Drug and Alcohol Dependence 156 (2015) 104–111

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Mortality among heroin users and users of other internationally regulated drugs: A 27-year follow-up of users in the Epidemiologic Catchment Area Program household samples

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ARTICLE INFO

Article history:
Received 21 February 2015
Received in revised form 27 August 2015
Accepted 28 August 2015
Available online 3 September 2015

Keywords:
Heroin
Opioids
Drug use
Drugs
Mortality
Death
Survivorship

ABSTRACT

Background: In contrast to research on more restricted samples of drug users, epidemiological studies open up a view of death rates and survivorship of those who have tried heroin a few times, with no acceleration toward sustained use patterns often seen in treatment and criminal justice samples. At their best, epidemiological estimates of heroin effects on risk of dying are not subject to serious selection biases faced with more restricted samples.
Methods: Data are from 7207 adult participants aged 18–48 years in United States Epidemiologic Catchment Area Program field surveys, launched in 1980–1984. US National Death Index (NDI) records through 2007 disclosed 723 deaths. NDI enabled estimation of heroin-associated risk of dying as well as survivorship.
Results: Estimated cumulative mortality for all 18–48 year old participants is 3.9 deaths per 1000 person-years (95% confidence interval, CI = 3.7, 4.2), relative to 12.4 deaths per 1000 person-years for heroin users (95% CI = 8.7, 17.9). Heroin use, even when non-sustained, predicted a 3–4 fold excess of risk of dying prematurely. Post-estimation record review showed trauma and infections as top-ranked causes of these deaths.
Conclusions: Drawing strengths from epidemiological sampling, standardized baseline heroin history assessments, and very long-term NDI follow-up, this study of community-dwelling heroin users may help clinicians and public health officials who need facts about heroin when they seek to prevent and control heroin outbreaks. Heroin use, even when sporadic or non-sustained, is predictive of premature death in the US, with expected causes of death such as trauma and infections.

1. Introduction

Heroin user deaths are in the news for good reason, and this study's main aim is to understand whether heroin users might be at an increased risk of premature death, even when the use is limited and without the complexity of progression into sustained near-daily heroin use. Epidemiological evidence on this topic is needed in order to clarify premature death risks faced by young people who intend to try heroin no more than a few times, with no expectation of becoming regular users. The expectation of these young people might be that trying heroin on multiple occasions, without sustained use, has little or nothing to do with risk of dying prematurely.

Newsworthy epidemiologic estimates now show an increased prevalence of heroin use in the United States (US), with more than 650 thousand active heroin users in recent years versus an estimated 350–400 thousand in 2007 (SAMHSA, 2013). Concurrently,

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http://dx.doi.org/10.1016/j.drugalcdep.2015.08.030
0376-8716/

exponentially increasing numbers of heroin user deaths are being seen, sometimes when heroin use has displaced use of prescription pain relievers (Cicero et al., 2014; Rudd et al., 2014; Volkow, 2014a).

The observed pattern of heroin displacement of prescription pain relievers (PPR) might lead one to believe that heroin deaths and PPR deaths are exchangeable. Nonetheless, when studying the epidemiology of PPR deaths versus epidemiological profiles for heroin deaths, Cerdá and colleagues (2013) discovered marked differences. It is for this reason that the current research report is focused on estimation of risks of dying and survivorship, as experienced by heroin users in the community versus area-matched non-users, with differentiation of sustained near-daily heroin users versus non-sustained users. That is, the evaluation addresses whether excess risk is seen only for sustained near-daily heroin users, versus an alternative possibility – namely a history of sporadic or non-sustained heroin use also predict and account for an excess risk of dying prematurely.

