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Original Contribution

Mortality Among Young Injection Drug Users in San Francisco: A 10-Year Follow-up of the UFO Study

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This study examined associations between mortality and demographic and risk characteristics among young injection drug users in San Francisco, California, and compared the mortality rate with that of the population. A total of 644 young (<30 years) injection drug users completed a baseline interview and were enrolled in a prospective cohort study, known as the UFO ("U Find Out") Study, from November 1997 to December 2007. Using the National Death Index, the authors identified 38 deaths over 4,167 person-years of follow-up, yielding a mortality rate of 9.1 (95% confidence interval: 6.6, 12.5) per 1,000 person-years. This mortality rate was 10 times that of the general population. The leading causes of death were overdose (57.9%), self-inflicted injury (13.2%), trauma/accidents (10.5%), and injection drug user-related medical conditions (13.1%). Mortality incidence was significantly higher among those who reported injecting heroin most days in the past month (adjusted hazard ratio = 5.8, 95% confidence interval: 1.4, 24.3). The leading cause of death in this group was overdose, and primary use of heroin was the only significant risk factor for death observed in the study. These findings highlight the continued need for public health interventions that address the risk of overdose in this population in order to reduce premature deaths.

drug users; epidemiology; hepatitis C; mortality; overdose; young adult

Abbreviations: CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ICD, *International Classification of Diseases*; IDU, injection drug user; IQR, interquartile range; IRR, incidence rate ratio; NDI, National Death Index; UFO, "U Find Out."

Injection drug use has been associated with excess morbidity and mortality (1, 2). A number of studies have reported incidence that greatly exceeds that of the general population (3–5). Risk factors that have been associated with mortality among injection drug users (IDUs) from prior studies include infectious diseases, such as human immunodeficiency virus (HIV) and hepatitis C virus (HCV) (3, 6–8). Given improvements in medical care for HIV and HCV as well as more widespread implementation of public health interventions for IDUs (needle exchange, overdose prevention, opiate substitution treatment, and so on), current studies are needed to assess whether the incidence and causes of mortality have shifted over time. Additionally, studies of unique subpopulations such as young IDUs are needed to understand the patterns and risk factors for mortality in order to inform future tailored interventions.

The current study was undertaken to assess the incidence of mortality and risk factors for mortality among young injection drug users in San Francisco, California. Given that the UFO ("U Find Out") Study has been collecting detailed information on young IDUs since the late 1990s, it provides a unique opportunity to study mortality trends and risk factors for mortality in this population. The specific aims of the study were as follows: 1) to investigate trends in mortality incidence overall and overdose-specific mortality, 2) to calculate standardized mortality ratios, and 3) to identify risk factors for mortality in young injectors in San Francisco between 1997 and 2007.

MATERIALS AND METHODS

Beginning in 1997, young (<30 years) IDUs in San Francisco have been offered participation in multiple prospective studies under variations of the shared title known as the UFO Study and described previously (9–11). In brief, young IDUs were recruited by peer outreach workers familiar with neighborhoods in San Francisco where young IDUs congregate, using study invitation cards and flyers, contacts with youth friendly neighborhood groups and community providers, and word of mouth. Inclusion criteria for screening were the following: 1) less than 30 years of age; 2) self reported use of injection drugs in the past 30 days, 3) ability to provide informed consent, 4) understanding spoken English and, after 2005, 5) self-reported HCV-negative or unknown status. The UFO Study had 3 waves of data collection between November 1997 and December 2007. In the first wave from 1997 to 1999, subjects completed a baseline screening interview and underwent counseling and serologic testing for HIV, hepatitis B, and hepatitis C virus. Subjects without evidence of acute or chronic hepatitis B virus (HBV) infection or immunization to HBV were eligible for enrollment in a prospective study of HBV vaccination (UFO-2 Study). Starting in 2000, subjects who were HCV negative at the baseline screening were eligible for enrollment into the UFO-3 Study. The UFO-3 Study had 2 waves of recruitment, from 2000 to 2002 and from 2003 to 2007. Participants were included in this analysis only if they were enrolled prior to December 31, 2007, the end date for searching for death records. All research protocols and informed consent were approved by the Institutional Review Board of the University of California, San Francisco.

