boost that effect

when in combination with any of the opioids, including fentanyl. For this reason, it is important to document the extent of polydrug use and misuse in combination.

Education and Veteran Status Derived Provided by Vital Records (n = 556)

We did not have direct access to the final death certificate during data collection, and we sent a request for education and veteran status to New Hampshire Vital Records early in the study period. The dataset used for this request was generated from a preliminary list of potential cases, which had included 556 cases of unintentional fentanyl- and heroin-induced deaths.

Data Collection Process

The data were collected on site from the medical examiner files in December 2016 by three staff members using identical data collection: Microsoft® Excel™ spreadsheets, a common codebook developed prior to data collection, and direct examination of the data sources. Calibration was accomplished through initial and interim group meetings to discuss data variation. Initial cleaning frequencies were run using IBM® SPSS™. In those few instances where we discovered variation in how staff had collected qualitative data elements, we went back and recoded cases as needed. Data were analyzed using SPSS or Excel.

Subpopulations

In addition to age and sex variables, subpopulations identified for additional analysis included decedents with the following characteristics, based on the ADME Report:

- History of opioid abuse
- History of chronic pain
- History of previous overdose
- History of recent opioid prescription
- Death investigation included an autopsy
- Death event included EMS response
- Homeless

It is important to recognize that although these variables were often explicitly mentioned on the ADME Report, the death investigators did not always comment on each of these variables. The variables that tended to be included were the ones that were most salient to them during their examination. Thus, our counts for the subpopulations are likely underestimates.

Results

Overview and Occurrent Ratios

The state of New Hampshire has experienced an unprecedented rapid increase in deaths caused by nonpharmaceutical fentanyl and fentanyl analogs, often combined with other opioid co-intoxicants, such as heroin or synthetic opioids. These deaths occur throughout the state, but they are concentrated in areas that have higher population density and are close to interstate highways. The following section reports the overall rates and explores the variables associated with spatial distribution.

Table 1 displays the occurrent ratios for 2013–2016 using data collected in our preliminary study for 2013–2015 with a 4/17/17 update for 2016 provided by the New Hampshire OCME. Most of these deaths are unintentional; nevertheless, the totals in this table include all manners of death. Because we are reporting occurrent deaths rather than resident deaths, the results will differ from a crude death rate calculated for New Hampshire residents.

Spatial Analysis

Three variables in this study reflect spatial variability: township of residence, township where injury occurred, and township of death. Although these locations often co-occur for a given case (**Figure 2**), in many cases decedents have traveled some distance to the location of fatal drug use. Also, many decedents must be transported some distance, usually by ambulance, to a hospital, which is the place of death in these cases. Of 505 decedents with a recorded residence, 21 (4%) lived out of state, with 14 (3%) from Massachusetts, 1 each from Georgia and Connecticut, and 5 (1%) from Maine (**Figure 3**).

Population Density

Fentanyl deaths are concentrated in Hillsborough County, which has 30.6% of the state population, but was the residence of 39.6% of decedents, and the location of 43.6% of the deaths (**Table 2**). Manchester, which is the population center of Hillsborough County, had 134 (26.5%) of the state's unintentional fentanyl overdoses in this period, and Nashua was a distant second place with 50 (9.9%). All counties other than Hillsborough had fewer of the residence and death locations, except two. Strafford County, which had slightly more: comprises 9.5% of the population but accounted for 10.1% of the residence locations and 11.3% of death locations. Carroll County has 3.6% of the population but accounted for 4.2% of the residence locations and 4.4% of the death locations.

As shown in the middle map in **Figure 2**, fatal drug use is distributed in townships statewide, but it is concentrated in the southeastern part of the state, mirroring the higher state population density in those areas. Manchester has the largest concentration, which is displayed on the map as the largest dot.

Urbanity

We examined the relationship between the location of injury and the RUCA⁵ classification of the township areas as urban, micropolitan, small town, or rural (**Figure 4**). Decedent injuries occurred in 51 townships that are classified as metropolitan and in 21 townships that are classified as rural. The results of a chi-square test further demonstrate that deaths are significantly more likely to occur in an urban rather than in a rural or micropolitan township, as defined by proximity to urban resources as well as population density ($\chi^2 = 14.446$, $df = 9$, $p = .09$).

To explore the impact of population density alone, we measured the relationship between the frequency distribution of decedent location of injury and population density alone, by township (**Figure 5**). Fatal drug use is significantly more likely to occur in townships with greater population density ($R^2 = 0.6206$, $df = 258$, $F = 422$, $p < .001$).

Proximity to Interstate Highways

Proximity to drug distribution routes is a major factor influencing the location of injury. In fact, 70% of injuries occurred within 5 miles of an interstate highway across 48 towns (**Figure 6**), 14% between 5 and 10 miles of the interstate (29 towns); 9% between 10 and 15 miles (17 towns); and only 12% greater than 15 miles from the interstate (21 towns).

Sociodemographics

We examined relationships between the spatial distribution of decedents' town of residence and several sociodemographic factors (**Figure 7**): 1) the percentage of people older than age 16 in 2015 who are employed by township; 2) the median household income by township; and 3) the percentage of residents with bachelor's degrees by township. By using ordinary least-squares regression, we first tested whether decedent residence distributions were related to a combination of all three of these factors; the relationship was not significant (F statistic = 1.076 on 3 and 256 df ; multiple $R^2 = 1.01245$; adjusted $R^2 = 0.0008791$; $p = .3598$). We removed the education variable and tested for a combination of employment rate and median income; again, the relationship was not significant (F statistic = 1.526 on 2 and 257 df ; multiple $R^2 = 0.01174$; adjusted $R^2 = .004049$; $p = .2193$).

Distance Between Place of Residence, Fatal Drug Use, and Death

We explored 70 trajectories involved when the decedents' residences and the townships of injury differed (**Figure 8**). The blue dots on the map signify deaths where the residence and fatal drug use locations were the same: 423 cases (86% of 493 cases where both locations were known). The green lines illustrate the distances when the locations differ (70 of 493 cases), often when the residence was out of state. Some decedents traveled a long way, based on

⁵ The Rural-Urban Commuting Area (RUCA) code is defined by the USDA, dividing census tracts into rural, small-town, micropolitan, and urban areas (<https://www.ers.usda.gov/data-products/rural-urban-commuting-area-codes/>). The year 2010 is the most recent.

street network distances: 12 trajectories were less than 8 miles (17% of 70); 22 were between 8 and 15 miles (32%); 30 were between 15 and 82 miles (43%); and 6 traveled 83 miles or more (9%).

In 529 of the 541 cases, both the township locations of fatal drug use and death were available. Of these, 486 (92%) were in the same town. In 43 cases (8% of 529), the towns were different (**Figure 9**), ranging from less than 6 miles (8, 19% of 43), 6 to 13 miles (14, 33%), 13 to 24 miles (15, 35%), and 25 miles or more (6, 14%). These represent an ambulance transport from out of town. **Figure 10** shows the spatial patterns for the 98 cases with a hospital listed as the place of death. Most of these hospital deaths occurred in the same town as the fatal drug use. Arrows show trajectories for those deaths transported from out of town.

Decedent Characteristics (*n* = 505)

Demographics

Table 3 shows that two thirds of male and one half of female decedents were ages 20 to 39. The mean age of decedents is 36.2 (standard deviation [s.d.] = 10.6). Males are slightly younger than females on average, 35.9 compared with 37.4. Males comprise 78% of the decedent population, 394 out of 505. The age distribution within the male and female population is similar, with decedents in their 20s and 30s, and with each decile cohort comprising approximately a third of the whole group. Females tend to skew slightly older than males; 20% of females were 50 or older compared with 14% of males.

Figure 11 displays the decedent age distribution, sexes combined, against a backdrop of the New Hampshire population, illustrating the disproportionately high frequency of young adults in their 20s and 30s.

New Hampshire's population is predominantly White, 93.9% according to the U.S. Census estimated 2015 population. The population of decedents mirrors the statewide racial composition, with 95.0% White decedents (**Table 4**).

Education and Veteran Status (*n* = 556)

New Hampshire Vital Records provided aggregate education statistics using a dataset of 556 victims of unintentional fentanyl and heroin overdose in 2015–2016 (**Table 5**). Among these decedents, 16.8% had fewer than 12 years of school or lacked a diploma, 60.8% had a high school diploma or GED, 5.8% also had an associate's degree, and 3.6% had a bachelor's degree. The U.S. Census data (2011–2015) for New Hampshire includes statewide rates for comparison: 92.3% are high school graduates, and 34.9% have a bachelor's degree or higher.

Among the 498 decedents in this sample for whom veteran status was known, 19 (3.8%) were veterans. The U.S. Census (2011–2015) reports there are 106,827 veterans and 1,040,535 persons 18 or older in New Hampshire, which is a percentage of 10.3%.

Medical History

Among the 505 decedents for whom we had full record documentation, the ADME Report identified 48 (9.5%) as having a history of chronic pain, 320 (63.4%) with a history of opioid abuse, and 64 (12.7%) with a history of previous overdose. Among those 320 with a history of opioid abuse, the ADME Report specified that 261 (81.6%) had abused heroin, 15 (4.7%) abused “pills,” and 23 (7.2%) abused a combination of heroin and pills.

The OCME does not have access to the Prescription Drug Monitoring Program data; nevertheless, current or recent (previous 12 months) prescriptions for an opioid were identified in the ADME Report for 75 (14.8%) of the 505 decedents, including 5 who had a prescription for fentanyl.

Among the decedents in our sample, 287 had an explicitly documented history of injection drug use. History of injection drug use was determined if the presence of track marks was noted on either external exam or autopsy or was documented as the route of administration for the death event.

A history of mental health treatment was mentioned by the ADME for 107 (21.2%) of the decedents; among those, only one had been recently released (within the last two weeks) from treatment.

An additional 15 (3.0%) other decedents had been recently released from substance abuse treatment programs.

Preexisting comorbid conditions are often found at autopsy. Some of these can potentially increase fatality risk for drug users, particularly problems with the heart, lungs, or liver. Among the 189 decedents who had an autopsy, the pathologist identified 114 (60.3%) with a preexisting cardiovascular problem (e.g., arteriosclerotic heart disease, cardiomegaly, and valve disease) and 93 (49.2%) with preexisting liver pathology (e.g., hepatitis-C, steatosis, cirrhosis, and gall bladder disease). There were also 124 (65.6%) with identified pulmonary pathology. Nevertheless, most of the findings in this category are the results of opioid respiratory depression and how it appears postmortem. Only 37 (19.6%) of cases had pulmonary pathology that was preexisting, such as asthma, emphysema, sarcoidosis, pleural adhesions, or tumors.

