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Trends in unintentional polysubstance overdose deaths and individual and community correlates of polysubstance overdose, North Carolina, 2009-2018

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Abstract

Background: Polysubstance involvement is increasing among fatal drug overdoses. However, little is known about the epidemiology of polysubstance drug overdoses. This paper describes

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emerging trends in unintentional polysubstance overdose deaths in North Carolina (NC) and examines associations with individual and community factors.

Methods: Using 2009–2018 NC death certificate data, we identified unintentional drug overdose deaths and commonly involved substances (opioids, stimulants, benzodiazepines, alcohol, and antiepileptics). We examined polysubstance combinations, comparing opioid and non-opioid involved deaths. We examined individual level correlates from death certificate data and community level correlates from the American Community Survey and Robert Wood Johnson Foundation County Health Rankings to quantify associations.

Results: From 2009–2018, 53% of opioid and 19% of non-opioid overdose deaths involved multiple substances. During this period, polysubstance overdose death increased dramatically, from 2.9 to 12.1 per 100,000 persons, with the greatest increases among drug combinations involving stimulants. The most common polysubstance combinations were: opioids and stimulants (12.1% of overdose deaths); opioids and benzodiazepines (9.0%); opioids and alcohol (5.1%); opioids, stimulants, and benzodiazepines (3.1%); and opioids, benzodiazepines, and antiepileptics (2.2%). Compared to overdoses involving opioids alone, overdoses involving combinations of opioids, stimulants, and benzodiazepines involved younger individuals (53.7% in 15–34 years of age vs. 40.7%). Men comprised two-thirds of overdoses involving opioids alone, however, overdoses involving opioids, benzodiazepines, and antiepileptics were predominantly among women (60.6%).

Conclusions: Polysubstance involvement has increased among overdose deaths in NC. These findings can be used to inform public health interventions addressing polysubstance deaths and associated individual and community level factors.

Keywords

Drug overdose; Polysubstance use; opioids; stimulants; benzodiazepines; alcohol; antiepileptics

1. Introduction

Drug overdose is a substantial public health problem in the United States (Hedegaard et al., 2020). Opioids have been consistently noted as the foremost contributor to drug overdose deaths (Hedegaard et al., 2020; Scholl et al., 2019). Increases in opioid-involved overdoses since 2013 are largely attributable to the introduction of fentanyl into the drug supply (Spencer et al., 2019). In conjunction with opioids, the emergence or re-emergence of specific substances, such as benzodiazepines and stimulants, have highlighted the importance of conducting ongoing surveillance of changing patterns in overdose deaths (Kariisa et al., 2019; Bachhuber et al., 2016).

Simultaneous use of different substances (i.e., polysubstance use) can increase risk of overdose (Connor et al., 2014; Al-Tayyib et al., 2017; Hernandez et al., 2018). Recent research noted increases in polysubstance overdose deaths (Barocas et al., 2019; Gladden et al., 2019; Golladay et al., 2020; Karissa, et al., 2019; Rhee et al., 2019). To date, most polysubstance overdose research has focused exclusively on deaths involving opioids, has broadly categorized polysubstance (e.g., binary outcomes such as monosubstance versus polysubstance), or has been limited to a select subset of substances (e.g., opioids, stimulants,

benzodiazepines) (Barocas et al., 2019; Gladden et al., 2019; Kandel et al., 2017). Overdose deaths involving non-opioid substances are also increasing, indicating a need for further examination (Ruhm, 2019).

Root causes of the overdose crisis and polysubstance use are complex and attributable to a variety of factors (Dasgupta et al., 2018). To identify factors that may be indicative of the underlying social causes of substance use, it is important to examine both individual and community level characteristics associated with polysubstance overdose deaths.

Accordingly, the purpose of this study was to: 1) identify common polysubstance combinations among overdose decedents and 2) examine individual and community level factors associated with these combinations. Recognizing geographic heterogeneity in types of substances involved in these deaths (Hedegaard et al., 2019), we examined emerging trends in polysubstance overdose deaths in a large southeastern state, North Carolina (NC). This analysis can provide a framework for future geographic-specific comparisons.