Survey instrument and measures

Eligible consenting participants were interviewed, counseled, and tested for antibodies to HCV (anti-HCV) and presence of viremia (HCV RNA) at baseline. Follow-up included monthly ''check-ins'' and quarterly study visits that included structured interviews to assess risk (principally drug-related and sexual) exposures, HCV status (including anti-HCV and HCV RNA testing), and risk reduction counseling and referrals. In the first and second study waves, testing for antibodies to HIV and HBV was performed at baseline and follow-up visits. Deaths were ascertained though the National Death Index (NDI) through the end of 2007. Methods for establishing a match are described in detail on the NDI Web site (http://www.csc.gov/nchs/ndi.htm). In brief, records are matched by first and last name, date of birth, sex, and state of birth. Causes of death were obtained from the NDI-Plus. The underlying cause of death was based on the *International Classification of Diseases* (ICD), Tenth Revision. The primary outcome for this analysis was date of death as identified by an NDI match. Causes of death were reviewed, and overdose death was defined as ICD, Tenth Revision, codes X42, X44, X62, and Y14. Sociodemographic variables included in the analyses were age, gender, race/ethnicity (Caucasian vs. non-Caucasian), educational level (less than high school vs. high school or greater), recent (past 3 months) homelessness, and incarceration. Starting in wave 2, participants were asked about participation in drug treatment programs in the past 3 months and in the past week in wave 3. Recent drug treatment programs included drug detoxification, residential treatment, methadone or buprenorphine maintenance, and 12-step programs. Risk-related exposures included duration of injection drug use; frequency of injection; injection of heroin, cocaine, methamphetamine, crack, or heroin mixed with methamphetamine or cocaine; noninjection crack use; and nonfatal heroin overdose. Overdose was defined as a loss of consciousness where at least one intervention was attempted by a third party.

Data analysis

We calculated mortality incidence overall and by demographic and risk characteristics reported at the baseline interview. Standardized mortality ratios were calculated in 3-year intervals adjusting for age, sex, and race by using national mortality statistics from the National Center for Health Statistics. Standardized mortality ratios were calculated overall, separately for males and females, and for overdose-related deaths only; 95% confidence intervals were calculated by assuming that the observed deaths followed a Poisson distribution. Cox regression models with time-varying covariates were used to identify predictors of mortality. Survival time was defined as the time from initiation of injection (self-reported as age at first injected drugs) to death. Given that subjects were current injectors at the start of the study, data were left truncated. Subjects entered into the analysis at the baseline visit, and they remained until the date of death or were censored at December 31, 2007, or the last interview date if the last interview was after December 31, 2007. Covariates were included in the multivariate model if the incidence rate ratio for mortality reached statistical significance at a level of $P < 0.10$ in the bivariate analysis or were potential confounders (study wave, age, gender, HCV status, and duration of injection drug use). Baseline characteristics including age, gender, duration of injection, and study wave were entered into the model as fixed covariates. Drug use and injection-risk behaviors, overdose, and HCV status were entered as time-varying covariates. All analyses were conducted with the Stata statistical software package (release 11.2; StataCorp LP, College Station, Texas).

RESULTS

A total of 644 participants completed a baseline interview and were enrolled in the prospective cohort from November 1997 to December 2007. The median age was 22.0 years (interquartile range (IQR): 19.8–25.0), and participants had injected for a median of 4.0 years (IQR: 1.7–6.7) at the baseline interview. Sixty-eight percent of participants were male, and 78% were Caucasian (Table 1); 47% had less than a high school education, and 68% reported being homeless or marginally housed. At the most recent interview, the drug most often injected in the past 30 days was heroin (63%) followed by methamphetamine (27%); 31% reported injecting every day in the past month, 68% used a syringe exchange in the past month, and 32% were anti-HCV positive.