Recent Release from Custody

In the medical examiner setting, many unintentional overdoses are immediately preceded by a recent release from an in-custody situation where the victim has been abstinent. Now less opioid-tolerant, he or she may be more apt to take the pre-abstinent dose or amount of drug, increasing the risk of fatality. In this study population, 24 (4.8%) were recently released (past two weeks) from jail or prison.

Literal Cause of Death Drug Frequencies

All 505 cases had fentanyl, a fentanyl analog, or both listed on the death certificate as a cause of death. **Table 6** displays the frequencies of key drugs and drug categories mentioned on the death certificates for these decedents. These categories are not mutually exclusive. For example, many cases of “fentanyl”-caused deaths had a fentanyl analog also listed as a cause. The number of “fentanyl” cases is fewer than 505 because some cases had only a fentanyl analog listed as a cause but not fentanyl. In 53 (10.5%) cases, one or more fentanyl analogs were listed as a cause. The only other drugs found in 10% or more of the cases other than fentanyl and acetyl fentanyl are heroin (10.5%) and cocaine (12.7%)

Fentanyl was the only drug listed on the death certificate in 290 (57.4%) cases. An analysis of the most common death certificate co-intoxicant combinations mentioned with fentanyl and/or fentanyl analogs includes the following: fentanyl or fentanyl analog and at least one other drug (173, 34.3%); fentanyl and heroin in 58 (11.5%) of cases; fentanyl and heroin and at least one other drug in 21 (4.2%) of cases; fentanyl and/or fentanyl analogs and at least one pharmaceutical opioid in 35 (6.9%) of cases; fentanyl and/or fentanyl analog and at least one benzodiazepine in 11 (2.2%) of cases; and fentanyl and/or fentanyl analog and ethanol in 46 (9.1%) of cases.

Toxicology Findings: Polydrug Complexity

There are 114 different drugs and metabolites identified in the toxicology reports for this study population, many more than would be identified on the death certificate. **Table 7 Part A** focuses on key drug categories for this study (opioids, benzodiazepines, ethanol) in addition to other substance categories with a frequency of 50 or more. Metabolites of heroin and cocaine are also itemized. **Part B** itemizes the frequencies of all parent drug substances. Referring to **Part B**, decedents ranged widely in the number of parent substances identified: one substance (49 decedents) to 19 substances (1 decedent). The mean was 6.23 parent drugs.

Analysis of Fentanyl Levels

Postmortem levels of fentanyl confirmed for blood samples in our sample ($N = 497$) range widely from 0.75 to 113.00 ng/mL, with a mean of 9.96 ng/mL, s.d. = 9.27. To explore the possible impact of co-intoxicants, specified as any other opioid, any benzodiazepine, or alcohol, we analyzed the subsample of cases ($n = 48$) in which fentanyl was the only drug found. The range for that subsample is also wide, 2.70 to 36.00 ng/mL (mean = 10.52, s.d. = 7.51). When this subsample is compared with the subsample of those cases containing both fentanyl and one or more of the identified co-intoxicants ($n = 287$, range 0.75 to 113.00, mean = 9.56, s.d. = 10.22), the distributions are not significantly different (two-tailed t -test p value = .532). We also tested the fentanyl-only subsample against the subsample of cases that contained none of the specified co-intoxicants but did contain other drugs ($n = 108$, mean = 10.99, s.d. = 8.28); again, the distributions were not statistically different (two-tailed t -test p value = .736).

Expanded Toxicology of Urine Samples (n = 136)

We submitted 136 urine specimens from the study population, which were collected at autopsy, to the Armed Forces Medical Examiner System (AFMES) to screen quickly for a wide range of drugs.

Table 8 shows that 98% of the urine specimens tested positive for any form of fentanyl, including metabolites. Some fentanyl deaths occur very quickly, reaching the blood before metabolites reach the urine, explaining why not all urine specimens were positive for fentanyl. In addition, 52% tested positive for a non-fentanyl opioid. Marijuana and cocaine were identified in more than one third of the specimens. Most specimens contained drugs in addition to fentanyl: 60% contained three or more drugs or drug categories (of 7). These specimens contain an average of 2.88 drugs/drug categories, and multiple drugs/drug categories were found in specimens from males and females and at all age levels.⁶

These results underscore the importance of obtaining an extensive medical and drug use history for decedents with a suspected fentanyl-related overdose, as with all other drug deaths. Because drugs may interact synergistically, medical examiner guidelines suggest including mention of all co-intoxicants on the death certificate (Davis, 2014).

The additional urinalysis specimens may not be representative of all persons who died from a fentanyl-related overdose. We compared the demographic characteristics of the 136 decedents in the additional urine specimen subpopulation with 372 others in the primary study population of 505. There is no significant difference between the two groups in the proportion of males and females. There are significantly more older decedents (age 40 and older) among the expanded urine toxicology subgroup of 136 with all others ($p = .043$). Using the blood toxicology results for both the urine sample and the non-urine sample subgroups, we compared the proportion with pharmaceutical opioids present in each subgroup. There were significantly fewer decedents with pharmaceutical opioids among the expanded urine specimen subgroup ($p < .001$). These differences are likely a result of the bias in selecting individuals to autopsy, i.e., those whose cause of death is less immediately apparent.

Death Event Characteristics (n = 505)

There is considerable variation in the events surrounding the overdose. Deaths are significantly more likely to occur on the weekends than on other days of the week (**Table 9**): (Friday 19.3%, Saturday 18.7%), slightly fewer on Thursday (14.4%) and Sunday (14.3%), and fewest Monday through Wednesday (11.5%, 10.9%, and 10.9%; chi-square for Goodness of Fit, $p < .05$).

⁶ A comparison of toxicological findings from AFMES, NMS, and NHFL is beyond the scope of this study. The labs each test for a broad range of drugs, but they may use different detection methods and sensitivities for screening. The AFMES lab provided screening but not quantitation in this study.

Most victims were reported to be alone when they took the drug that produced the overdose ($n = 316$, 62.6%). Slightly fewer reported to be alone when they died ($n = 291$, 57.6%). In 32 (6.3%) cases, the victim was found in a decomposed state. The ADME reported only 70 (13.9%) victims for whom there was a witness aware that the victim was taking the drug.⁷

In 62 (12.3%) cases, the ADME commented that the victim had believed the substance he or she took to be heroin. We checked this group of 62 and found that only 18 (29.0%) had heroin/morphine in the toxicology. In 90 (17.8%) cases, the ADME reported that the overdose was very rapid. We checked the toxicology data for this group ($n = 88$)⁸ and found their fentanyl levels (mean = 10.4, s.d. = 9.2) were not significantly different from those without a rapid overdose reported (mean = 9.9 ng/mL, s.d. = 9.3).

911 was called in 467 cases (92.5%), and EMS responded in 313 (62.0%) cases. In 59 (11.7%) cases, the ADME reported that naloxone was administered, 47 by EMS (79.7% of the reported naloxone administrations). A friend, relative, or girlfriend/boyfriend administered it in 4 (0.8%) cases; the other 9 (1.8%) were unspecified as to who administered it. Within the toxicology data, there were 88 (17.4%) cases positive for naloxone,⁹ 27 more than reported by the ADME. Some victims probably received naloxone in the emergency department. In 75 (14.9%) cases, the victim was taken to the emergency department, and in 25 cases (5.0%), he or she was admitted to the hospital.

Table 10 shows the location type for both the fatal injury and the death. Most victims ingested the drug(s) at their own residence (69.9%) and died there (60.4%). Many others were at another person's residence when they took the drug(s) (17.6%) and died there (13.3%). Overall, 86 (17.0%) of all victims died in the hospital/emergency department.

Comparison of Decedent Subpopulations

Autopsy or No Autopsy Subpopulations

Autopsies are routinely done for cases in which the likely cause of death is unclear or for cases that could potentially be overdose but other causes cannot be ruled out. This could be because the person does not have a primary care provider or because there is no clear history or evidence of drug abuse. Autopsies are also done in cases that may result in a prosecution; this is a decision made by the Attorney General's Overdose Task Force.

In our primary study population of 505, there are 189 decedents who received an autopsy (**Table 11**). Surprisingly, autopsies are significantly more likely to be done on cases with female

⁷ It is important to emphasize that these variables are not explicit questions on the ADME Report; frequencies are based on the ADME narrative alone.

⁸ One subsample case level was >50 ng/mL, which was excluded from calculation. The other subsample case had a fentanyl analog but no fentanyl in the toxicology.

⁹ We excluded those cases that were also positive for buprenorphine to eliminate any decedents who had taken Suboxone.

decedents ($p = .036$) and on decedents who are older (40 and older; $p = .035$), comparing autopsied versus nonautopsied decedents. Confirming the OCME policy, we found that those with an autopsy are significantly less likely to have an ADME-reported history of opioid abuse ($p < .001$).

Age Group Subpopulations

The age distribution of fentanyl deaths is not statistically normal (**Figure 11**). There is a large proportional bulge in the late 20s/early 30s and another, weaker bulge in the late 40s. Technically, this distribution does not qualify as bimodal, however.

We were interested in whether the younger and older decedents differed significantly in demographic or behavioral characteristics, so we divided the study population into two arbitrary segments; one younger ($n = 331$, age range 17–39) and one older ($n = 174$, age range 40–68), and we tested those categorical associations using the Pearson chi-square (**Tables 12 and 13**).

Decedents in the older group were significantly less likely to have had a reported history of opioid abuse, 50.6% versus 70.1% ($p < .001$), and were significantly more likely to be categorized overall as “opioid naïve,”¹⁰ 42.0% versus 26.9% ($p = .001$). However, those in the older group were significantly more likely to have pharmaceutical opioids present in their toxicology findings, 32.2% compared with 17.2% for the younger decedents ($p < .001$), and were significantly more likely to have a history of chronic pain, 19.5% versus 4.2% ($p < .001$). Older decedents were also more likely to have a pharmaceutical opioid prescription in the last 12 months, 23.0% compared with 10.6% ($p < .001$). Older decedents were significantly less likely to have EMS respond to the overdose, 55.7% versus 65.3% ($p = .036$). There was no statistical difference, however, in the proportion receiving naloxone or the proportion with heroin in their toxicology. Nor was there a statistical difference between older and younger decedents in the proportion who had a history of previous overdose, or the proportion who were alone when they took the fatal drug dose. Older decedents were significantly more likely to be living in a rural area, 32.8% versus 22.7% ($p = .04$), and to be living alone, 29.2% versus 15.0% ($p < .001$).