2. Material and methods

2.1 Fatal overdose identification:

We used 2009–2018 vital statistics death certificate data for NC residents. All suspected drug overdose deaths in NC are investigated by the Office of the Chief Medical Examiner (NC OCME). In the late 2000s, NC OCME implemented a statewide process to develop standardized assessments and reporting procedures for suspected overdose deaths, including a standard toxicology panel that screens for more than 600 compounds, including fentanyl. We defined overdose deaths as those for which the primary cause of death was certified as an unintentional drug overdose with the International Classification of Disease, 10th revision (ICD-10) codes X40-X44.

2.2 Polysubstance overdose:

We classified overdose deaths into categories based on the substances most frequently listed as contributing causes on the death certificate using ICD-10 T-codes (T36-T51). We categorized contributing substances into the most commonly reported substance classes: opioids (T40.0-T40.4, T40.6), stimulants (T40.5, T43.6), benzodiazepines (T42.4), alcohol (T51.0, T51.1, T51.9, X45, Y15), and antiepileptics (T42.5, T42.6, T42.7). We defined polysubstance deaths as those with more than one substance class listed as a contributing cause and monosubstance deaths as those with only one substance class. Thus, an overdose involving heroin and methamphetamine was considered a polysubstance death, but a death involving multiple opioids (e.g., heroin and fentanyl) was considered monosubstance. Substance classes did not distinguish drug source (i.e. illicit and prescription).

We included substances that were not categorized into one of these classes (e.g., antidepressants, antihistamines, antidiarrheals) in an “other substance” class due to small numbers. The ICD-10 code T50.9 (other and unspecified drugs) is used when a specific substance is unable to be determined or is undistinguishable from other substances. As such, we excluded deaths with *only* T50.9 listed on the death certificate. We assumed that deaths with both a T50.9 code and one other substance code (e.g., T40.1) represented a death with

only one substance class, as the T50.9 code could have been used for another drug in the same class (e.g., in this example, another opioid drug).

Given the large contribution of opioids to overdose deaths, we examined substance combinations separately for opioid and non-opioid involved deaths.

2.3 Individual and Community Characteristics:

We identified individual level demographic characteristics from the death certificate and characteristics of decedents' county of residence from the National Center for Health Statistics (NCHS) for measures of urbanization (Ingram & Franco, 2014), the American Community Survey (ACS) for measures of social and economic factors, and the Robert Wood Johnson Foundation for overall county health outcomes. For each county level characteristic, excluding urbanization, we calculated the median for all NC counties and calculated the percent of overdose deaths for each polysubstance combination occurring in counties below the NC median. We compared individual and county level characteristics for deaths involving only opioids, deaths involving opioids and additional substances, and non-opioid involved deaths.

We calculated frequencies and proportions for specific substance types and combinations using SAS 9.4 (Cary, N.C.). No more than 2% of observations overall had missing data for the selected characteristics; therefore, we did not include missing data in Table 1 calculations. We conducted chi-square statistical tests to compare characteristics of persons who died from polysubstance or non-opioid overdose with those who died from monosubstance opioid overdose. We assessed trends over time using Joinpoint regression analyses to estimate annual changes and corresponding 95% confidence intervals (National Cancer Institute, 2020). This study was approved by the University of North Carolina at Chapel Hill's Institutional Review Board.

3. Results

Of 12,802 unintentional drug overdose deaths among NC residents during 2009–2018, 11,990 (93.7%) had at least one substance identified and 812 (6.4%) had no specific substance listed (i.e., either T50.9 only or no substance code). Of deaths involving one or more substances, the most frequently identified substances included opioids (84.3%), stimulants (30.3%), benzodiazepines (20.2%), alcohol (12.2%), antiepileptics (8.4%), and other substances (9.5%); note that percentages sum to >100% because of polysubstance deaths. From 2009–2018, death rates rose for overdoses involving these substances (Figure 1a). Polysubstance overdoses accounted for 52.5% (n=6,298) of all fatal overdoses.

3.1 Trends in polysubstance overdose:

The rate of polysubstance overdose rose from 2.9 to 12.1 per 100,000 persons from 2009 to 2018. In 2009, polysubstance overdoses accounted for 31.6% (n=268) of unintentional drug overdoses. This rose to 62.3% (n=1,210) by 2018.

