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Increased risk of opioid overdose death following cold weather: A case–crossover study

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Abstract

Background: The United States is in the midst of an opioid overdose crisis. Little is known about the role of environmental factors in increasing risk of fatal opioid overdose.

Methods: We conducted a case–crossover analysis of 3,275 opioid overdose deaths recorded in Connecticut and Rhode Island in 2014–2017. We compared the mean ambient temperature on the day of death, as well as average temperature up to 14 days prior to death, to referent periods matched on year, month, and day of week.

Results: Low average temperature over the 3 to 7 days prior to death were associated with higher odds of fatal opioid overdose. Relative to 11°C, an average temperature of 0°C over the 7 days prior to death was associated with a 30% higher odds of death (OR: 1.3; 95% CI: 1.1–1.5).

Conclusions: Low average temperature may be associated with higher risk of death due to opioid overdose.

Keywords

Drug Overdose; Temperature; Analgesics; Opioid; Fentanyl; New England

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Conflicts of Interest: None declared.

Data Access: Given the sensitive nature of overdose deaths, the raw data used in this study on accidental drug-related deaths in Rhode Island cannot be made available. However, the raw data on accidental drug-related deaths in Connecticut is available online in the public domain from the Office of the Chief Medical Examiner. The raw data on ambient temperature is available online in the public domain from the PRISM Climate Group of Oregon State University. All R code used to generate the case–crossover dataset and fit the conditional logistic regression models are available in the Digital Repository of Brown University.

INTRODUCTION

The United States is experiencing an epidemic of opioid overdose with more than 300,000 opioid-related overdose deaths occurring since 2000.[1,2] The rate of fatal opioid overdose continues to increase, driven largely by the involvement of highly potent synthetic opioids, such as fentanyl and its related analogs.[3,4]

Although the proximal causes of opioid overdose death are well studied,[5] the risk of fatal drug overdose may be intensified by environmental exposures that influence the pharmacologic effects of substances.[6–9] For example, previous research suggests that the risk of death from cocaine overdose is associated with higher outdoor temperatures,[10–12] putatively because cocaine use increases core body temperature, decreases heat perception, and impairs sweating and skin blood flow, thus increasing the risk of hyperthermia on hot days.[13] Opioids are also known to affect thermoregulation, reducing core temperature and the temperature thresholds for both shivering and vasoconstriction.[14,15] Moreover, cold weather[16] and opioids[17] both promote respiratory depression, although whether opioids modify the respiratory response to cold weather has not been documented. Given the potential adverse interactions between cold weather and opioids, the risk of fatal opioid overdose may be increased at low temperatures. However, to our knowledge, this hypothesis has not been previously examined. Accordingly, we evaluated the association between daily changes in ambient temperature and acute risk of fatal opioid overdose in two states in New England (Connecticut and Rhode Island), hypothesizing that colder temperatures would be associated with higher risk of opioid overdose death.

METHODS

Data Sources

We conducted a retrospective case review of accidental drug overdose fatalities occurring in Connecticut and Rhode Island between January 1, 2014 and June 30, 2017.[18,19] Deaths were considered to be confirmed accidental drug overdose fatalities if: (a) the death was pronounced in Connecticut or Rhode Island; (b) the final manner of death was deemed an accident by the medical examiner; and (c) a drug is listed on the death certificate as the primary cause of death or a significant contributing factor. For our analyses, cases were limited to those that listed an opioid on the death certificate. Data regarding the demographic characteristics of the decedent, toxicologic analyses, and circumstances of the overdose were abstracted from medical examiner files. As all patient data was de-identified, the study was deemed exempt from ethics review by the Rhode Island Department of Health.

We obtained daily estimates of population-weighted mean temperature and relative humidity for each of the 13 counties in the study area using a gridded meteorologic dataset as previously described.[20] We linked a daily temperature time-series to each death by the recorded date of death and the reported county of overdose occurrence. Our primary hypothesis focused on the risk of opioid overdose death associated with average temperature on the day of death, but we also calculated the average temperature over the 1 to 14 days prior to death, given prior research demonstrating the cumulative associations between cold weather and mortality.[21]

Analytical Approach

We used a time-stratified case–crossover design[22] to assess the association between ambient temperature and the odds of opioid overdose death. This method is suitable for evaluating the effects of time-varying exposures that transiently and acutely increase the risk of events with a clear onset time.[23] In this design, each individual's exposure immediately before the event is compared to that same individual's exposure during referent periods in which the outcome did not occur (see eFigure). Because exposures during case and referent periods were matched within individuals, characteristics that were relatively stable over time (such as sex, race/ethnicity, socioeconomic status, living conditions, and medical history) did not confound the results.[24]