There were 490 out of 505 decedents for whom living arrangements were known. Among these 490, decedents in the older group are significantly more likely to be living alone, 29.2% compared with 63.8% of those in the younger group ($p < .001$).

Male and Female Subpopulations

Males constitute 78.0% of the study population, 74.1% of the older subpopulation 40 and older, and 80.1% of the subpopulation younger than 40. Males proportionally exceed females among

¹⁰ For this study, “opioid naïve” was defined as lacking any history of opioid abuse, recent opioid prescription, or previous overdose.

decedents 25 to 29 (males 21.8%; females 13.5%) and 30 to 34 (males 20.6%; females 16.2%). They are a proportionally smaller frequency by 1% to 2% in all other age cohorts, except those 50 to 54, where females are much greater (males 7.6%; females 14.4%). The overall sex differences by age are not statistically significant.

In most variables, males and females are not significantly different. The proportion of males with an ADME-reported history of opioid abuse, 64.2%, is slightly, but not significantly, greater than the proportion of females, 60.4%. They are slightly, but not significantly, more likely to be living alone (20.3% males; 16.2% females), and they are more likely to be alone when they took the fatal overdose (64.0%; females 57.7%).

Females are slightly more likely to be living with a boyfriend or girlfriend (19.8% females; 12.9% males) and more likely to be homeless (6.3% females; 3.8% males), but neither of these differences are statistically significant. Females are more likely to have heroin/morphine in their toxicology results (females 27%; males 18.8%) and less likely to have any pharmaceutical opioid (excluding fentanyl or heroin/morphine; females 26.1%; males 21.3%); neither of these differences is statistically significant. Although females are more likely to have had a previous overdose (females 17.1%; males 11.4%), this difference is not significant.

A few differences are statistically significant. Females are significantly more likely to have had a prescription for an opioid in the previous 12 months (females 25.2%; males 11.9%; $p < .001$). They are significantly more likely to have an EMS response (females 71.2%; males 59.4%; $p = .024$) and significantly more likely to have naloxone in their toxicology findings (females 25.2%; males 15.2%). Females are more likely (21.6%) to die in the hospital or emergency department than males (15.7%), but this difference is not statistically significant.

Subpopulation with History of Chronic Pain

Within the study population, 48 (9.5%) had an ADME-reported history of chronic pain. Among those with chronic pain, 37.5% also had a mental health diagnosis, 25.0% were living alone, 8.3% were homeless, and 25.0% were disabled. Significantly more of those with chronic pain were older than the age of 40: 70.8% compared with 29.2% for those younger than 40 ($p < .001$).

More than half (58.3%) had a history of opioid abuse, which is not significantly different from those in the study population without a history of chronic pain. Those with a history of chronic pain were significantly more likely to have had had an opioid prescribed within the previous 12 months (50.0% compared with 11.2%; $p < .001$) and significantly more likely to have a pharmaceutical opioid in their toxicology findings (41.7%, compared with 20.4%; $p < .001$). They were not significantly different from those without a history of chronic pain in terms of whether they had a history previous overdose, died alone, EMS responded, or naloxone was found in their toxicology.

Subpopulation with Opioid Prescription in Previous 12 Months

Only 75 (14.9%) of the 505 decedents in the study population had an opioid prescription during the previous 12 months, but only 40.0% of those that had an opioid prescription had a pharmaceutical opioid in their toxicology. This was, however, significantly higher than the percentage without a recent opioid prescription, 19.3% ($p < .001$). Within this subpopulation, significantly more had a history of chronic pain (32.0%, compared with 5.6% of those without an opioid prescription; $p < .001$). Rapid overdoses were significantly less common among decedents with a recent opioid prescription, 6.7% compared with 19.8% ($p = .006$), but they were no more likely to have naloxone in their toxicology findings.

Subpopulation with History of Opioid Abuse

A majority of decedents, 320 (63.4%), had a history of opioid abuse reported by the ADME. Only a small minority of these, 8.8%, also had a history of chronic pain. Overall, 15.9% had had a prescription for an opioid in the previous 12 months, and 22.8% had a pharmaceutical opioid present in their toxicology. Of those with an opioid abuse history, 31.8% were unemployed, 7.5% were disabled, 18.8% were living alone, and 3.8% were homeless. None of these patterns were significantly different from those without a reported opioid abuse history.

Those with an opioid abuse history were significantly less likely to be alone when they died (53.8%, compared with 46.3%; $p = .021$). They were also significantly more likely to have an EMS response (65.6% compared with 34.4%; $p = .026$) but no more likely to have naloxone present in toxicology (16.9% compared with 18.4%; n.s.). They were significantly more likely to have an ADME-reported history of previous overdose (17.5% compared with 4.3%; $p < .001$). They were also significantly more likely to have been recently released (previous two weeks) from jail or substance abuse treatment (6.6% compared with 1.6%; $p < .001$).

Subpopulation with History of Previous Overdose

Based on the ADME reports, there were 64 (12.7%) decedents for whom there was a history of previous overdose. This subpopulation did not appear significantly different from those without such a history in terms of the variables in this study. Specifically, 18.8% had naloxone present in toxicology, which is not significantly different from those without a history of previous overdose, 17.2%. Within this subpopulation, EMS responded in 59.4% of the cases, 62.5% of the decedents were alone when they took the fatal dose, 54.7% were alone when they died, 18.8% had an opioid prescription in the 12 months before they died, 18.8% had pharmaceutical opioids in their toxicology, and 10.9% had a history of chronic pain. But none of these percentages were statistically different from those without an overdose history.

Homeless Subpopulation

There are 22 decedents reported to be homeless, 4.4% of our primary sample, 15 males and 7 females. Of these 22, the majority (13, 59.1%) are younger than 40. There are 12 (54.5%) who have an ADME-reported history of opioid abuse. A minority of these decedents have a history of chronic pain (4, 18.2%) or any history of an opioid prescription in the previous 12 months (3, 13.6%).

Discussion and Conclusions

This observational study focused on fentanyl-induced overdoses in New Hampshire during 2015 and 2016. The rate of death caused by fentanyl, heroin, and other opioids has risen sharply during this time period. So it is vital to learn what we can about these decedents, these death events, and the characteristics of fentanyl deaths.

Compared with the New Hampshire census population, the study population proportionally oversamples males approximately 2:1, and oversamples males and females in their 20s and 30s, as well as, to a slightly lesser extent, those in their 40s and early 50s. This is comparable to other fentanyl mortality populations recently reported, e.g., in Florida (Lee et al., 2016) and Massachusetts (Somerville et al., 2017). It is likely that the decedent population contains older, more physically and/or more medically vulnerable individuals than the living population of nonfentanyl drug users. Thus, our findings should not be generalized to this population without elucidating the potential differences.

The GIS analytical support provided by NDEWS helped to elucidate spatial distribution relationships. Although fentanyl-associated mortality has reached most communities in the state, it is disproportionately located in urban centers in the southeast quadrant of the state, especially in Hillsborough County. We ruled out statistically significant relationships between decedent residence location and township-level socioeconomic factors of employment, income, and educational level. The concentration of deaths is, however, related to population density, urban status of the area, and close proximity to major highways.

Data were gathered from primary sources from the Office of Chief Medical Examiner files, including the medical examiner report, death investigator (ADME) report, autopsy report, toxicology report, and data used for the death certificate. The ADME report provided rich data about the characteristics of the decedents' medical and social history and about the death event itself. Although this report is structured and contains similar data across cases, it is largely narrative, and most of the variables collected from it are qualitative. The characteristics mentioned by the death investigator can be considered present in a given case, but we cannot assume that the characteristics not mentioned are always absent. For example, in cases where there are no witnesses for the death investigator to speak to, or the decedent lacks a medical record, the ADME narrative may simply be silent. For this reason, the statistical frequencies of the study variables based on the ADME reports are minimum estimates within this population.

Decedents who unintentionally ingested fatal amounts of fentanyl typically have toxicology findings demonstrating polydrug use. By using data from the medical examiner's toxicology tests of (primarily) blood specimens, we demonstrated that the average decedent had multiple drugs present, with an average of 6.23 per specimen. Then, by using supplemental toxicology screening tests of urine specimens from a subsample of autopsied cases, NDEWS assessed the overlap of seven major co-intoxicant categories (fentanyl, other opioid, marijuana, cocaine, benzodiazepines, antidepressants, and amphetamines), finding an average of 2.88 per

specimen. Decedents' polydrug profiles often include co-intoxicants that are potentially synergistic with fentanyl, that is, substances that can produce central nervous system and respiratory depression. Co-intoxicant category frequencies in the larger study population include other opioids (34.5% of decedents) including heroin/morphine (20.6%); alcohol (32.9%); benzodiazepines (27.5%); and cocaine (31.1%), among others.

Despite the ubiquitous presence of multiple drugs in these decedents, the effects of fentanyl were evidently so strong that there were no statistical differences in the fentanyl level (mean and standard deviation) with or without the presence of these co-intoxicants. The range of fentanyl levels was wide, from 0.75 to 113 ng/mL, with an average of 9.96 ng/mL; nevertheless, the distributions of fentanyl levels were statistically the same, whether fentanyl was the only drug in the toxicology or one of several synergistic co-intoxicants. This suggests that fentanyl presence alone seems to be sufficient to cause death, which are findings similar to those found in Sorg et al., 2016.

Most (64.0%) decedents in the study population received some type of medical intervention: EMS response (62.0%), naloxone administration (17.4%), emergency room visit (14.9%), or hospital admission (5.0%). Certain subpopulations, however, were less likely to receive any of these interventions. Older decedents (40 or older) were significantly less likely (59.8% vs. 73.1%) to receive any medical intervention, compared with those younger than 40 ($p = .002$). Similarly, decedents we categorized as "opioid-naïve" (those who lacked any history of opioid abuse, recent opioid prescription, or previous overdose) were less likely (62.7% vs. 71.0%) to receive any of these medical interventions ($p = .066$). Finally, those decedents residing in rural or micropolitan townships, as defined by the Office of Management and Budget (OMB) standard,¹¹ were significantly less likely (60.3% vs. 72.8%) to receive any of these medical interventions ($p = .001$). Age plays a significant role in these patterns. Older decedents 40 and older are significantly more likely than those younger than 40 to be living alone (28.7% vs. 14.5%, $p = .001$), residing in a rural township rather than in a micropolitan or metropolitan area (32.4% vs. 22.7%, $p = .040$), and more likely to be categorized as "opioid naïve" (37.4% vs. 25.7%, $p = .006$).