Epidemiological estimates of the type reported here can be important in prevention and risk communication initiatives. A potential under-statement of risk is faced when the count of heroin deaths in a risk estimate's numerator is based solely on death certificates that mention heroin explicitly. Potential over-statement of risk may be present when mortality estimates are based on heroin users found via treatment and criminal justice facility records or via injecting drug user outreach or network sampling, for a variety of reasons suggested elsewhere. For example, Robins et al. (1975) and Mowbray et al. (2010) noted that restricted samples of heroin users might be considered a non-random subset of all heroin users in the community – i.e., those with more extreme pre-heroin life circumstances, severe impairment, or maladaptation. It follows that the experiences of this non-random subset of heroin users, in living and in dying, might be not at all representative of heroin users in the community at large. To the extent that epidemiological samples provide a more complete representation of the full spectrum of heroin involvement, mortality studies based on epidemiology's field survey samples should promote a more balanced perspective on how limited heroin use might eventually translate into a premature risk of dying.

Prior studies on this topic generally have produced heroin death rates for populations as a whole (e.g., see Cerdá et al., 2013), with no estimates of risk of dying for heroin users per se because this estimation task requires pre-mortem ascertainment of a positive heroin history in pre-selected individuals observed prior to death. Past estimates with pre-mortem heroin ascertainment generally involved identification of heroin users after entry to a treatment or criminal justice facility, more rarely via 'outreach' to injecting drug use communities, and even more rarely from samples of military veterans.

On one side of the coin, all of these prior estimates can be regarded as important, irrespective of ascertainment or sampling approaches, because they help quantify what heroin overdose death certificates do not disclose. Namely, heroin use can affect risk of dying via mediational mechanisms such as development of heroin dependence syndromes, HIV/AIDS complications or other infections caused by unsanitary injecting drug use or unsafe sex, via exposure to other noxious agents or trauma, suicide, and homicide, or via treatment-related complications (Ball et al., 1983; Degenhardt et al., 2010; Evans et al., 2012; Goldstein and Herrera, 1995; Hser et al., 2001; Price et al., 2001; Vlahov et al., 2005, 2008).

On the other side of the coin, substantial numbers of community residents in the US have used heroin without injecting, without becoming heroin dependent, and without treatment for heroin problems, if we are to believe estimates from many prior epidemiological studies in the US (Anthony et al., 1994; Brittingham et al., 1998; SAMHSA, 2005, 2013; Wu et al., 2011). To the extent that restricted sample subsets of heroin users in the US are skewed toward more serious heroin involvement, the estimates of risk of dying based on these studies might be dismissed as irrelevant by young people in the general population who might start using heroin with an intention to try it no more than a few times.

For these reasons, we sought an opportunity to derive epidemiological field survey estimates on the issue of whether using heroin, per se, might be followed by an excess risk of premature death, *even when sustained heroin use is absent*, and to investigate possible heroin-caused excess risk of dying and reduced survivorship. The study estimates are based on four large US community cohorts sampled and recruited in the early-mid 1980s for the Epidemiologic Catchment Area Program (ECA).

By linking ECA heroin data with the National Death Index registry of all US deaths (NDI), we estimate the degree to which a heroin use history might predict and account for increased risk of dying prematurely. Focused on heroin, this work extends prior ECA mortality research on alcohol and other drug dependence syndromes (Eaton et al., 2013; Neumark et al., 2000).

A note about 'premature death' may be in order. This concept is grounded in relation to expected death ages for the sample as observed at baseline. For US adults age 45–49 years old 25–30 years ago, dying prematurely means dying somewhat before age 80, given survivorship statistics (National Center for Health Statistics, 2010). All deaths described in this report occurred before age 80.

2. Materials and methods

2.1. Study design, study population and sample

As previously described in detail by the ECA team (Eaton et al., 1984), this prospective cohort study was launched in 1980–83 with multi-stage area probability sampling and IRB-approved recruitment of adult household residents from five US communities (mean participation, 76%). This study of deaths is based on 7207 18–48 year old participants from ECA sites in New Haven, CT (1980–1981); Baltimore, MD (1981); Saint Louis, MO (1981–1982); Durham, NC (1982–1983). A total of 78 decedents had uncertain NDI records (e.g., uncertainty in the identity matching), and were excluded in these estimates. The Los Angeles site did not retain identifying data for NDI matching. ECA participants 49+ years were excluded because heroin use was too rare for death rate estimation. Supplementary Material 1 provides a more detailed methods description.