Among opioid-involved overdoses, polysubstance involvement was present in 28.0% (n=198) of deaths in 2009 and rose to 69.1% (n=1,141) in 2018 (Figure 1b). Among

overdoses involving opioids, the proportion of deaths involving one additional substance increased by 2.3 percentage points (95% CI=2.0, 2.6) per year (Supplemental Table 1). The proportion involving two additional substances increased and by 2.6 percentage points (95% CI=2.0, 3.2) per year. Likewise, polysubstance was present in 13.4% (n=19) of non-opioid overdoses in 2009 and rose to 23.6% (n=69) in 2018 (Figure 1c). The proportion of non-opioid overdoses involving two substances increased by 0.01 (95% CI= 0.00, 0.02) per year.

The most common polysubstance combinations included opioids and stimulants (n=1,445, 12.1% of overdose deaths); opioids and benzodiazepines (n=1,084, 9.0%); opioids and alcohol (n=617, 5.1%); opioids, stimulants, and benzodiazepines (n=366, 3.1%); and opioids, benzodiazepines, and antiepileptics (n=259, 2.2%). Rates of all combinations increased from 2009 to 2018 (Supplemental Table 2). The largest increases in rates were among overdoses involving opioids and stimulants (annual percent change (APC)=31.2%, 95% CI=22.1%, 41.0%) and opioids, stimulants, and benzodiazepines (APC=45.3%, 95% CI=27.4%, 65.7%) (Figure 1d).

Due to small numbers for specific substance combinations in non-opioid involved deaths, we do not enumerate non-opioid combinations. However, the most common substances included in non-opioid deaths were cocaine (56.7%), alcohol (13.8%), other psychostimulants (11.3%), and benzodiazepines (8.6%). Among overdose deaths involving opioids alone, 19.8% involved more than one type of opioid (polydrug monosubstance opioid deaths) and this rate rose over the study period (0.7 per 100,000 persons in 2009 to 5.5 in 2018).

3.2 Factors associated with polysubstance overdose:

Most overdose deaths involving opioids alone occurred among younger individuals (40.7% ages 15–34 years), men (65.6%), and non-Hispanic whites (90.6%) (Table 1). The reference group for the following individual and community comparisons was overdoses involving opioids alone. Overdoses involving opioids and stimulants (n=1,445) included more individuals who were non-Hispanic Black (14.1% vs. 6.3%) and never married (51.7% vs. 42.9%). Persons who overdosed with opioids and alcohol (n=617) tended to be slightly older (67.9% vs 59.2% 35 years) and were more likely to be men (82.3% vs. 65.6%). Overdoses involving opioids, stimulants, and benzodiazepines (n=366) were more common among individuals aged 15–34 years (53.7% vs. 40.7%). Overdoses involving opioids, benzodiazepines, and antiepileptics (n=259) included more women (60.6% vs 34.3%). Individuals who overdosed with opioids, benzodiazepines, and antiepileptics were more likely to be 35 years or older (81.0% vs. 59.2%). Older age (31.0% vs. 11.9% 55 years) and non-Hispanic Black race (30.8% vs. 6.3%) were more common among non-opioid overdoses.

There were also differences in community characteristics (Table 1). Individuals whose overdose involved opioids and alcohol were more likely to live in a medium or small metropolitan area (55.3% vs. 48.6%). Those who died of overdoses involving opioids and stimulants (79.5%); opioids, stimulants, and benzodiazepines (89.1%); and opioids, benzodiazepines, and antiepileptics (90.0%) were more likely to live in counties with a higher percent of the population insured compared to those involving opioids alone (56.5%). Compared to those whose overdose involved opioids alone (69.8%), those involving opioids

and stimulants (77.6%); opioids and alcohol (75.7%); and opioids, stimulants, and benzodiazepines (76.5%) were more likely to live in counties with higher levels of education. Those whose overdose involved opioids and benzodiazepines (42.1%) and opioids, benzodiazepines, and antiepileptics (44.8%) were more likely to live in counties with worse county health rankings compared to those involving opioids alone (37.1%).

4. Discussion

These results demonstrate an increase in polysubstance overdose deaths, consistent with several other states (Rhee et al., 2019; Gollady et al., 2020). We identified simultaneous opioid and stimulant use as the most common unintentional polysubstance overdose death in NC, similar to studies conducted nationally and in Massachusetts and Tennessee (McCall et al., 2017; Kariisa et al., 2019; Golladay et al., 2020). In addition, we noted increases in all other polysubstance combinations. Alcohol and antiepileptics individually contributed to a sizeable number of overdoses. However, these substances are not a common source of discussion in the literature in comparison to stimulants and benzodiazepines.