In conclusion, the findings from our research shed new light on the population of decedents who died in 2015 and 2016 as a result of unintentional fentanyl poisoning. They focus attention on a mixture of rural and urban decedents from a primarily White population who died in New Hampshire. By using primary sources generated in the death investigation by the statewide Office of Chief Medical Examiner system, we studied victim characteristics, death event characteristics, and victim toxicology. Victims who were older, who lived in more rural areas, and who lacked an opioid-related history had significantly less access to care. Although most of these decedents were found to use multiple drugs, fentanyl levels ranged broadly among them,

¹¹ <https://www.census.gov/programs-surveys/metro-micro/about.html>

with no significant relationship to the presence of other co-intoxicants or to their opioid-related history.

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Table 1. Occurrent ratio of fentanyl overdoses, 2013-2016

Year	Number of Fentanyl Overdoses (All Manners of Death)	Occurrent Ratio of Fentanyl Deaths per 100,000 Population*
2013	18	2.40
2014	145	10.90
2015	284	21.34
2016	326	24.50

Source: New Hampshire OCME, 4/10/17 Update

* Population used for this calculation was the estimated 2015 population of the State of New Hampshire
(<https://www.nh.gov/oep/data-center/population-estimates.htm>)

Table 2. Population densities, decedent residences and deaths by county

County	Percent NH Population U.S. Census 2015 N = 1,330,608		Decedent County of Residence N = 479*		Decedent County of Death N = 505	
	n	%	n	%	n	%
Belknap	60,641	4.6%	20	4.0%	21	4.2%
Carroll	47,285	3.6%	21	4.2%	22	4.4%
Cheshire	75,909	5.7%	9	1.8%	9	1.8%
Coos	31,212	2.3%	7	1.4%	7	1.4%
Grafton	89,320	6.7%	12	2.4%	13	2.6%
Hillsborough	406,678	30.6%	200	39.6%	220	43.6%
Merrimack	147,994	11.1%	34	6.7%	45	8.9%
Rockingham	301,777	22.7%	96	19.0%	103	20.4%
Strafford	126,825	9.5%	51	10.1%	57	11.3%
Sullivan	42,967	3.2%	8	1.6%	8	1.6%

*26 decedents in our study population had a county of residence that was either unknown or outside of the state of New Hampshire

Table 3. Age and sex distribution of analytical study population

	Total	Percent	Male	Percent	Female	Percent
0–9	0	0.0%	0	0.0%	0	0.0%
10–19	7	1.4%	5	1.3%	2	1.8%
20–29	155	30.7%	126	32.0%	29	26.1%
30–39	169	33.5%	134	34.0%	35	31.5%
40–49	97	19.2%	74	18.8%	23	20.7%
50–59	70	13.9%	49	12.4%	21	18.9%
60–69	7	1.4%	6	1.5%	1	0.9%
70+	0	0.0%	0	0.0%	0	0.0%
Total	505	100.0%	394	100.0%	111	100.0%
Row %	505	100.0%	394	78.0%	111	22.0%

Table 4. Race distribution in analytical study population compared with U.S. Census population estimate for New Hampshire, 2015

Race	Number	Percent	NH Percent 2015
White	475	95.0%	93.9%
American Indian	0	0.0%	0.3%
Asian	1	0.2%	1.5%
Asian/Pacific Islander	1	0.2%	2.6%
Black/African American	7	1.4%	1.5%
Hispanic/Latino	12	2.4%	3.4%
Other	4	0.8%	9.3%
Total*	500	100%	100.0%

*5 cases of the 505 were coded as unknown.

Table 5. Education level among unintentional fentanyl and heroin overdose victims provided by New Hampshire Vital Records (n = 556)

Year	8th or Less	9-12, No Diploma	HS Grad, GED	Some College	Assoc. Degree	Bachelor's Degree	Master's Degree	PhD	Not Reported	Total
Total	12 2.2%	81 14.6%	338 60.8%	64 11.5%	32 5.8%	20 3.6%	1 0.2%	1 0.2%	7 1.3%	556 100.0%

Table 6. Drugs mentioned on the death certificate as a cause of death

Death Certificate Mentions		
Drug or Drug Category*	Frequency	Percent (N = 505)
Fentanyl	502	99.4%
Acetyl Fentanyl	51	10.5%
Fluoro-Fentanyl	1	0.2%
Furanyl Fentanyl	1	0.2%
Co-intoxicant Illicit Drugs		
Heroin or Heroin/Morphine	53	10.5%
Morphine	6	1.2%
Cocaine	64	12.7%
Methamphetamine	6	1.2%
Co-intoxicant Pharmaceutical Opioid Drugs	35	6.9%
Buprenorphine	6	1.2%
Hydrocodone	9	1.8%
Methadone	9	1.8%
Oxycodone	18	3.6%
Oxymorphone	1	0.2%
Tramadol	1	0.2%
Co-intoxicant Benzodiazepines	11	2.2%
Alprazolam	6	1.2%
Clonazepam	3	0.6%
Diazepam	4	0.8%
Lorazepam	3	0.6%
Temazepam	1	0.2%
Other Drugs		
Amitriptyline	1	0.2%
Butalbital	1	0.2%
Carisoprodol	1	0.2%
Chlorpromazine	1	0.2%
Cocaethylene (cocaine metabolite)	1	0.2%
Cyclobenzaprine	1	0.2%
Duloxetine	1	0.2%
Ethanol	46	9.1%
Gabapentin	3	0.6%
Ketamine	1	0.2%
Zolpidem	1	0.2%

*Categories are not mutually exclusive.

Table 7. Frequency of drugs present in toxicology tests ordered by the medical examiner, using primarily blood samples

Part A Key Drugs¹ Present in Primary Toxicology Report: Includes Key Parent Drugs and Metabolites		
Drug or Drug Category	Number	Percent N = 505
Any fentanyl or fentanyl analog or fentanyl metabolite	505	100.0%
Fentanyl	497	98.4%
Norfentanyl (metabolite)	192	38.0%
Fentanyl/Metabolite	96	19.4%
Any fentanyl analog	59	11.7%
Acetyl Fentanyl	56	11.1%
Despropionyl-Fentanyl (4-ANPP)	1	0.2%
Furanyl Fentanyl	3	0.6%
Heroin/Morphine or metabolite	104	20.6%
6-MAM	66	13.1%
Morphine	101	20.0%
Any cocaine or cocaine metabolite	157	31.1%
Cocaine	82	16.2%
Benzoylconine (cocaine metabolite)		
Cocaethylene (cocaine metabolite)	24	4.8%
Cocaine/Metabolites	49	9.7%
Any non-fentanyl opioid (excludes fentanyl and fentanyl analogs)	174	34.5%
Any pharmaceutical opioid (excludes fentanyl, fentanyl analogs, heroin/morphine, heroin/morphine metabolites)	113	22.4%
Buprenorphine	8	1.6%
Codeine	22	4.4%
Hydrocodone	13	2.6%
Hydromorphone-Free	2	0.4%
Methadone	12	2.4%
Mitragynine	3	0.6%
Opiates NOS	36	7.1%
Oxycodone	40	7.9%
Oxycodone/Oxymorphone	10	2.0%
Oxymorphone-Free	11	2.2%
Tramadol	10	2.0%
Any benzodiazepine parent or metabolite	139	27.5%
Benzodiazepine NOS	27	5.3%
Alprazolam	39	7.7%
Chlordiazepoxide	1	0.2%
Clonazepam	27	6.3%
Diazepam	14	3.6%
Lorazepam	12	2.4%
Oxazepam	5	1.0%
Tamazepam	5	1.0%
Marijuana (cannabinoids or metabolites)	152	30.1%

Cannabinoids	58	11.5%
Delta-9 Carboxy THC	131	25.9%
Delta-9 THC	123	24.4%
11-Hydroxy Delta-9 THC	25	5.0%
Other substances ≥ 50		
Ethanol	166	32.9%
Naloxone	89	17.6%
Nicotine	50	9.9%
Part B Frequency of All Parent² Drugs Detected Per Specimen Metabolites Excluded		
Number of Parent Drugs Detected	Frequency	Percent N = 505
1	49	9.7
2	46	9.1
3	55	10.9
4	55	10.9
5	50	9.9
6 – Mean = 6.23	45	8.9
7	39	7.7
8	38	7.5
9	30	5.9
10	20	4.0
11	24	4.8
12	10	2.0
13	11	2.2
14	7	1.4
15	8	1.6
16	6	1.2
17	8	1.6
18	3	.6
19	1	.2

¹**Any fentanyl** includes: Fentanyl, Fentanyl/Metabolite, Norfentanyl, 4-ANPP (Despropionyl fentanyl), Acetyl fentanyl, Furanyl fentanyl.

Any non-fentanyl opioid includes: Morphine, 6-Monoacetylmorphine (6-MAM), Codeine, Dihydrocodeine/Hydrocodol-Free, Hydrocodone, Buprenorphine, Norbuprenorphine, Hydromorphone, Methadone, EDDP, Methadone/Metabolite, Oxycodone, Oxycodone/Oxymorphone, Oxymorphone-Free, Tramadol, O-Desmethyiltramadol, Mitragynine, Opiates NOS

Any benzodiazepine includes: 7-Aminoclonazepam, α -Hydroxyalprazolam, Alprazolam, Benzodiazepine NOS, Clonazepam, Diazepam, Lorazepam, Nordiazepam, Oxazepam, Temazepam

²**Any fentanyl** includes: Fentanyl, Fentanyl/Metabolite, Norfentanyl, 4-ANPP (Despropionyl fentanyl), Acetyl fentanyl, Furanyl fentanyl.