2.2. Study variables and their assessment

The outcome of interest is death as observed in the NDI; otherwise, survivorship is assumed. NDI matching algorithms and death cause classifications are described in Eaton et al. (2013). All other measured variables, including heroin, alcohol and other drug history, are from multi-item Diagnostic Interview Schedule modules (DIS) administered soon after recruitment and again roughly one year later.

Anthony and Helzer (1995) published a detailed description of the DIS modules covering heroin use and extra-medical use of other internationally regulated drugs, as well as inhalants (IRD), including specific items for a composite "IRD used at baseline" exposure variable, indicative of those who never used an IRD versus those using compounds 'to get high' or for other extra-medical reasons at least every day for two weeks. A 'drug use status' history variable cross-classified users by heroin history and sustained use as follows: (1) heroin and one or more other (1+) IRD taken daily or near-daily for 2+ weeks; (2) 'non-daily' use of heroin, sometimes with non-daily extra-medical daily use of 1+ IRD; (3) never used heroin, but sustained daily or near-daily extra-medical use of 1+ IRD (i.e., 'daily' users of IRD other than heroin); (4) never used heroin, with 'non-daily' use of 1+ IRD on 5+ occasions in the lifetime; (5) Never used heroin, with 'non-daily' use of 1+ IRD on <6 occasions; (6) never used an IRD (i.e. no extra-medical IRD use). DIS items are listed elsewhere (DHHS, NIMH, 1992; http://dx.doi.org/10.3886/ICPSR06153.v1).

Other suspected determinants of premature death measured in multi-site DIS assessments were: sex (male versus female), age when recruited (with an age-squared term included to model non-linearity in age-specific risk of dying), ethnic self-identification as non-Hispanic Whites vs. other (given that >90% of non-Whites self-identified as African-American), community (Yale, Hopkins, Washington University, Duke urban, Duke rural), IRD use onset before age 18 (yes versus no), and alcohol use disorder onset before age 18 (yes versus no). The multi-site ECA DIS did not assess route of administration, location of use, heroin use onset, heroin use duration, concomitant use of heroin at the same time as other drugs (e.g., lethal combinations with cocaine, benzodiazepines, or alcohol), heroin treatment, abstinence intervals, intercurrent illness, commercial sex work, HIV/AIDS status, or nicotine use. We acknowledge this limitation.

Table 1
Estimated mortality seen for individuals age 18–48 years old at baseline. Data from five communities within four cities participating in the United States Epidemiologic Catchment Area Program, 1980–2007 ($n = 7207$)[a].