We identified 38 deaths over the follow-up period through 2007 using the NDI. The overall mortality rate over 4,167

Table 1. Selected Baseline Sociodemographic and Behavioral Characteristics at Last Quarterly Follow-up Visit for Young Injection Drug Users in the UFO Study, San Francisco, California, 1997–2007

Characteristic	No.	%	Proportion Mortality, %	No. of Person-Years	Mortality Rate/1,000 Person-Years	Incidence Rate Ratio	95% CI
Overall	644	100.0	5.9	4,167.36	9.12		
Study wave							
1997–1999	133	20.7	11.3	1,148.92	13.06	1.00	Referent
2000–2002	334	51.9	5.4	2,395.66	7.51	0.55	0.27, 1.14
2003–2007	177	27.5	2.8	622.78	8.03	0.80	0.51, 1.27
Age, years							
15–19	164	25.5	6.7	1,113.37	9.88	1.00	Referent
20–24	292	45.3	5.1	1,902.58	7.88	0.79	0.36, 1.76
25–30	188	29.2	6.4	1,151.41	10.42	1.03	0.68, 1.55
Gender							
Female	204	31.7	4.4	1,383.47	6.51	1.00	Referent
Male	440	38.3	6.6	2,783.89	10.42	1.60	0.76, 3.38
Education							
Less than high school	300	47.0	4.3	2,009.27	6.47	1.00	Referent
High school or more	339	53.0	7.1	2,136.13	11.24	1.74	0.88, 3.41
Race/ethnicity							
Caucasian	502	78.1	5.6	3,261.45	8.45	1.00	Referent
Non-Caucasian	141	21.9	7.1	842.90	11.78	1.39	0.71, 3.17
Homeless, past 3 months							
No	207	32.2	4.4	1,322.38	6.81	1.00	Referent
Yes	436	67.8	6.7	2,840.29	10.21	1.50	0.71, 3.17
Sexual behavior							
Female	204	31.7	4.5	1,383.47	6.51	1.00	Referent
Heterosexual male	261	40.5	8.4	1,710.26	12.86	1.89	0.93, 3.83
Men who have sex with men	179	27.8	3.9	1,074.62	6.52	1.00	0.61, 1.64
Hepatitis C virus positive							
No	433	67.9	4.9	2,782.30	7.55	1.00	Referent
Yes	205	32.1	8.3	1,356.27	12.53	1.66	0.88, 3.15
Human immunodeficiency virus positive							
No	565	95.8	6.4	3,780.08	9.52		
Yes	25	4.2	0.0	149.89	0.00		
Age of first drug injection, years							
<17	243	37.7	6.6	1,589.72	10.06	1.00	Referent
17–19	217	33.7	6.0	1,452.42	8.95	0.89	0.43, 1.84
≥20	184	28.6	4.9	1,125.22	8.00	0.89	0.60, 1.33

Table continues

person-years of follow-up was 9.12 (95% confidence interval (CI): 6.63, 12.53) per 1,000 person-years of observation. In females, the mortality rate was 6.51/1,000 person-years of observation and, in males, 10.42/1,000 person-years of observation. The median age at death was 26 years (IQR: 23–30), and the median time from initiation of injecting until death was 7.7 years (IQR: 4.9–11.3).

Increased mortality was observed among those who identified heroin or heroin mixed with other drugs as the drug injected most days in the 30 days prior to the most recent interview, relative to those who injected methamphetamine (incidence rate ratio (IRR) = 3.03, 95% CI: 1.47, 6.23) (Table 1). The incidence of mortality was significantly higher in those who reported having an overdose in the past 3 months compared with those who did not (IRR = 2.71, 95% CI: 1.35, 5.47). Mortality rates were elevated among HCV-seropositive individuals compared with negatives but did not reach statistical significance (IRR = 1.66,