Individual and community level characteristics differed by polysubstance combination and may provide insight for public health intervention. Persons who were 15–34 years old comprised more than half of overdoses involving opioids, stimulants, and benzodiazepines, whereas generally 40% or less of other overdose combinations occurred in this age group. Additionally, older individuals were more commonly represented in overdoses involving non-opioids and overdoses involving opioids, stimulants, and antiepileptics. Age may be an important factor when designing prevention strategies for polysubstance overdose.

Men were more commonly represented in all substance combinations except for overdoses involving opioids, benzodiazepines, and antiepileptics, where women comprised 61% of deaths. Some research has suggested that gabapentin, a common antiepileptic, is more commonly misused among women (Smith et al., 2015). In addition to its use as an antiepileptic, clinical use of gabapentin includes a mental health disorder treatment and pain control. Reported reasons for gabapentin misuse include enhancing the high associated with other substances and alleviating opioid withdrawal symptoms (Quintero, 2017). Future research should further explore reasons for use and misuse, particularly among women, and risks associated with simultaneous use of opioids and gabapentin.

At the community level, economic and social characteristics varied across substance combinations. For example, persons whose overdose involved three substances (i.e., opioids, stimulants, and benzodiazepines; opioids, benzodiazepines, and antiepileptics) resided in counties with higher health insurance coverage. This may suggest possible associations with health care access, which could influence the availability of prescription drugs. Additional research is needed to explore the source of these substances (prescription vs. illicit) and availability of non-pharmacologic treatments to manage conditions for which these drugs might be dispensed.

Our analysis has limitations. First, the substance classes are broad and can contain a variety of drugs within each class. For example, the opioid category includes both prescription and

illicit drugs and does not explicitly distinguish fentanyl from other opioids. Given increases in fentanyl-involved overdoses, future research may benefit from examinations of both polysubstance (e.g., opioids and stimulants) and polydrug (e.g., fentanyl and heroin) trends. While specific drugs may differ within substance classes, these classes are still useful in describing emerging patterns that can be further explored using toxicology or literal text data. Second, there is potential for misclassification of intent of drug overdose deaths (Rockett et al., 2015). Undetermined overdoses were not included in this analysis but comprised 2.6% of overdose deaths from 2009–2018. Third, improved toxicology testing could be partially responsible for some observed trends. While the percent of overdose deaths with an autopsy conducted has remained relatively stable, suggesting consistency in specific substance testing practices, the percent of drug overdoses without a specific substance listed varied from 2.4% in 2016 to 14.7% in 2011. However, these variations cannot fully account for changes in observed trends. Last, data are limited to deaths among NC residents and may not be representative of other states and countries. However, these results are useful for illuminating changes in substances contributing to overdose deaths over time and identifying populations that may be more likely to die as a result of particular combinations of substances. Results can be replicated and compared across other local areas to identify unique geographic and temporal patterns and inform both global and local prevention efforts.

This analysis presents critical data on emerging polysubstance patterns and associated factors. Overdose prevention efforts, such as naloxone distribution programs, should include education of risks associated with polysubstance use, particularly for substances posing a greater risk of overdose when used in combination with opioids. A singular focus on one specific substance class, such as opioids, is unable to provide public health practitioners with the context needed to adequately address the evolving state of the overdose crisis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