	Person-years	Crude mortality rate		Mortality weighted estimates		Vital status at 2007		p-value	Individuals 18–48 ($n = 7207$)		
		Per 1000 person-year	95% C.I.	%	SE	Death	Alive		n	Weighted column %[b]	
						n	n			%	SE
All study population	183,654	3.9	(3.7, 4.2)	9.4	0.39	723	6484		7207	100	–
Any heroin use											
Yes	2331	12.4	(8.7, 17.9)	25.5	5.35	29	72	<0.001	101	1.5	0.18
No[c]	180,035	3.8	(3.6, 4.1)	9.2	0.39	688	6366		7054	98.5	0.18
Missing	1288	4.7	(2.1, 10.4)	6.1	0.39	6	46		52		
Drug use status											
Heroin and one or more (1+) other IRD taken daily or near-daily for 2+ weeks	1112	15.3	(9.5, 24.6)	37.3	8.53	17	33	<0.001	50	0.6	0.11
'Non-daily' use of heroin, sometimes with extra-medical daily use of 1+ IRD[d]	1219	9.9	(5.6, 17.3)	16.8	5.82	12	39		51	0.8	0.14
Never used heroin, but sustained daily or near-daily extra-medical use of 1+ IRD	22,474	3.7	(3.0, 4.6)	8.7	0.87	84	794		878	12.3	0.47
Never used heroin, with 'non-daily' use of 1+ IRD on 5+ occasions in the lifetime	39,335	2.9	(2.4, 3.4)	7.5	0.86	112	1413		1525	20.9	0.61
Never used heroin, with 'non-daily' use of 1+ IRD on <6 occasions	20,533	2.8	(2.2, 3.7)	6.5	0.97	58	738		796	10.7	0.47
Never used an IRD	97,694	4.4	(4.0, 4.9)	10.5	0.58	434	3421		3855	54.7	0.76
Missing	1288	4.7	(2.1, 10.4)	6.1	2.63	6	46		52		
Sex											
Female	108,111	3.4	(3.0, 3.7)	7.4	0.47	362	3852	<0.001	4214	52.0	0.76
Male	75,543	4.8	(4.3, 5.3)	11.6	0.69	361	3632		2993	48.0	0.76
Ethnic self-identification[e]											
Non-Hispanic White	115,587	3.1	(2.8, 3.4)	7.9	0.46	354	4130	<0.001	4484	70.4	0.72
Other	67,908	5.4	(4.9, 6.0)	13.1	0.86	368	2349		2717	29.6	0.72
Missing	159	6.3	(0.9, 44.7)	9.4	0.39	1	5		6		
IRD use onset before age 18											
No (reference)	147,726	4.1	(3.8, 4.5)	9.8	0.41	610	5198	0.13	5808	79.1	0.54
Yes	35,928	3.2	(2.6, 3.8)	8.0	1.01	113	1286		1399	20.9	0.54
Missing											
Alcohol use disorder onset before age 18											
No	172,406	3.8	(3.6, 4.1)	9.2	0.42	662	6098	0.016	6760	94.3	0.30
Yes	9244	5.7	(4.4, 7.5)	13.1	2.24	53	315		368	5.7	0.30
Missing	2003.5	4.0	(2.0, 8.0)	6.2	2.81	8	71		79		
Community site											
New Haven (Yale)	47,569	3.0	(2.6, 3.6)	8.0	0.66	144	1654	<0.001	1798	31.2	0.59
Baltimore (Hopkins)	45,897	5.8	(5.2, 6.6)	16.5	1.04	267	1556		1823	17.2	0.40
St. Louis (WUSTL)	47,088	3.7	(3.2, 4.3)	8.2	0.92	173	1664		1837	17.2	0.90
Duke urban	23,628	2.4	(1.9, 3.1)	5.5	0.93	57	896		953	12.1	0.62
Duke rural	19,473	4.2	(3.4, 5.2)	10.3	1.28	82	714		796	8.5	0.39

[a] There were 78 deceased individuals who were excluded from the analyses as their death information was not properly recoded at the NDI.
[b] These column estimates are based on a denominator with non-missing values for each covariate.
[c] This group of individuals who never used heroin includes individuals who never used an IRD or used an IRD other than heroin.
[d] This group was composed of 15 individuals who used only heroin and 36 individuals who used heroin in combination with other IRD, but never daily.
[e] Ethnic self-identification status of the 29 decedents among heroin users was as follows: 'Non-Hispanic White' ($n = 9$); 'Non-Hispanic Black or African-American' ($n = 18$); American Indian/Alaskan Native ($n = 1$); and 'other' ($n = 1$). For this reason, heroin death rates are produced only for 'Non-Hispanic White' and for 'Other'. With respect to ESI status and the 368 deaths shown in the 'Other' row of this table, the numbers were as follows: 'Non-Hispanic Black or African-American' ($n = 344$); Hispanic ($n = 3$); Asian-Pacific Islander ($n = 5$); American Indian/Alaskan Native ($n = 14$); and 'other' ($n = 2$).