Table 1. Continued

Characteristic	No.	%	Proportion Mortality, %	No. of Person-Years	Mortality Rate/1,000 Person-Years	Incidence Rate Ratio	95% CI
Duration injecting, years							
≤2	194	30.2	5.2	1,281.74	7.80	1.00	Referent
>2–5	209	32.5	5.3	1,377.33	7.99	1.02	0.44, 2.41
>5	240	37.3	7.1	1,503.37	11.31	1.20	0.82, 1.75
Injected every day, past month							
No	446	69.3	5.2	2,840.64	8.10	1.00	Referent
Yes	198	30.7	7.6	1,326.72	11.31	1.40	0.73, 2.68
Drug injected most days, past month							
Speed/methamphetamine	168	26.5	1.2	1,100.15	1.82	1.00	Referent
Heroin/heroin mix	441	69.6	7.9	2,900.47	12.07	3.03*	1.47, 6.23
Other	25	3.9	4.0	137.45	7.28	3.08	0.51, 18.66
Injected alone, past 3 months[a]							
No	338	53.7	5.0	2,184.05	7.78	1.00	Referent
Yes	292	46.3	7.2	1,879.04	11.18	1.44	0.76, 2.72
Syringe exchange, past month							
No	203	32.0	5.4	1,270.33	8.66	1.00	Referent
Yes	432	68.0	6.3	2,833.50	9.53	1.10	0.55, 2.22
Ever overdosed							
No	391	60.9	4.9	2,519.38	7.54	1.00	Referent
Yes	251	39.1	7.6	1,638.79	11.59	1.54	0.81, 2.90
Overdose, past 3 months[a]							
No	563	88.1	4.8	3,595.02	7.51	1.00	Referent
Yes	76	11.9	14.5	539.66	20.38	2.71*	1.35, 5.47
Incarcerated, past 3 months[a]							
No	404	63.0	559	2,561.85	8.59	1.00	Referent
Yes	237	37.0	6.8	1,586.35	10.09	1.17	0.62, 2.24
Drug treatment, past 3 months ($n = 504$)[b]							
No	379	75.2	4.0	2,218.70	6.76	1.00	Referent
Yes	125	24.8	6.4	754.29	10.61	1.57	0.67, 3.70

Abbreviations: CI, confidence interval; UFO, "U Find Out."
* $P < 0.01$.
[a] Time frame is past year for participants surveyed in 1997–1999.
[b] Data not collected in wave 1. Time frame is past week for participants surveyed in 2003–2007.

Table 2. Age-, Race-, and Sex-adjusted Standardized Mortality Ratios for Young Injection Drug Users in San Francisco, California, Using National Reference, 1999–2007

Year	Overall				Females			Males		
	UFO Mortality Rate/1,000 Person-Years	Crude National Mortality Rate/1,000 Person-Years	Adjusted SMR	95% CI	Mortality Rate/1,000 Person-Years	Adjusted SMR	95% CI	Mortality Rate/1,000 Person-Years	Adjusted SMR	95% CI
1999–2001	13.1	8.5	15.3	7.6, 27.3	7.1	20.0	2.4, 72.3	16.1	14.5	6.6, 27.6
2002–2004	9.4	8.4	10.6	5.8, 17.8	5.9	15.8	3.3, 46.1	11.3	9.7	4.9, 17.4
2005–2007	7.6	8.1	8.3	4.4, 14.3	7.2	19.1	5.2, 48.8	7.8	6.7	3.1, 12.7

Abbreviations: CI, confidence interval; SMR, standardized mortality ratio; UFO, "U Find Out."

Table 3. Incidence of Overdose Mortality Among Young Injection Drug Users in San Francisco, California, 1999–2007

Year	Overall		Females		Males	
	Mortality Rate/1,000 Person-Years	95% CI	Mortality Rate/1,000 Person-Years	95% CI	Mortality Rate/1,000 Person-Years	95% CI
1999–2001	7.1	3.2, 15.9	0		10.7	4.8, 23.8
2002–2004	6.0	3.1, 11.6	2.0	0.3, 13.9	8.2	4.1, 16.4
2005–2007	4.1	2.0, 8.6	1.8	0.3, 12.7	5.2	2.3, 11.6

Abbreviation: CI, confidence interval.

95% CI: 0.88, 3.15) at $P < 0.05$. Mortality incidence did not differ by age, race/ethnicity, ever having overdosed, duration of injection, or incarceration in the past 3 months.