Any non-fentanyl opioid includes: Morphine, 6-Monoacetylmorphine (6-MAM), Codeine, Dihydrocodeine/Hydrocodol-Free, Hydrocodone, Buprenorphine, Norbuprenorphine, Hydromorphone, Methadone, EDDP, Methadone/Metabolite, Oxycodone, Oxycodone/Oxymorphone, Oxymorphone-Free, Tramadol, O-Desmethyiltramadol, Mitragynine, Opiates NOS

Any benzodiazepine includes: 7-Aminoclonazepam, α -Hydroxyalprazolam, Alprazolam, Benzodiazepine NOS, Clonazepam, Diazepam, Lorazepam, Nordiazepam, Oxazepam, Temazepam

Table 8. Percentage of autopsy-derived urine specimens testing positive for 7 key drugs/drug categories*, testing performed by AFMES

7 Key Drugs/Drug Categories	Percent Positive N = 136
Any Fentanyl	98%
Any Non-Fentanyl Opioid	52%
Marijuana	38%
Cocaine	37%
Any Benzodiazepine	28%
Any Antidepressant	24%
Any Amphetamine	10%
Number of Drugs/Drug Categories Detected in Each Specimen (of 7 Key Categories)	Percent
1	12%
2	28%
3	31%
4	20%
5	9%
Total	100%
Mean Number of Key Drugs/Drug Categories Detected per Specimen	2.88

* **Any Fentanyl** includes: Fentanyl, Norfentanyl, 4-ANPP (Despropionyl fentanyl), Acetylfentanyl, Furanylfentanyl.

Any Non-Fentanyl Opioid includes: Morphine, Oxycodone, 6-Monoacetylmorphine (6-MAM), Codeine, Norbuprenorphine, Oxycodone, Tramadol, Buprenorphine, Hydrocodone, Hydromorphone, Methadone (EDDP), Tapentadol.

Any Benzodiazepine includes: 7-Aminoclonazepam, α -Hydroxyalprazolam, Alprazolam, Nordiazepam, Oxazepam, Temazepam, Lorazepam, Clonazepam, Demoxepam, Diazepam.

Any Antidepressant includes: Trazodone, Citalopram, Sertraline, Bupropion, Desmethylvenlafaxine/Desvenlafaxine, Amitriptyline, Nortriptyline, Paroxetine, Venlafaxine, Fluoxetine.

Any Amphetamine includes: Amphetamine, Methamphetamine, MDMA.

Table 9. Day of the week the death occurred among all unintentional fentanyl-induced deaths

Deaths by Day of the Week		
	Number (n = 541)	Percent
Sunday	77	14.3%
Monday	62	11.5%
Tuesday	59	10.9%
Wednesday	59	10.9%
Thursday	78	14.4%
Friday	104	19.3%
Saturday	101	18.7%
Unknown	1	n/a

Table 10. Locations of injury and death for decedents in analytical study population

Place of Injury	Number (n = 505)	Percent
Residence	353	69.9%
Other Residence	89	17.6%
Hospital/ER	1	0.2%
Other Location	53	10.5%
Unknown	9	1.8%
Place of Death		
Residence	305	60.4%
Other Residence	67	13.3%
Hospital/ER	86	17.0%
Other Location	47	9.3%
Unknown	0	0.0%

Table 11. Demographic profiles for autopsy cases compared with those without an autopsy within analytical study population (n = 505)

	Autopsy n = 189	No Autopsy n = 316
Sex distribution	Males 138 (73%) Females 51 (27%)	Males 256 (81%) Females 60 (19%)
Age distribution	Mean age 37.1 Range 17–63	Mean age 35.7 Range 18–68

Table 12. Statistically significant associations with older age group

	Opioid Prescription Within Last 12 Months <i>p</i> < .001		Pharmaceutical Opioid in Toxicology <i>p</i> < .001		Opioid Naïve <i>p</i> = .001		Reported History of Chronic Pain <i>p</i> < .001		Lives Alone* <i>p</i> < .001	
Age Category	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
Younger Age 17–39 <i>n</i> = 331	35 10.6%	296 89.4%	57 17.2%	274 82.8%	89 26.9%	242 73.1%	14 4.2%	317 95.8%	48 15.0%	271 85.0%
Older Age 40–68 <i>n</i> = 174	40 23.0%	135 77.0%	56 32.2%	118 67.8%	73 42.0%	101 58.0%	34 19.5%	140 80.5%	50 29.2%	121 70.8%
Total <i>n</i> = 505	75 14.9%	430 85.1%	113 22.4%	392 77.6%	162 32.1%	343 67.9%	48 9.5%	457 90.5%	98 20.0%	392 80.0%

*Subsample size for the *Lives Alone* variable was 490. Living arrangements for 15 decedents were unknown.

Table 13. Statistically significant associations with younger age group

Age Category	History of Opioid Abuse <i>p</i> < .001		Resides in Metro Area <i>p</i> = .04			EMS Response <i>p</i> = .036	
	Yes	No	Metro	Micro	Rural	Yes	No
Younger Age 17-39 n = 331	232 70.1%	99 29.9%	229 69.2%	27 8.2%	75 22.7%	216 65.3%	115 34.7%
Older Age 40-68 n = 174	88 50.6%	86 49.4%	102 58.6%	15 8.6%	57 32.8%	97 55.7%	77 44.3%
Total n = 505	320 63.4%	185 36.6%	331 65.5	42 8.3%	132 26.1%	313 62.0%	192 38.0%

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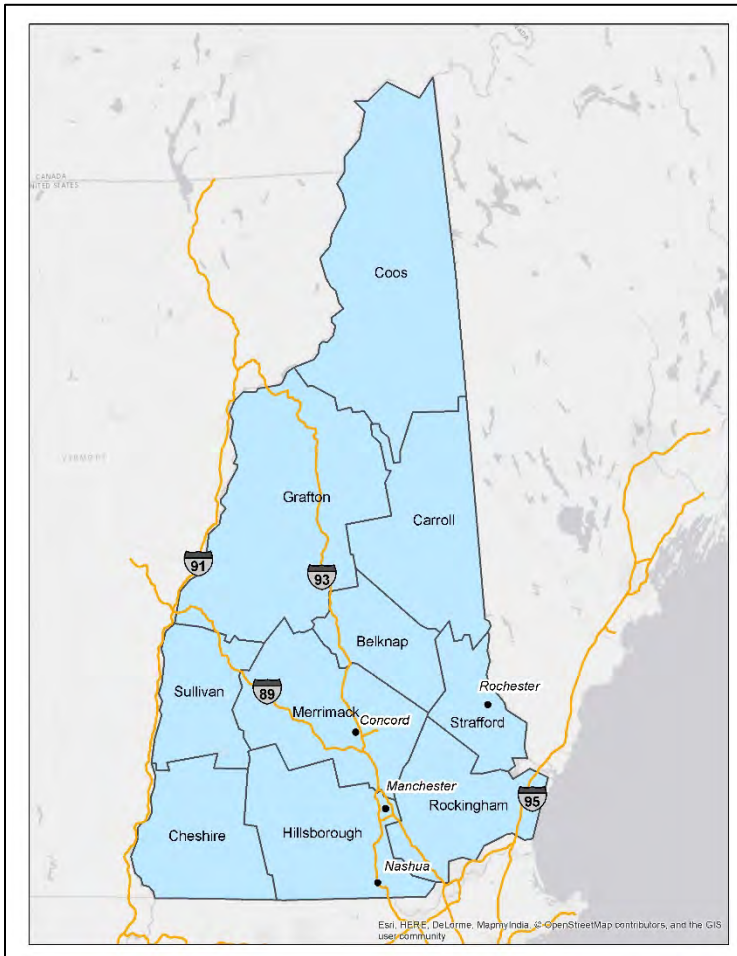


Figure 1. Map of New Hampshire depicting counties, major cities and interstate highways

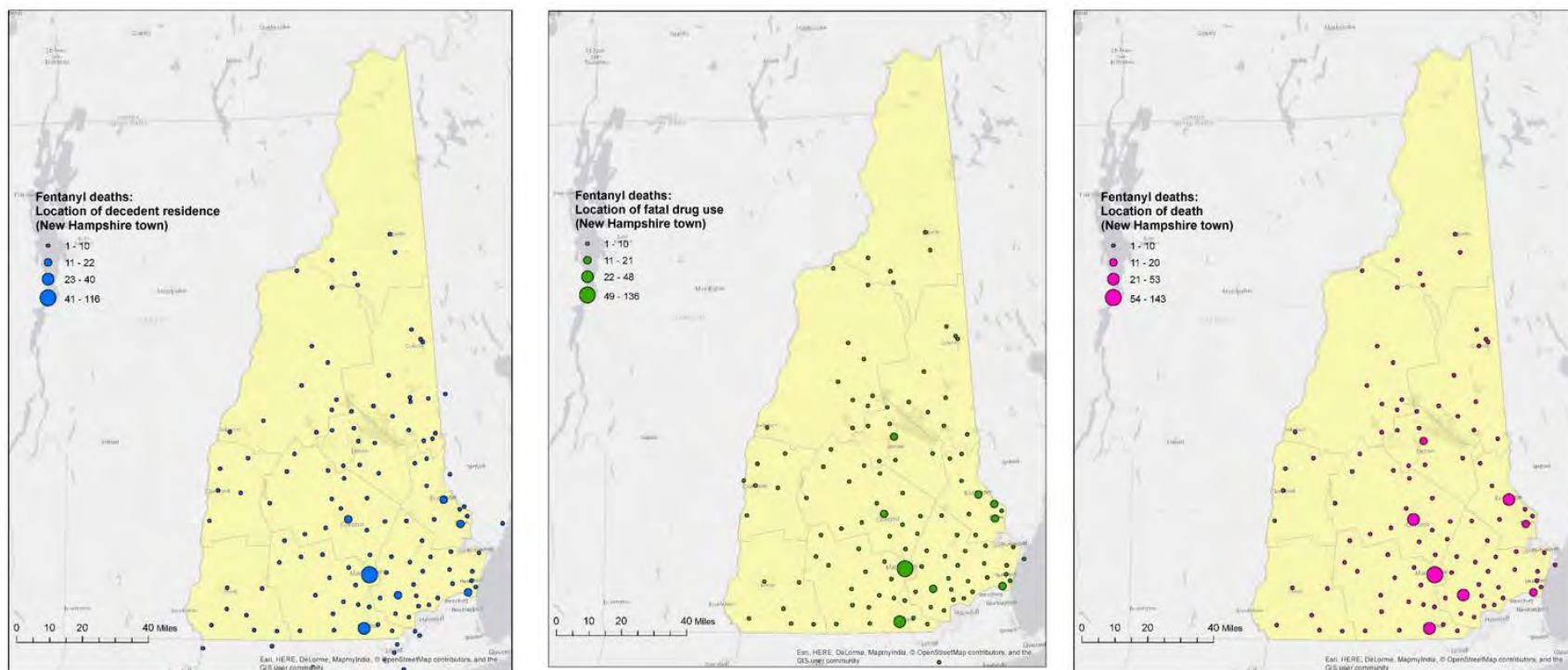


Figure 2. Fentanyl deaths by location of decedent residence, fatal drug use, and death