2.3. Data analyses

After Tukey-style pre-estimation work-up, the first analysis/estimation step aggregated unweighted sample counts across sites for estimation of crude mortality rates per 1000 person-years, with comparative analysis-weighted case fatality rates. Next, participants were matched on area of residence and time to event for a conditional logistic regression analysis to derive a heroin effect estimate. Stratified conditional logistic regression models and multivariable models with interaction terms were also framed to assess effect modification and residual confounding. Because some readers might prefer analysis-weighted unconditional discrete time survival analyses without area-matching; estimates with ECA analysis weights (i.e. SW3) are shown. Final exploratory analysis steps are described under 'Results,' which focuses attention on estimation and 95% confidence intervals (CI), with p-values to aid inference.

3. Results

Table 1 shows noteworthy sample facts. In aggregate, during 24–27 years of follow-up, the 7207 18–48 year olds lived through 183,654 person-years (p-y) (Table 1, Column 1, Row 1). For 101 adults with a positive history of heroin use at baseline, the cumulative person-year count is 2331 p-y (Table 1, Col 1).

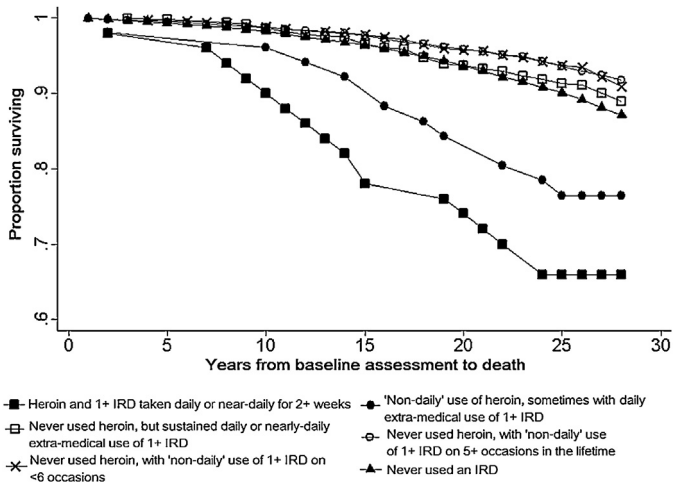

Fig. 1. Estimated proportion surviving in each of the drug use subgroups, plotted across years of elapsed time from baseline assessment. Data from the United States Epidemiologic Catchment Area Program, 1980–2007 ($n = 7207$).

Table 1 also presents estimates from two useful approaches for answering questions about the absolute risk or rate of dying during follow-up. A 'rate' approach involves forming ratios by dividing numbers of deaths by numbers of person-years. A 'risk' approach ignores person-year details.

What is the estimated death rate for the total study population? It is 723 deaths divided by 183,654 p-y – i.e., just under four per 1000 person-years (3.9/1000 p-y; 95% CI = 3.7, 4.2). *And the estimate for heroin users?* 29 deaths divided by 2331 p-y, or roughly 12 deaths per 1000 p-y (12.4/1000 p-y; 95% CI = 8.7, 17.9). As for the 52 adults with missing positive heroin history values, an estimated 4 per 1000 p-y is seen, not appreciably different from the overall estimate. Table 1 shows corresponding death rates for a selection of other variables, but with no adjustment for age, the between-group variation cannot be interpreted clearly. Readers interested in social and economic variations (including estimates for detailed ethnic self-identification subgroups) are referred to already published death rates in Eaton et al. (2013).

An alternative approach is one that avoids person-years complexities and applies ECA analysis weights. Analogies are 5–25-year 'case fatality rates' for how many deaths are observed during intervals since first diagnosis/ascertainment, divided by numbers of individuals diagnosed/ascertained. Using ECA's analysis weights and an interval of ~25 years, we estimate risk of dying as about one death for every 11 ECA adult participants (9.4%; standard error, SE = 0.39). In contrast, among heroin users, the risk of dying is one death for every 4 users (25.5%; SE = 5.35) (Table 1, Column 4).

Right-hand columns of Table 1 show unweighted numbers and proportions for these estimates. For example, an estimated 1.5% of ECA community residents had DIS-identified positive history of heroin use (standard error, SE = 0.18%).