By use of national mortality as the reference, the overall adjusted standardized mortality ratio for 1999–2001 was 15.3 (95% CI: 7.6, 27.3), which decreased to 10.6 (95% CI: 5.8, 17.8) in 2002–2004 and 8.3 (95% CI: 4.4, 14.3) in 2005–2007 (Table 2). When data were stratified by wave of recruitment, temporal declines in mortality persisted (data not shown). In females, the adjusted standardized mortality ratios were higher than in males across all time bands. Furthermore, there did not appear to be a trend toward a decreasing standardized mortality ratio over time among women, as there appeared to be for men. Incidence of overdose mortality also declined between 2000 and 2007 (Table 3). However, women had lower rates of overdose mortality compared with men, and their rates did not appear to decline. The principal cause of death for the overall cohort was overdose (57.9%), followed by self-inflicted injuries (13.2%), other drug-related medical conditions (13.2%), trauma or accidents (10.5%), and other causes (5.3%).

In Cox regression with time-varying covariates adjusting for age and duration injecting, participants who used heroin or heroin mix most days or who had a recent overdose had elevated mortality (Table 4). Of these factors, heroin/heroin mix as the drug used most days in the past month was the only one independently associated with mortality (adjusted hazard ratio = 5.76, 95% CI: 1.37, 24.30) ($P < 0.05$). Having a recent nonfatal overdose was associated with higher relative hazards of death, although this did not quite meet statistical significance. After adjustment for other covariates, being HCV infected was not significantly associated with increased relative hazards of death.

DISCUSSION

This study of young IDUs in San Francisco between 1997 and 2007 found overall mortality rates 10 times higher than those in the general population. Mortality appeared to decline over the 10-year period; however, stratified results suggested that declines were restricted to males. The leading cause of death in this cohort was overdose, and primary use of heroin was the only significant independent risk factor for death that was observed in the study. Together, these findings highlight the substantial mortality risk associated with injecting drugs for young persons and point to a continued need for public health interventions that address the risk of overdose in this population in order to reduce premature deaths.

The overall mortality rate observed in this study of IDUs in San Francisco was 9.12 per 1,000 person-years of observation. Another study of young and recent-onset injectors that included data from 5 different cities in the United States

Table 4. Multivariate Cox Proportional Hazards Model of Independent Predictors of Mortality Among Young Injection Drug Users in San Francisco, California, 1997–2007[a]

Characteristic	Adjusted Hazard Ratio	95% CI	*P* Value
Study wave			
1997–1999	1.00	Referent	
2000–2002	0.83	0.39, 1.75	0.62
2003–2007	0.82	0.28, 2.42	0.72
Age, years	1.00	0.89, 1.11	0.98
Duration injecting, years			
≤2	1.00	Referent	
>2–5	0.94	0.35, 2.51	0.90
>5	1.50	0.42, 5.36	0.54
Gender			
Female	1.00	Referent	
Male	1.62	0.73, 3.58	0.24
Hepatitis C virus status			
Negative	1.00	Referent	
Positive	1.36	0.68, 2.70	0.39
Drug injected most days in past month			
Methamphetamine	1.00	Referent	
Heroin/heroin mix	5.76	1.37, 24.30	0.02
Other	3.52	0.31, 39.44	0.31
Overdosed, past 3 months[b]			
No	1.00	Referent	
Yes	1.92	0.91, 4.06	0.09

Abbreviation: CI, confidence interval.

[a] Includes all variables associated at $P < 0.10$ in bivariate analyses and adjusting for age, duration injecting, gender, hepatitis C virus status, and study wave.

[b] Time frame is past year for participants surveyed in 1997–1999.

found a similar mortality rate (3). That study found an initial increase of mortality in the 2 years of the cohort study, followed by a decrease, which led the authors to hypothesize that the immediate years following initiation of drug use might be a period of higher risk. In contrast, our study found only a continuous decline in mortality over calendar periods. The prior study by Vlahov et al. enrolled only recently initiated IDUs (<5 years) and therefore did not include a range of age and duration of drug use to clarify period effects. Our study included participants with a wide range of injecting exposure time (median = 4 years, IQR: 1.7–6.7), and we performed multivariate Cox models to analyze the independent effects of age and duration of use. The results did not support an association between duration of use and mortality.