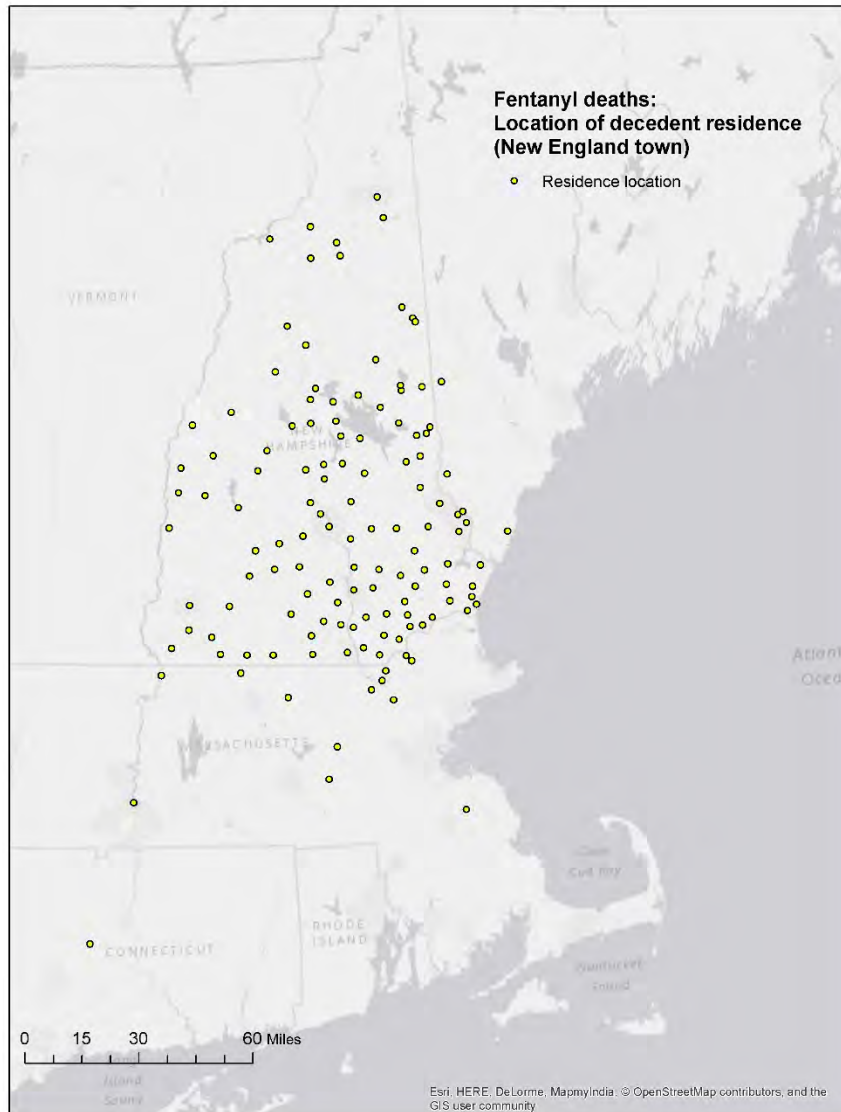


Figure 3. Fentanyl deaths occurring in New Hampshire by location of decedent residence, including all New England states

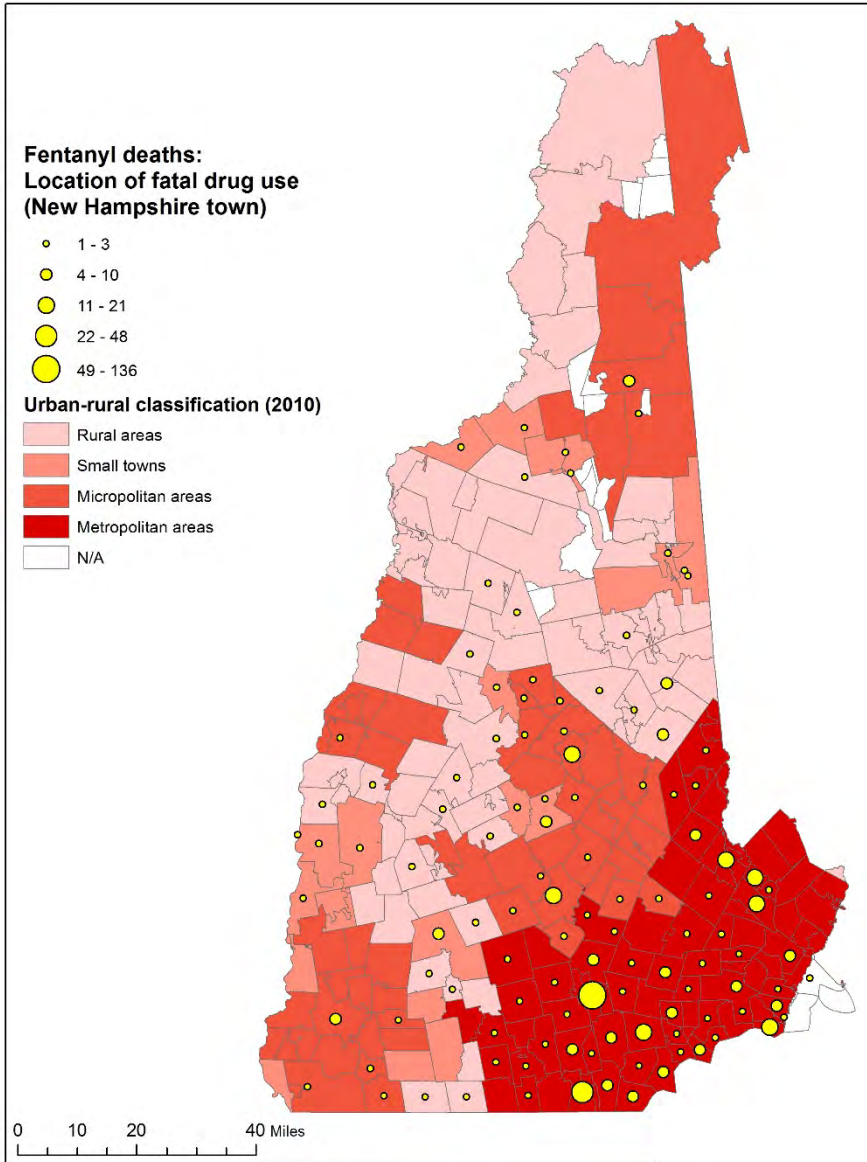


Figure 4. Fentanyl deaths by location of decedent fatal drug use and urban-rural classification

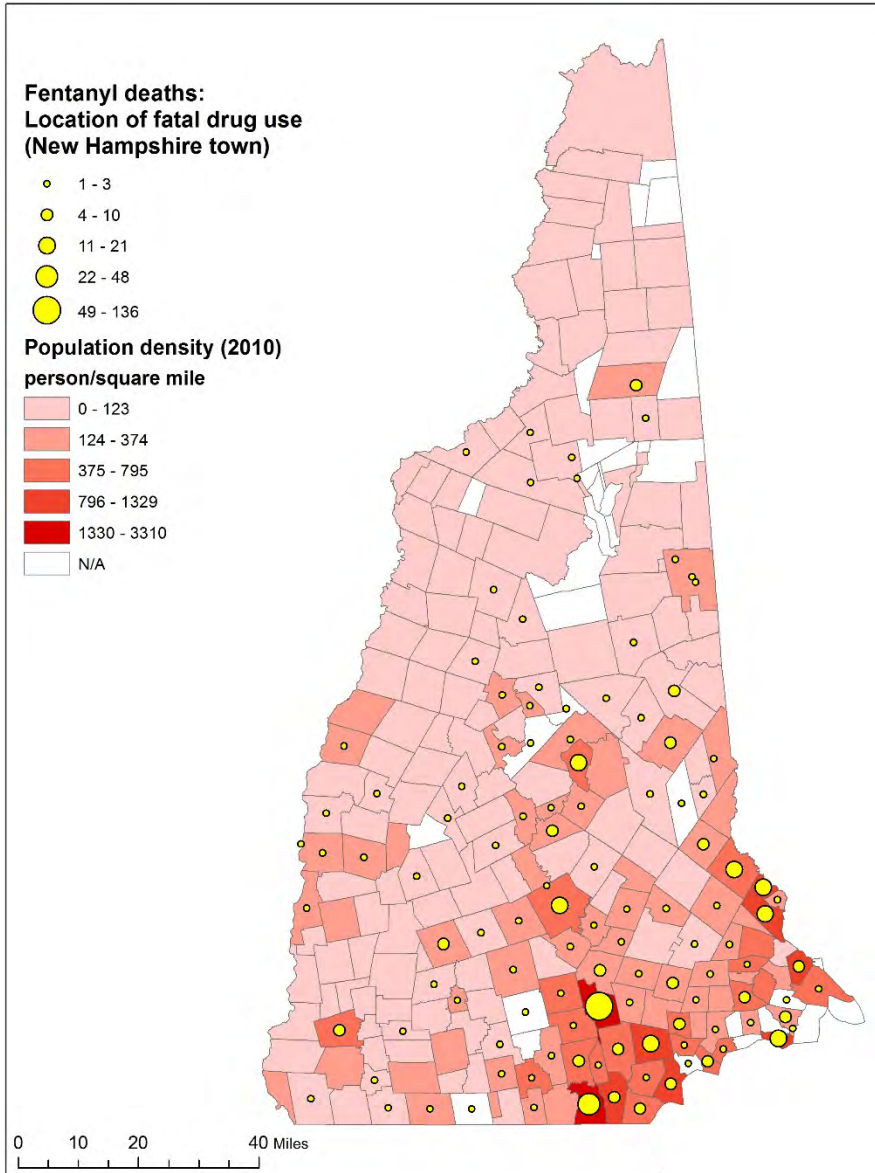


Figure 5. Fentanyl deaths by location of decedent fatal drug use and population density