Fig. 1 shifts attention to the probability of living (as opposed to dying prematurely), and compares heroin user survivorship with that of community-dwelling peers. For most drug-using subgroups, survivorship is not too distant from that of the reference category (never users). Two subgroups have exceptionally reduced survivorship: (1) those who used heroin daily or almost daily on a sustained basis (2+ weeks), and (2) non-daily heroin users who used some other internationally regulated drug on a sustained near-daily basis.

Table 2 (1st columns) presents relative risk (RR) estimates from area-matched conditional logistic regression analyses for discrete time data. *Does heroin history signal excess risk of dying?* A 3–4 fold excess risk of dying is discovered when individuals have a positive heroin history, with or without sex and age held constant (covariate-adjusted RR = 3.6; 95% CI = 2.4, 5.3; Table 2). RR estimates from post-estimation analysis without area-time matching are not appreciably different (RR = 3.7; 95% CI = 1.9, 7.0; Table 2; right-most columns). Similar conclusions are drawn when analyses exclude sustained near-daily users of other IRD compounds (Supplementary Material 2, Table 4) and with restrictions to individuals with extra-medical IRD use on at least one occasion (estimates not shown in a table).

Model 2 of Table 2 differentiates risk across two intensity levels for history of heroin use. Gauged in relation to adults in the reference subgroup with no history of extra-medical IRD use, RR estimates for the two levels of heroin use are statistically robust and consistent with a 3–4 fold excess risk of dying. The RR point estimate for sustained near-daily heroin users is 4.0 (95% CI = 2.4, 6.6). For lower intensity heroin users without sustained near-daily heroin use, the RR estimate is 3.4 (95% CI = 1.9, 6.2). Post-estimation analysis without area-matching leads to similar conclusions about heroin history, with overlapping 95% CI, albeit somewhat different RR point estimates (Table 2). Similar conclusions are drawn after additional post-estimation analyses to exclude sustained near-daily use of other IRDs (Supplementary Material 2, Table 4).

Table 2 also conveys important information about sustained near-daily extra-medical users of IRDs other than heroin. Excess risk of premature death for this subgroup is seen, as conveyed by an RR estimate of 1.3 (95% CI = 1.1, 1.7), not as strong as the excess risk for heroin users, but with clearly more risk of dying prematurely than is true for the reference category. Non-daily users of drugs other than heroin do not appear to be at excess risk of premature mortality (Table 2).

We also examined the crude mortality rate and mortality risk estimates from sex-stratified and ethnic self-identification-stratified conditional logistic regression models (Table 3). Results showed higher crude mortality rate and an excess risk of dying prematurely for sustained near-daily heroin users, and for sustained near-daily users of some other IRD (without sustained near-daily heroin use). The stratified analyses in Table 3 showed some evidence of subgroup variation with males and individuals who ethnically identified as 'others' and who never used heroin, but used 1+ IRD on less than six occasions having a lower risk of premature death when compared to never IRD users. (Results from models including product-terms are not included here, but are available upon request.) We also found that mean age at death did not vary appreciably in relation to the drug use status variables measured at baseline, including heroin (Table 3).

When we attempted to obliterate the heroin-associated excess risk of dying prematurely by making statistical adjustments for other potential confounding variables (e.g., IRD use onset before age 18; alcohol use disorder onset before age 18), we found no appreciable attenuation of these associations. For example, in these analyses, the estimated RR generally was close to 3.4 for sustained daily heroin users, and was close to 2.7 for non-sustained heroin users (Supplementary Material 3, Table 5).

3.1. Causes of death

Among the 29 decedents with a positive history of heroine use at baseline, NDI-listed causes of death encompassed HIV/AIDS ($n = 7$) and respiratory infections ($n = 2$), as well as trauma and injuries ($n = 5$). Five deaths were coded for poisoning by drugs, medicines, or other biologically active chemicals and other drug-related deaths (e.g., event of undetermined intent, poisoning by an exposure to narcotics and psychodysleptics [hallucinogens], not elsewhere classified, undetermined intent). Other causes were neoplasm ($n = 4$), cardiovascular disease ($n = 4$) and liver disease ($n = 2$). When an identified cause was listed for deaths of non-heroin users

Table 2
Estimates of the association linking drug history status in the early 1980s with subsequent mortality in five communities/four cities. Data from the United States Epidemiologic Catchment Area Program, 1980–2007 ($n = 7207$).