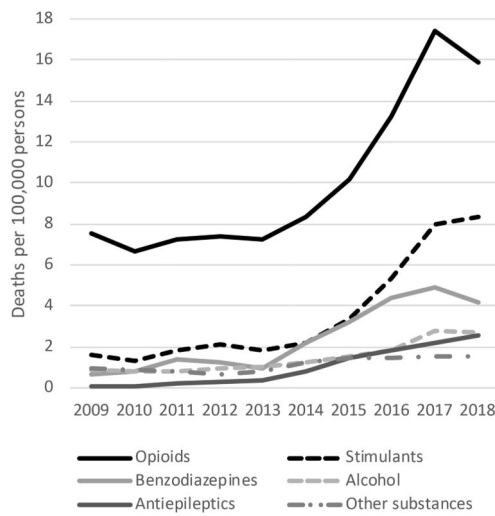
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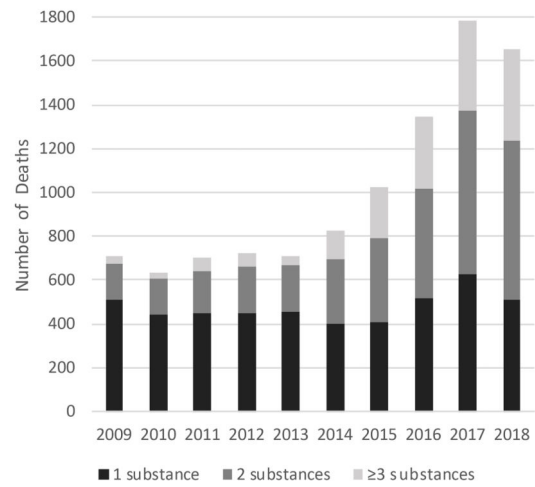
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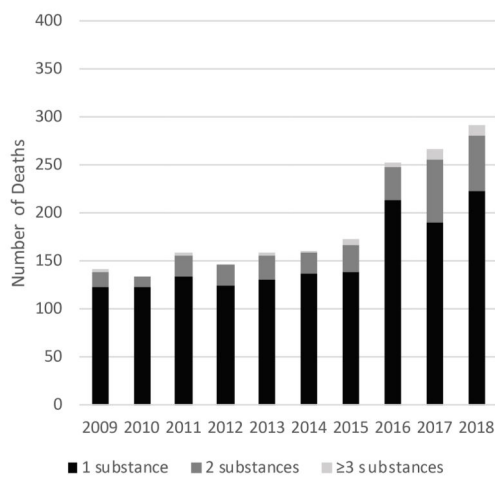
(a) Common substances involved in drug overdose deaths (n=11,990)^b



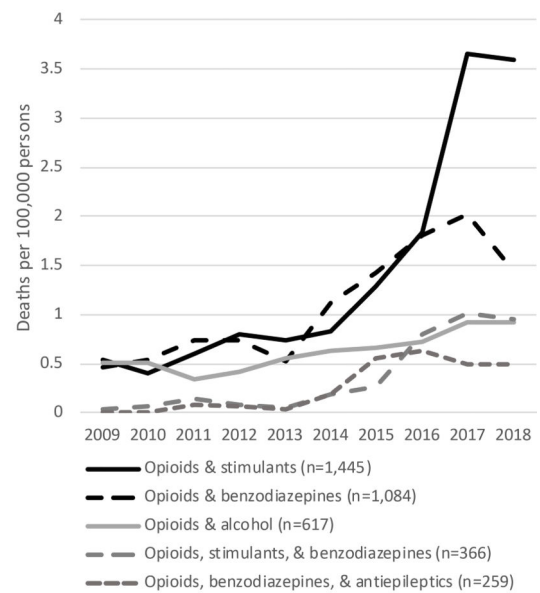
(b) Number of substances involved in opioid overdose deaths (n=10,108, 84% of drug overdose deaths)



(c) Number of substances involved in non-opioid deaths (n=1,882, 16% of drug overdose deaths)



(d) Common polysubstance combinations involving opioids (n=3,771)



^aData include unintentional drug overdose deaths with at least one substance indicated.

^bA single death could be present in multiple lines.

Figure 1: Trends in unintentional drug overdose deaths in North Carolina, 2009–2018 (n=11,990).^a

^aData include unintentional drug overdose deaths with at least one substance indicated.

^bA single death could be present in multiple lines.

Table 1.

Individual and community characteristics of unintentional overdose deaths involving opioids alone, common polysubstance overdose deaths, and non-opioid overdose deaths, North Carolina, 2009–2018.^a