We matched each death to 3 or 4 referent days occurring in the same year, month, and day of week. This matching strategy enabled us to isolate the effect of short-term changes in temperature on risk of overdose death that were not confounded by seasonal patterns or other long-term time trends. We used conditional logistic regression to estimate odds ratios (OR) and 95% confidence intervals (CI) for the association, adjusting for relative humidity and federal holidays (as patterns of substance use may be different on federal holidays).[25,26] To allow for potential non-linear exposure–response functions, we modeled temperature as a continuous variable using a natural cubic spline with three knots. We calculated all ORs relative to the median temperature observed during the study period (11°C). In a sensitivity analysis, we removed all deaths involving cocaine since the risk of fatal cocaine overdose may be elevated at high ambient temperatures.[10–12] All analyses were conducted in R Studio (Version 1.1.456).

RESULTS

There were 3,275 documented opioid overdose deaths in Connecticut ($n = 2{,}417$) and Rhode Island ($n = 858$) during the study period, predominantly among males (73%, Table). One in three deaths were among individuals under 35 years old (35%). Opioid overdose deaths involved a median of two substances (IQR: 2–3), with a median of one opioid drug (IQR: 1–2) and one non-opioid drug (IQR: 0–2). The most common opioid drugs implicated were heroin (55%) and fentanyl and related analogs (46%), while the most common non-opioid drugs were alcohol (25%) and cocaine (26%).

The association between temperature and risk of fatal opioid overdose appeared non-linear. Although there was no apparent association between low temperatures on the day of death and the risk of fatal opioid overdose (Figure 1A), low average temperatures averaged over 3 to 7 days prior to death (Figure 1 B) were associated with greater odds of death (Figure 2). For example, relative to 11°C, an average temperature of 0°C over the 7 days prior to death was associated with 30% higher odds of death (OR: 1.3; 95% CI: 1.1–1.5). Effect estimates were generally larger in sensitivity analyses excluding deaths also involving cocaine (eTable).

DISCUSSION

Our findings provide preliminary evidence for an association between cold ambient temperatures and higher risk of opioid overdose death. Although this association has not been previously reported, there are several pathways by which cold weather may plausibly contribute to the risk of opioid overdose death. First, the combination of opioid use and cold temperatures may act in synergy to depress respiratory function, thereby increasing the risk of death by respiratory failure. Second, opioids may adversely impact users' ability to thermoregulate during periods of cold weather, again raising the risk of death. Third, cold temperatures may alter patterns of drug use or impact networks of opioid supply and distribution. For example, opioid overdose deaths may be associated with cold weather if individuals are more likely to use opioids alone (i.e., in the absence of a bystander capable of administering the reversal agent naloxone if needed) during periods of cold weather. Similarly, cold weather may also alter patterns of drug trafficking and distribution, particularly during storms, potentially increasing the risk unintentional consumption of drugs adulterated with potent synthetic opioids. Further research should determine whether inclement weather or other noteworthy climatic events (e.g., blizzards) might explain some of the observed results.

Contrary to our primary hypothesis, cold temperature on the day of death was not associated with an increased likelihood of opioid overdose mortality. It is possible that this null association may be explained by some degree of misclassification regarding the timing of death, which is estimated during autopsy and may be inaccurate for some cases, particularly those that are not identified until several days after the overdose occurs. Nonetheless, our findings are consistent with the hypothesis that multiple days of cold weather exposure have a cumulative effect on fatal opioid overdose. The observed associations were also similar in sensitivity analyses restricted to deaths not involving cocaine. Nonetheless, future research is needed to quantify the extent to which observed associations may be altered in fatalities implicating multiple substances with varying impacts on thermoregulation.

These preliminary findings are not without limitation. First, the relatively small sample size limits statistical power, particularly at the extremes of temperature. Second, there are several sources of potential exposure classification, including a lack of knowledge about the geographic locations of individuals in the days leading up to death and whether individuals were indoors at the time of death. Third, the results may be subject to confounding by the presence of other meteorologic conditions. Fourth, we are unable to elucidate the mechanisms by which cold temperatures may alter the risk of opioid overdose death. Moreover, we are not able to distinguish whether cold temperatures are associated with the risk of experiencing an opioid overdose (regardless of whether or not it is fatal) rather than the risk of death conditional on experience of an opioid overdose. Fifth, the restriction of the sample to two states in New England may limit the generalizability of the results.