	Estimated relative risk (RR) from conditional logistic regression for discrete time data (area-time matched risk sets of survival data)				Estimated relative risk (RR) from unconditional logistic regression with weights and Taylor series variance approach[a]			
	RR	95% confidence interval		*p*-value	RR	95% confidence interval		*p*-value
Model 1								
Any heroin use								
Yes	3.6	2.4	5.3	<0.001	3.7	1.9	7.0	<0.001
No (reference)	1.0				1.0			
Model 2								
Drug use status at baseline								
Heroin and one or more (1+) other IRD taken daily or near-daily for 2+ weeks	4.0	2.4	6.6	<0.001	6.7	2.9	15.6	<0.001
'Non-daily' use of heroin, sometimes with extra-medical daily use of 1+ IRD[b]	3.4	1.9	6.2	<0.001	2.7	1.2	6.2	0.021
Never used heroin, but sustained daily or near-daily extra-medical use of 1+ IRD	1.3	1.1	1.7	0.029	1.5	1.1	2.0	0.007
Never used heroin, with 'non-daily' use of 1+ IRD on 5+ occasions in the lifetime	1.0	0.8	1.3	0.935	1.3	0.9	1.8	0.070
Never used heroin, with 'non-daily' use of 1+ IRD on <6 occasions	0.8	0.6	1.1	0.254	0.9	0.6	1.2	0.351
Never used an IRD (reference)	1.0				1.0			

Note: All models include covariate adjustment for sex, age (centered to the lowest age value), and age (centered) squared.
[a] Unconditional model also adjusted by community.
[b] This group included 15 individuals who used only heroin, but never daily, and 36 non-daily heroin users who also used 1+ IRD daily.

($n = 668$), there were much smaller proportions for deaths caused by HIV/AIDS ($n = 10$) and poisoning ($n = 14$).

4. Discussion

The first novel finding of note is that self-identified heroin users in these US community field survey samples from the early 1980s were an estimated 3–4 times more likely to die prematurely as compared to their non-using neighbors in the same areas. Second, heroin-predicted excess risk of dying is seen even when the measured intensity of heroin use was less than sustained near-daily use. The excess risk remained statistically robust when holding constant age differences and other known and suspected determinants of death under study. Third, the crude death rate for community residents with sustained near-daily heroin use was 12.4 deaths per 1000 p-y, larger than the rate for the community sample overall (3.9 deaths per 1000 p-y). Fourth, the mean age of death among heroin history positive individuals was 45 years, compared to 53 years for non-heroin-using individuals within the same age range at baseline (18–48 years old). Fifth, traumatic injuries and infections (e.g., HIV/AIDS; pneumonia), as well as poisoning, were prominent among listed causes of death for heroin users in the sample. Sixth, in the absence of heroin use and in the absence of a pattern of sustained daily use, the extra-medical drug users in these samples were not found to be at an increased risk of premature death.

Before a detailed discussion, limitations should be noted, many of which have already been described by Eaton et al. (2013). Here, we acknowledge reliance upon self-report interview data, and we note that estimates from community survey samples actually might understate the degree to which heroin use causes premature deaths to occur, just as past studies restricted to criminal justice and treatment samples might well have overstated heroin-associated excess mortality. As it happens, this study's estimates for sustained near-daily heroin users fall within the range of 7.1–41.5 per 1000 p-y previously observed for regular or dependent users of heroin and other opioids who have been studied by other research teams after recruitment of clinical, institutionalized, or military samples of heroin users in the US (Evans et al., 2012; Goldstein and Herrera, 1995; Hser et al., 2001; Price et al., 2001; Vlahov et al., 2005, 2008).