There are several potential explanations for the observed decline in mortality in our cohort of young injectors. First, it is possible that public health interventions could have led to fewer deaths over the years. In the past decade, several overdose prevention programs have been implemented in the United States including the distribution of the overdose-reversal drug, opiate antagonist naloxone (NARCAN; Endo Pharmaceuticals, Inc., Chadds Ford, Pennsylvania), to IDUs (12–16). One of the longest running naloxone prescription programs in the United States was implemented in San Francisco in 2003 and has provided overdose prevention training and prescribed naloxone to nearly 2,000 individuals as of December 2009 (16). Furthermore, improved access to treatment for opioid dependence may be a factor, as opioid substitution treatment in IDUs has been shown to be a significant factor in reducing the risk of mortality (17). There could have been a change in the purity of heroin over the years (18). Finally, because there was ongoing enrollment of our cohort, differences in mortality over time may be associated with unmeasured differences in the UFO Study population over time, such that subjects with lower risk were recruited during later phases of the study. To test this hypothesis, we included a variable for period of study recruitment in our Cox models. Although we did not find significant differences in the hazard ratios for death by enrollment wave, the hazard ratios were less than 1.0 comparing the later with earlier years, suggesting that this could be an underlying factor. Furthermore, when we investigated changes in the UFO Study population across the 3 waves of data collection, we found that participants in the first wave were more likely to inject heroin or heroin mixed with other drugs in the past month and were significantly less likely to inject methamphetamine in the past month at baseline (data not shown). Since primary use of heroin as the drug of injection was strongly predictive of death in our Cox models (hazard ratio = 5.76, 95% CI: 1.37, 24.30), this observed decline in heroin injection in later waves of study recruitment is a likely contributor to the decline in overdose mortality over time.

Our study of young injection drug users found the most common causes of death to be overdose and trauma, which is consistent with prior studies (3, 6, 7, 19). This supports a continued focus on overdose prevention in this age group. Of the risk factors examined in this study, only use of heroin as the main injecting drug was independently predictive of death. This contrasts with 2 prior studies of young IDUs that found HIV infection to be significantly associated with mortality (3, 6). This difference can likely be explained by the relatively small absolute number of participants included in our sample and the small number of persons with HIV. Also, HIV as a cause of death has been shown to have peaked in the 1990s (20, 21), before the advent of highly active antiretroviral therapy, and is less likely to impact mortality in young versus older injectors (7).

Our study showed differences in death rates between men and women. Although the incidence of death was higher among men compared with women, standardized mortality ratios were higher for women. Female injectors were 12 times more likely to die compared with females in the general US population; in contrast, male injectors were 8 times more likely to die compared with the male US population. A similar difference in sex-stratified standardized mortality ratios has been reported in a cohort of young IDUs in Canada (6). In addition, although rates of death appeared to decline over time among men, rates appeared relatively stable for women over the 10-year period. Sex-stratified results should be interpreted with caution however, as the sample size was relatively small and resulted in wide confidence intervals for period-specific mortality rates.

There were a number of important limitations to this study. Mortality rates may be underestimates because of deaths that were not captured by the NDI search criteria. A number of study participants were believed to have given pseudonyms rather than birth names, which would not allow matching, and incorrect birth dates may have been given. Causes of death were based on ICD codes on death certificates that may be inaccurate (22). Analyses used baseline predictor data, and some covariates measured constructs that could change over time (HIV and HCV infections, injecting behaviors, incarceration, and so on). Therefore, analyses of certain predictors should be interpreted with caution. Finally, the relatively modest sample size and small absolute number of deaths are limitations, particularly with regard to sex-stratified results.

In conclusion, this study of young IDUs in San Francisco demonstrated that injection drug use is associated with substantially increased risk for death, and that most of the excess risk is due to overdose and trauma. Results also suggest that, among young adult injectors in San Francisco, mortality rates are decreasing over time but are generally restricted to males. Research is needed to confirm these results and explore reasons for sex-specific differences in mortality in young IDUs.

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