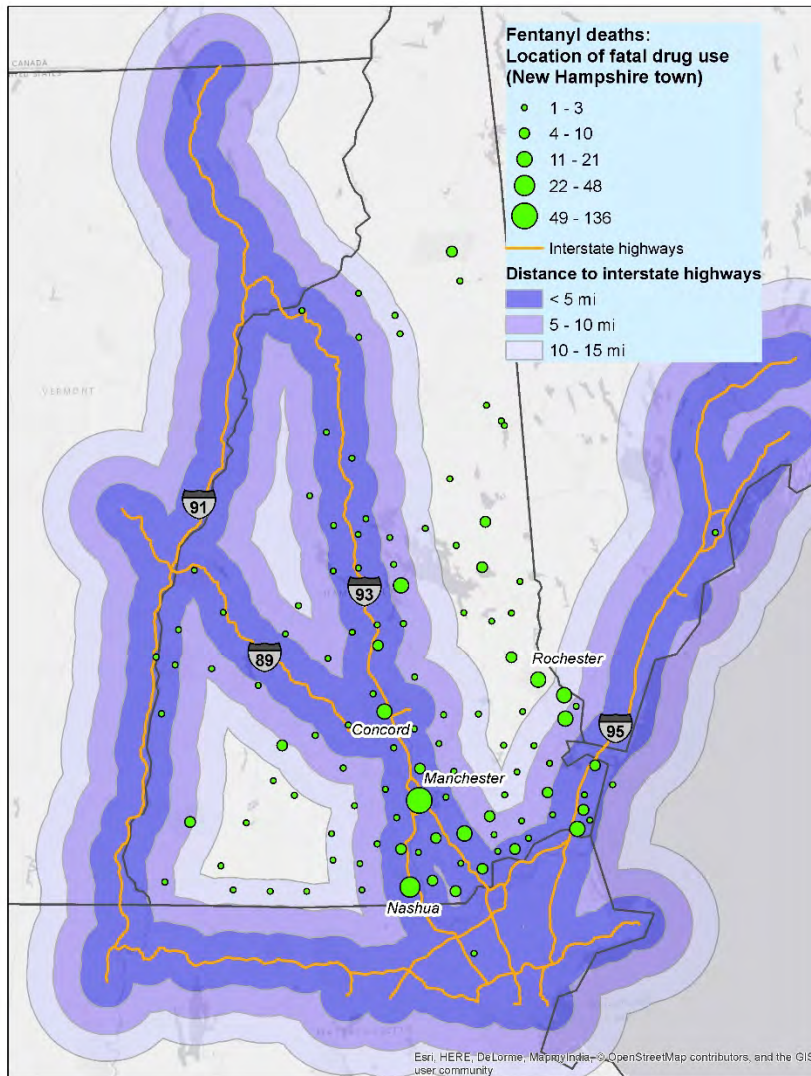


Figure 6. Fentanyl deaths showing proximity of fatal drug use to interstate highways

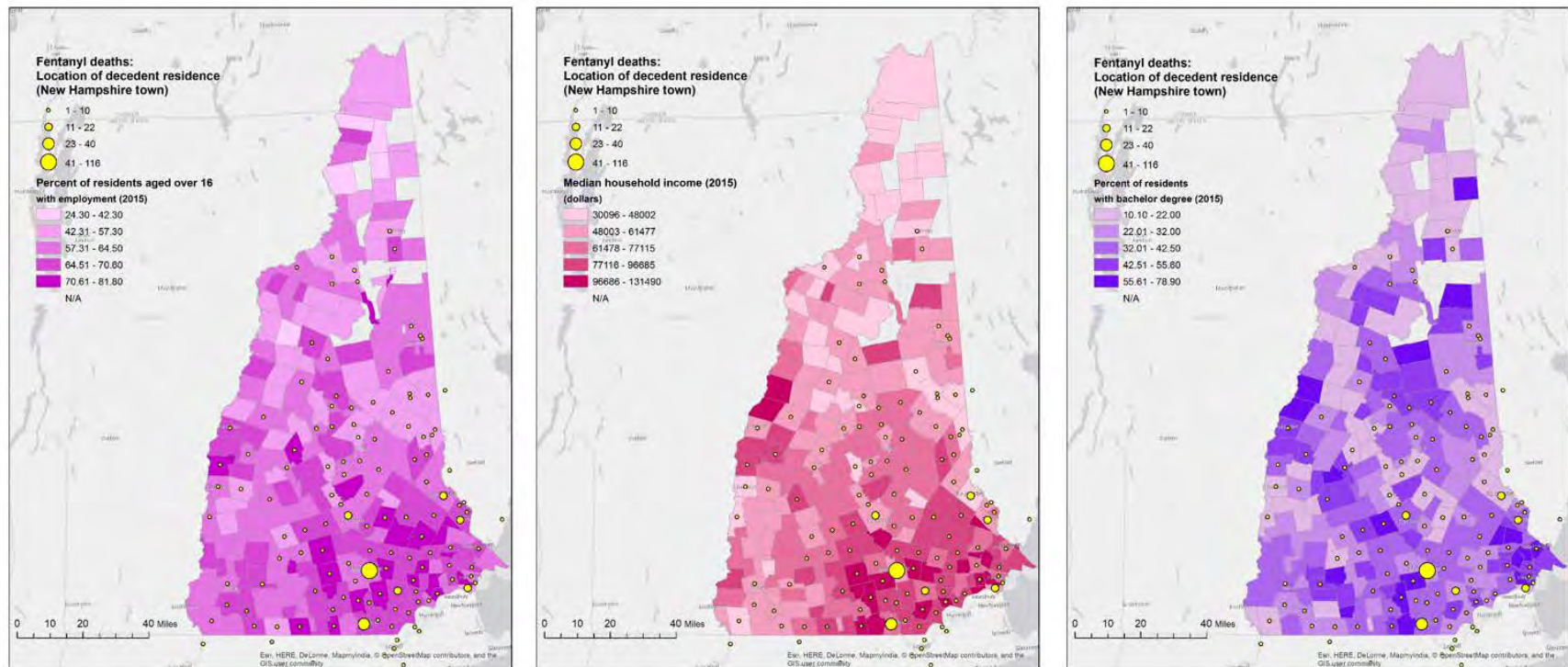


Figure 7. Fentanyl deaths by location of residence and socioeconomic factors: employment status, median household income, and education

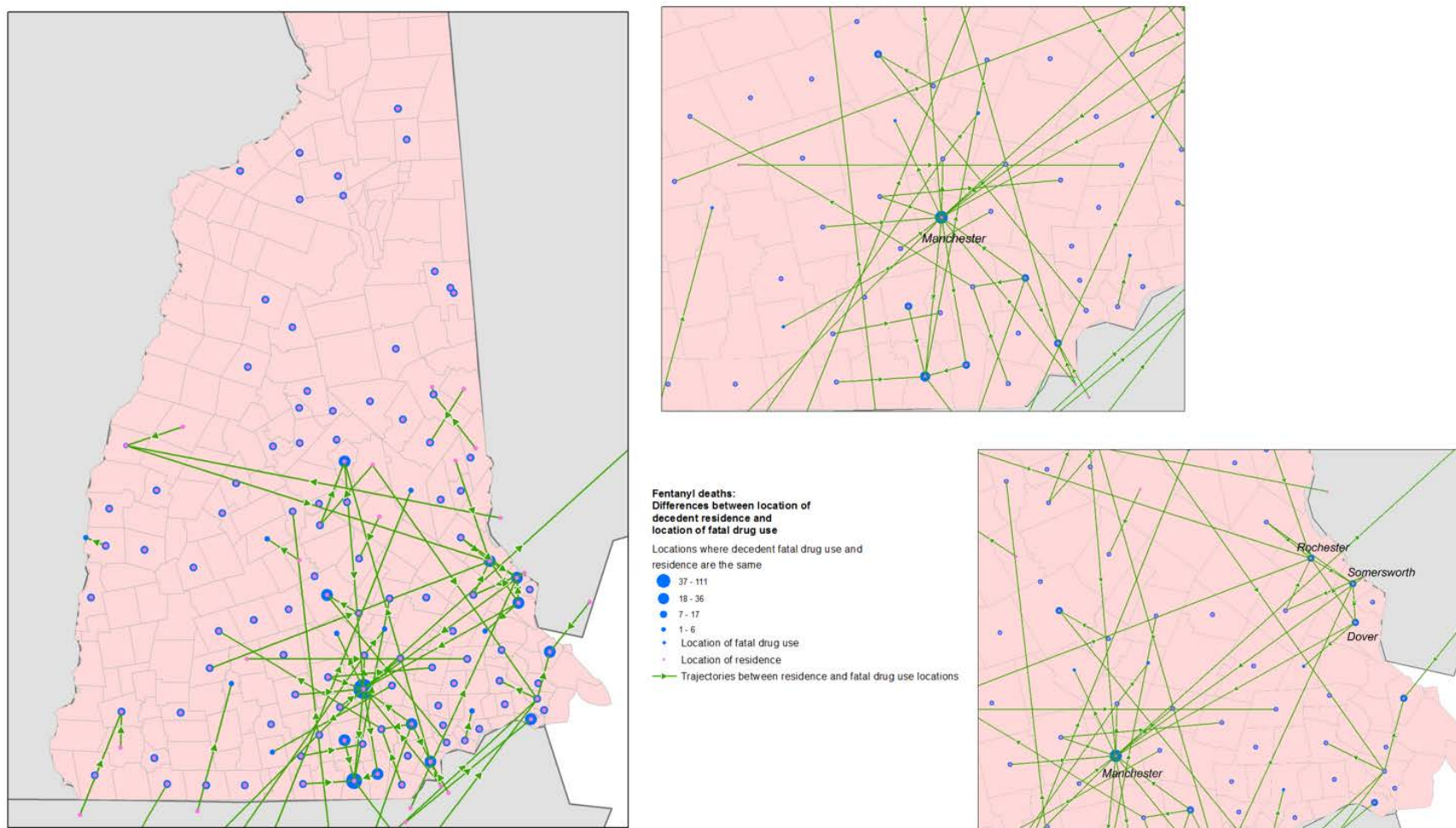


Figure 8. Fentanyl deaths by location of fatal drug use, depicting travel trajectories between locations of decedent residence and fatal drug use in cases where those locations were different