In summary, this study provides initial evidence that opioid overdose deaths are more common at lower temperatures. Further research is required to confirm or refute these findings, characterize associations in locations with varying weather patterns, and identify the potential pathways by which "cold snaps" may alter the risk of overdose death.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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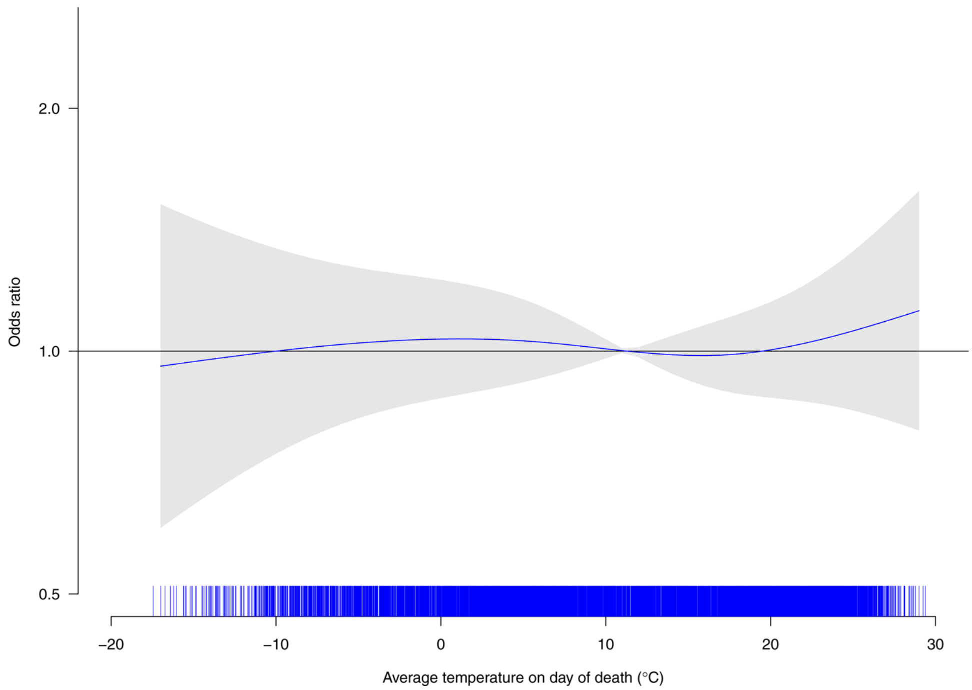

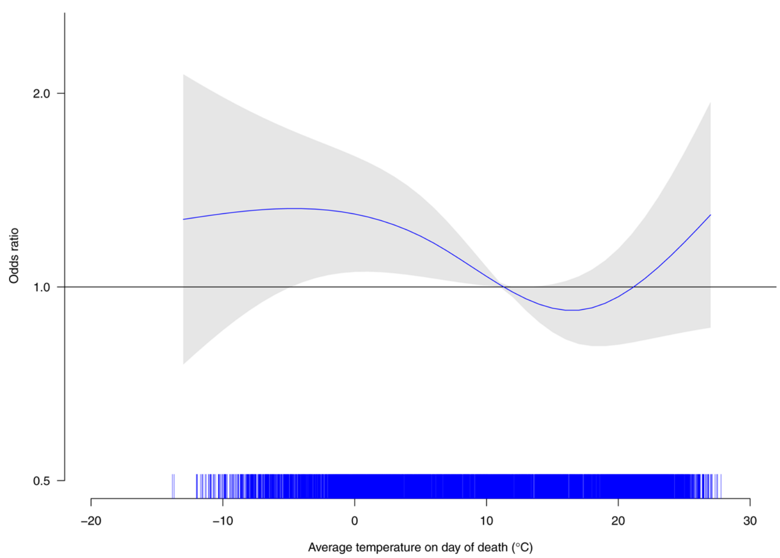

Figure 1.

Non-linear association of average temperature on the day of death (Panel A) and over the seven days (Panel B) prior to death with odds of opioid-involved overdose death in Connecticut and Rhode Island, January 2014 – June 2017 (*n* = 3,275)

Panel A

Panel B

Note: Case and referent periods were matched on year, month, and day of week and the association was adjusted for relative humidity and federal holidays.