| | Monosubstance Overdose | | | | | | Polysubstance Overdose | | | | | | | | | | |
|--------------------------------------|------------------------|----|----------------------|----|---------|---------------------------|------------------------|-------------------|-------|----|--|-------|----|--|-------|----|---------|
| | Opioids alone | | Opioids & stimulants | | P | Opioids & benzodiazepines | | Opioids & alcohol | | | Opioids, stimulants, & benzodiazepines | | | Opioids, benzodiazepines, antiepileptics | | | |
| | N=4,763 | % | N=1,445 | % | | N=1,084 | % | P | N=617 | % | P | N=366 | % | P | N=259 | % | P |
| Individual Characteristics | | | | | | | | | | | | | | | | | |
| Age group | | | | | 0.004 | | | 0.56 | | | <0.0001 | | | <0.0001 | | | <0.0001 |
| 15–34 | 1935 | 41 | 598 | 41 | | 435 | 40 | | 198 | 32 | | 196 | 54 | | 49 | 19 | |
| 35–44 | 1174 | 25 | 399 | 28 | | 251 | 23 | | 177 | 29 | | 94 | 26 | | 68 | 26 | |
| 45–54 | 1076 | 23 | 318 | 22 | | 255 | 24 | | 177 | 29 | | 49 | 13 | | 87 | 34 | |
| 55 | 564 | 12 | 127 | 9 | | 140 | 13 | | 65 | 11 | | 26 | 7 | | 54 | 21 | |
| Sex | | | | | 0.05 | | | 0.35 | | | <0.0001 | | | 0.87 | | | <0.0001 |
| Female | 1634 | 34 | 456 | 32 | | 388 | 36 | | 109 | 18 | | 124 | 34 | | 157 | 61 | |
| Male | 3129 | 66 | 989 | 69 | | 696 | 64 | | 508 | 82 | | 242 | 66 | | 102 | 40 | |
| Race/ethnicity | | | | | <0.0001 | | | 0.073 | | | <0.0001 | | | 0.008 | | | 0.82 |
| Black, non-Hispanic | 298 | 6 | 203 | 14 | | 46 | 4 | | 55 | 9 | | 38 | 10 | | 15 | 6 | |
| Hispanic | 66 | 1 | 26 | 2 | | 13 | 1 | | 22 | 4 | | 7 | 2 | | 2 | 1 | |
| White, non-Hispanic | 4308 | 91 | 1181 | 82 | | 1004 | 93 | | 522 | 85 | | 312 | 85 | | 237 | 92 | |
| Other | 79 | 2 | 31 | 2 | | 16 | 1 | | 16 | 3 | | 9 | 2 | | 5 | 2 | |
| Education | | | | | 0.01 | | | 0.071 | | | 0.39 | | | 0.49 | | | 0.19 |
| Less than high school | 1205 | 25 | 418 | 29 | | 305 | 28 | | 166 | 27 | | 90 | 25 | | 79 | 31 | |
| High school | 2072 | 44 | 622 | 43 | | 437 | 40 | | 252 | 41 | | 162 | 44 | | 99 | 38 | |
| Some college or Associate's degree | 1103 | 23 | 310 | 21 | | 269 | 25 | | 145 | 24 | | 91 | 25 | | 63 | 24 | |
| College or beyond | 326 | 7 | 77 | 5 | | 64 | 6 | | 51 | 8 | | 18 | 5 | | 15 | 6 | |
| Marital status | | | | | <0.0001 | | | 0.19 | | | 0.12 | | | <0.0001 | | | <0.0001 |
| Never married | 2026 | 43 | 735 | 51 | | 482 | 45 | | 274 | 44 | | 224 | 61 | | 68 | 26 | |
| Married | 1344 | 28 | 311 | 22 | | 313 | 29 | | 149 | 24 | | 64 | 18 | | 90 | 35 | |
| Widowed or divorced | 1345 | 28 | 377 | 26 | | 276 | 26 | | 185 | 30 | | 74 | 20 | | 97 | 38 | |
| Community Characteristics | | | | | | | | | | | | | | | | | |
| Resident of a county by urbanization | | | | | 0.02 | | | 0.73 | | | 0.006 | | | 0.32 | | | 0.13 |
| Large metropolitan | 1359 | 29 | 460 | 32 | | 302 | 28 | | 147 | 24 | | 116 | 32 | | 60 | 23 | |