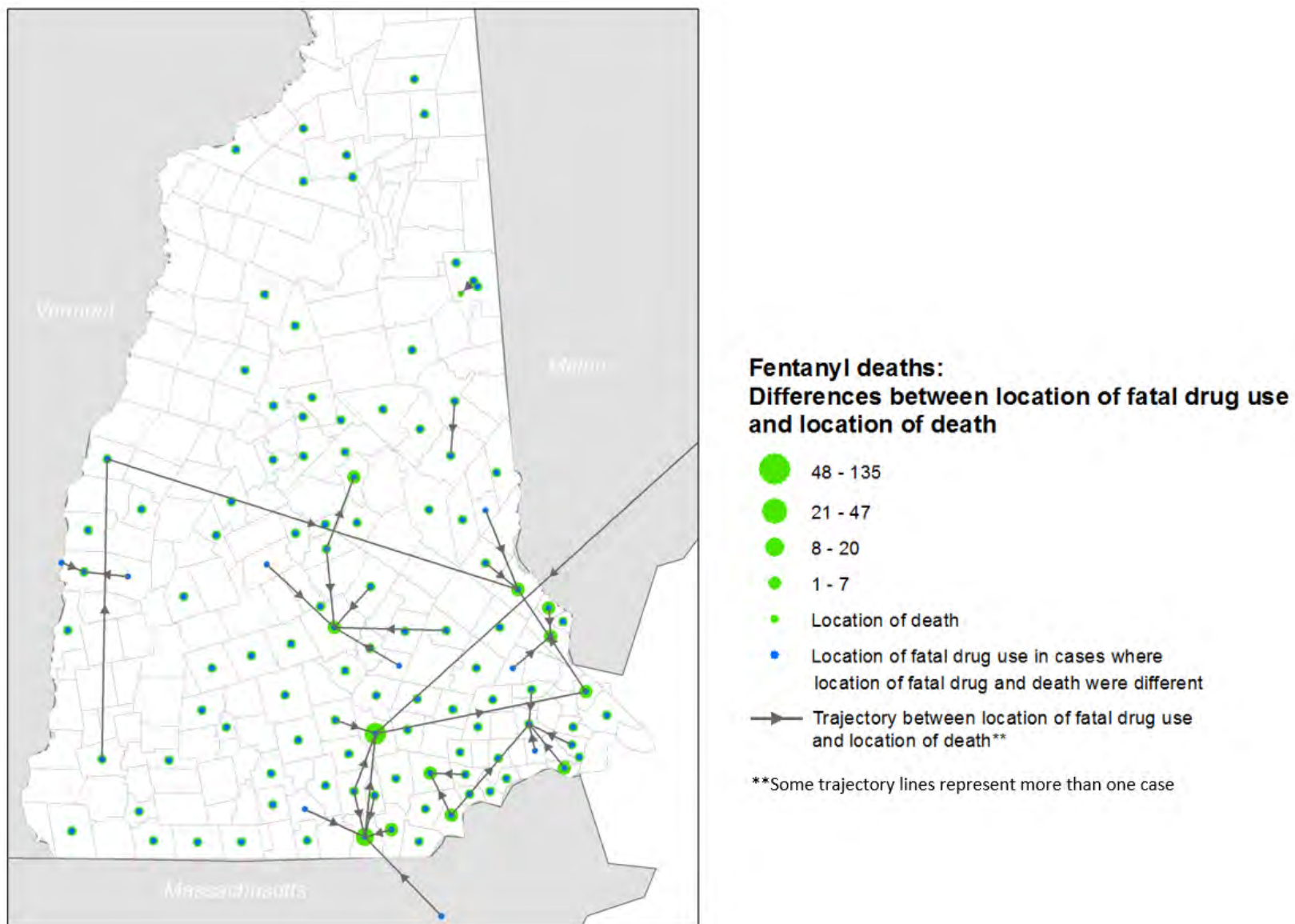


Figure 9. Fentanyl deaths by location of death, depicting travel trajectories between locations of decedent fatal drug use and locations of death in cases where those locations were different

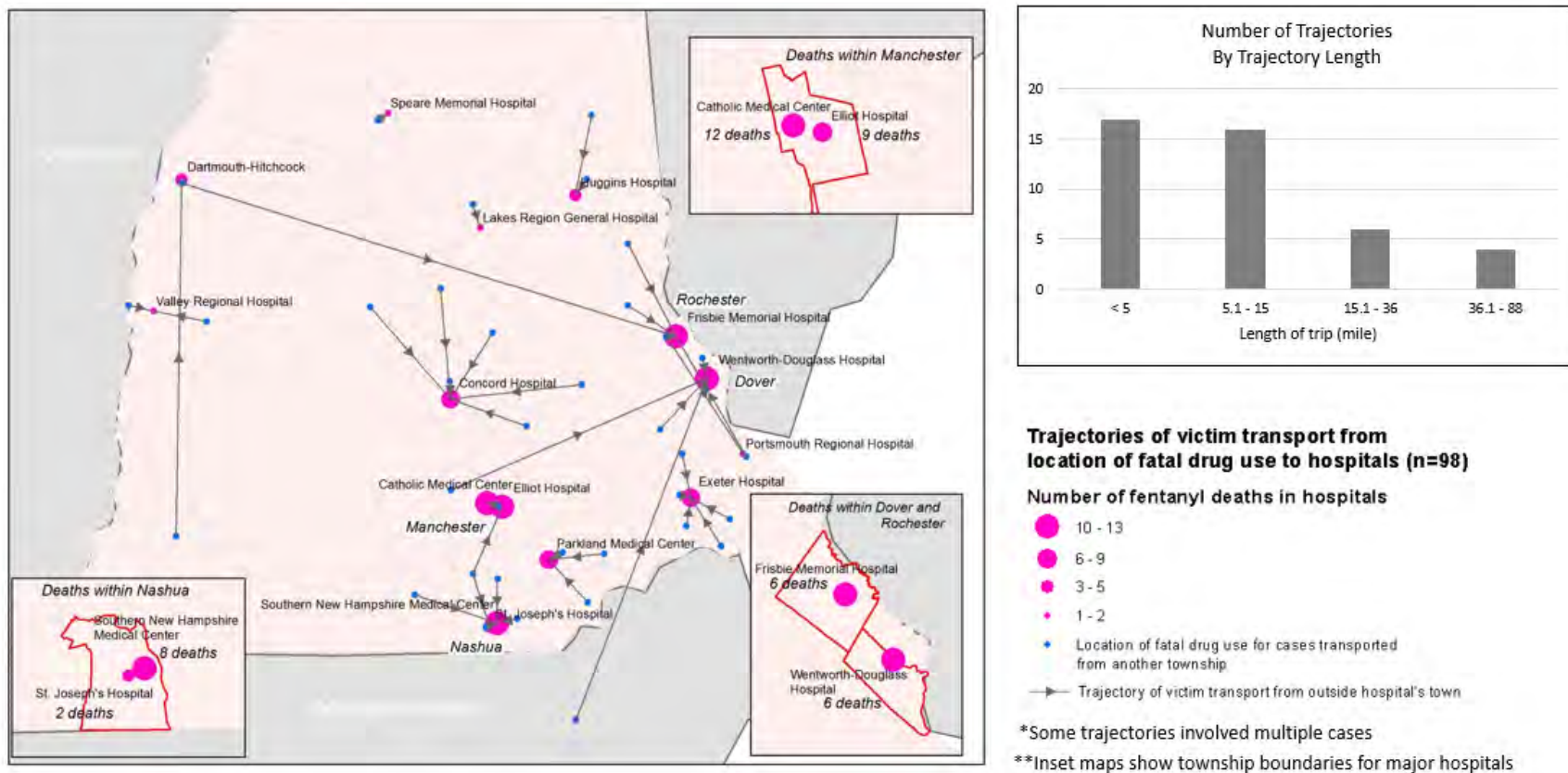


Figure 10. Fentanyl deaths transported to hospitals by hospital location, depicting trajectories of those cases transported from another township

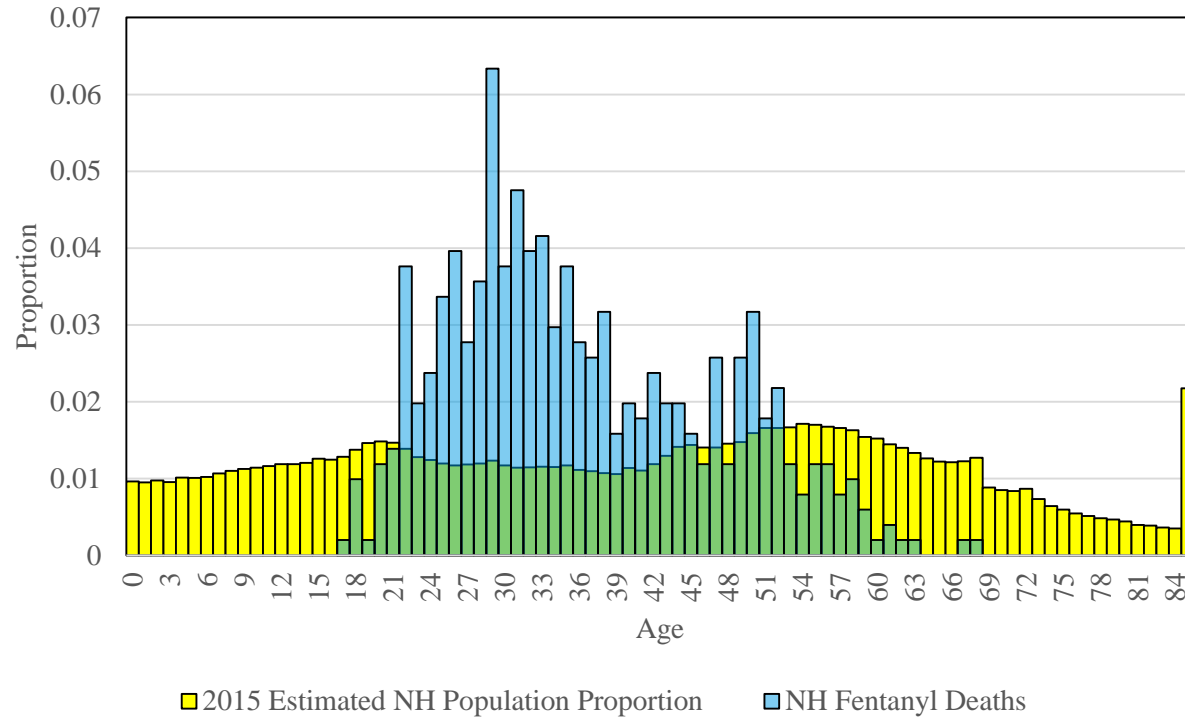


Figure 11. Proportional age distribution of fentanyl deaths compared to the 2015 estimated New Hampshire census population