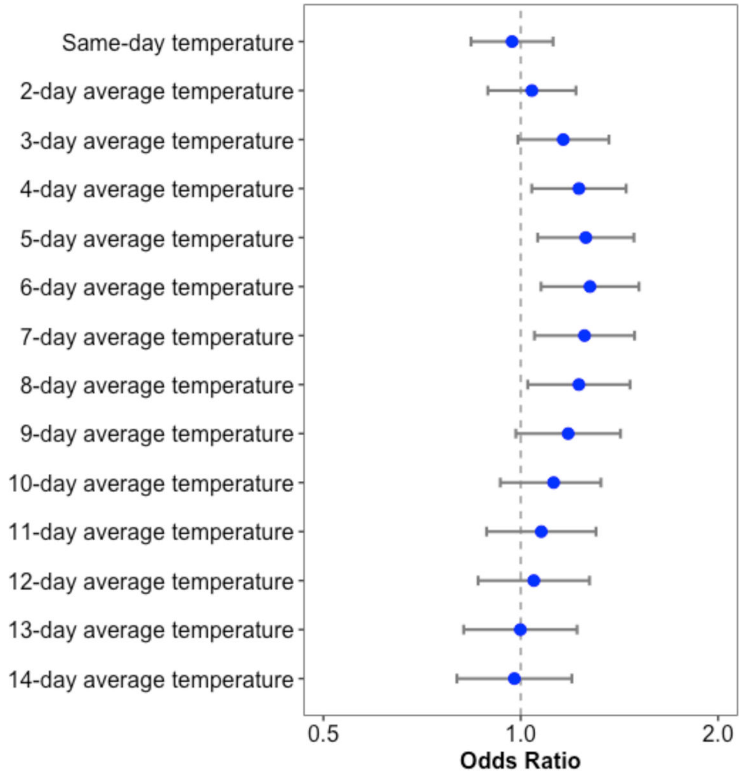

Figure 2.
Odds of opioid-involved overdose death at an average temperature at 0°C relative to the odds of opioid-involved overdose death at an average temperature of 11°C among deaths occurring in Connecticut and Rhode Island, January 2014 – June 2017 (n = 3,275)
Note: Case and referent periods were matched on year, month, and day of week and all associations are adjusted for relative humidity and federal holidays.

Table.

Characteristics of unintentional drug overdose deaths involving opioids in Connecticut and Rhode Island, January 2014 to June 2017 (*n* = 3,275)

	Overall (*n* = 3,275)	Connecticut (*n* = 2,417)	Rhode Island (*n* = 858)
Year, % (*n*)			
Jan. to Dec. 2014	21 (682)	20 (474)	24 (208)
Jan. to Dec. 2015	27 (884)	26 (634)	29 (250)
Jan. to Dec. 2016	34 (1118)	35 (841)	32 (277)
Jan. to June 2017	18 (591)	19 (468)	14 (123)
Age, % (*n*)			
18 to 24 years old	8 (255)	8 (182)	9 (73)
25 to 34 years old	27 (870)	26 (617)	29 (253)
35 to 44 years old	23 (759)	24 (579)	21 (180)
45 to 54 years old	25 (820)	25 (615)	24 (205)
55 years and older	17 (571)	18 (424)	17 (147)
Sex, % (*n*)			
Female	27 (878)	26 (629)	2 (249)
Male	73 (2397)	74 (1788)	71 (609)
Substances Involved (Opioids), % (*n*)			
Heroin	55 (1794)	64 (1547)	29 (247)
Fentanyl (includes fentanyl analogues)	46 (1495)	42 (1012)	56 (483)
Oxycodone	14 (471)	15 (359)	13 (112)
Methadone	11 (359)	11 (261)	11 (98)
Substances Involved (Non-Opioids), % (*n*)			
Alcohol	25 (831)	26 (631)	23 (200)
Cocaine	26 (844)	25 (594)	29 (250)
Alprazolam	12 (405)	13 (314)	11 (91)
Clonazepam	8 (254)	9 (214)	5 (40)
Diazepam	6 (207)	7 (167)	5 (40)
Substances Involved (Median [IQR])			
Total Number of Drugs Involved	2 (2–3)	3 (2–3)	2 (1–3)
Total Number of Opioid Drugs Involved	1 (1–2)	1 (1–2)	1 (1–2)
Total Number of Non-Opioid Drugs Involved	1 (0–2)	1 (0–2)	1 (0–2)