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| | Monosubstance Overdose | | | | | | | | Polysubstance Overdose | | | | | | | | |
|--|------------------------|----|----------------------|----|---------|---------------------------|----|---------|------------------------|----|-------|--|----|---------|--|----|---------|
| | Opioids alone | | Opioids & stimulants | | | Opioids & benzodiazepines | | | Opioids & alcohol | | | Opioids, stimulants, & benzodiazepines | | | Opioids, benzodiazepines, antiepileptics | | |
| | N=4,763 | % | N=1,445 | % | P | N=1,084 | % | P | N=617 | % | P | N=366 | % | P | N=259 | % | P |
| Medium or small metropolitan | 2314 | 49 | 693 | 48 | | 522 | 48 | | 341 | 55 | | 176 | 48 | | 130 | 50 | |
| Micropolitan or noncore | 1090 | 23 | 292 | 20 | | 260 | 24 | | 129 | 21 | | 74 | 20 | | 69 | 27 | |
| Resident of a county where % of population having a Bachelor's degree was: | | | | | <0.0001 | | | 0.082 | | | 0.002 | | | 0.007 | | | 0.31 |
| NC median | 3323 | 70 | 1122 | 78 | | 727 | 67 | | 467 | 76 | | 280 | 77 | | 173 | 67 | |
| < NC median | 1440 | 30 | 323 | 22 | | 357 | 33 | | 150 | 24 | | 86 | 24 | | 86 | 33 | |
| Resident of a county where % of population in the workforce was: | | | | | 0.001 | | | 0.007 | | | 0.14 | | | 0.10 | | | <0.0001 |
| NC median | 3592 | 76 | 1153 | 80 | | 775 | 72 | | 482 | 78 | | 290 | 79 | | 165 | 64 | |
| < NC median | 1171 | 25 | 293 | 20 | | 309 | 29 | | 135 | 22 | | 76 | 21 | | 94 | 36 | |
| Resident of a county where % of population with health insurance was: | | | | | <0.0001 | | | <0.0001 | | | 0.00 | | | <0.0001 | | | <0.0001 |
| NC median | 2690 | 57 | 1149 | 80 | | 804 | 74 | | 396 | 64 | | 326 | 89 | | 233 | 90 | |
| < NC median | 2073 | 44 | 297 | 21 | | 280 | 26 | | 221 | 36 | | 40 | 11 | | 26 | 10 | |
| Resident of a county where % of population below the poverty line was: | | | | | 0.002 | | | 0.40 | | | 0.61 | | | 0.001 | | | 0.74 |
| NC median | 1406 | 30 | 366 | 25 | | 306 | 28 | | 176 | 29 | | 79 | 22 | | 74 | 29 | |
| < NC median | 3357 | 71 | 1079 | 75 | | 778 | 72 | | 441 | 71 | | 287 | 79 | | 185 | 72 | |
| Resident of a county in where county health outcome ranking was: | | | | | 0.15 | | | 0.002 | | | 0.042 | | | 0.55 | | | 0.013 |
| NC median | 1767 | 37 | 506 | 35 | | 456 | 42 | | 203 | 33 | | 130 | 36 | | 116 | 45 | |
| < NC median | 2996 | 63 | 939 | 65 | | 628 | 58 | | 414 | 67 | | 236 | 65 | | 143 | 55 | |

^aNumbers reflected in this table include: unintentional drug overdose with at least one substance indicated (n=11,990). Monosubstance includes opioids alone (n=4,763). Polysubstance includes: opioids & stimulants (n=1,445), opioids & benzodiazepines (n=1,084), opioids & alcohol (n=617), opioids, stimulants, & benzodiazepines (n=366), and opioids, stimulants, & antiepileptics (n=259). Polysubstance or monosubstance include non-opioids (n=1,882).

^bPolysubstance combinations could include any combination of the following substance categories: opioids, stimulants, benzodiazepines, alcohol, antiepileptics, or other substances. Specific combinations listed are the five most common combinations identified during 2009–2018.

^cIncludes any drug overdose deaths where at least one non-opioid substance was listed without the presence of an opioid.

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^dP values correspond to chi square statistical test results comparing each substance combination category with those in the opioids alone category.

^eThe following characteristics were dichotomized using the state median (median value in parentheses): health insurance (85.6), poverty line (18.0), bachelor's degree (18.4), workforce (58.1), and health outcomes (50th ranked county). For example, among persons who fatally overdosed from opioids alone, 69.8 resided in a county where the county's population with a bachelor's degree was above the median for all counties in North Carolina.

^fCounty health outcomes rankings are based on the Robert Wood Johnson Foundation County Health Rankings, which rank each county within the state from best to worst health outcomes. Health outcome rankings are based on premature death, self-reported health status, and percent of newborns who are low birthweight. Rankings higher than NC median indicate worse health outcomes.