It is true that many deaths among heroin users in this sample might be described as due to 'unnatural' causes or as due to causes connected in some way to heroin use, including traumatic injury and infections; similar causes of death have been observed in other samples (Goldstein and Herrera, 1995; Harrell et al., 2012). Nonetheless, one should not expect observed evidence about specific causes of death of heroin users to remain constant; the observed values might not hold for other places or other times (Copeland et al., 2004; Esteban et al., 2003; Kimber et al., 2010). In addition, causes of mortality can shift over time and place, as might be true for risk of premature mortality. In this context, we note a global research overview that quantified 20.9 deaths per 1000 person-years among heroin users (Degenhardt et al., 2010), somewhat larger than this study's estimate for the US. The smaller US value might be traced to early outreach and treatment of HIV infections in the US (Copeland et al., 2004; Palella et al., 1998; Vlahov et al., 2005), but between-country variations in the spectrum of intensity of heroin use also must be addressed in any speculation along these lines.

As another limitation, we note that heroin use was studied here as a fairly static 'exposure history' variable even though this exposure state can change over time (e.g., see Robins et al., 1975). A process of changing exposure status might help account for similarity of RR estimates for the two heroin history levels. Some of the non-sustained heroin users in the early 1980s might have become daily users in later years, and vice versa.

We also acknowledge that some 'non-exposed' individuals might have become heroin users after DIS assessment, serving to illustrate what has been called the 'Len Bias bias', which tends to elevate death rates among apparent non-users, due to undercounting of deaths from drug misadventure. Attention to this bias was noted in dissertation research on cocaine-related mortality (Rosenberg, 2001), with details about a promising University of Maryland basketball star named Len Bias. That is, during an early cocaine experience in 1986, Mr. Bias died of a cardiac arrhythmia judged by medical examiners to have been induced by cocaine 'overdose.' If he had been surveyed in 1981, his cocaine exposure status would have been 'never user' at that time; his drug-caused death would be counted in the death rate numerator for the cocaine-non-exposed subgroup. In fact, a cause-specific mortality

Table 3
Specific age of death, sex and ethnic self-identification estimates for the association linking drug history status in the early 1980s with subsequent mortality in five communities/four cities. Data from the United States Epidemiologic Catchment Area Program, 1980–2007.

	Mean age of death (in years) (SD)[a]	Crude mortality rate (CMR in person-years, p-y) and estimated (Est.) relative risk (RR) of mortality across heroin and drug use categories from conditional logistic regression for discrete time data (area-time matched risk sets of survival data)							
		Male		Female		White		Other	
		CMR (per 1000 p-y) (95% C.I.)	RR (95% C.I.)[b]	CMR (per 1000 p-y) (95% C.I.)	RR (95% C.I.)[b]	CMR (per 1000 p-y) (95%C.I.)	RR (95% C.I.)[c]	CMR (per 1000 p-y) (95% C.I.)	RR (95% C.I.)[c]
Any heroin use									
No (reference)	52.9 (10.9)	4.6 (4.1–5.1)	1.0	3.3 (3.0–3.7)	1.0	3.0 (2.7–3.3)	1.0	5.2 (4.7–5.8)	1.0
Yes	45.2 (9.7)	12.9 (8.6–19.4)	3.3 (2.9–3.8)	11.1 (5.0–24.5)	3.8 (3.0–4.8)	7.8 (4.2–14.4)	2.9 (2.4–3.4)	18.2 (11.6–28.6)	3.3 (2.9–3.9)
Drug use status at baseline									
Heroin and one or more (1+) other IRD taken daily or near-daily for 2+ weeks	46.9 (10.1)	14.6 (8.3–25.7)	3.0 (2.5–3.7)	17.3 (7.2–41.5)	5.2 (3.9–6.9)	10.1 (4.5–22.5)	3.0 (2.3–3.8)	21.2 (11.7–38.1)	3.9 (3.1–4.8)
'Non-daily' use of heroin, sometimes with extra-medical daily use of 1+ IRD[d]	42.8 (9.1)	11.4 (6.3–20.6)	3.9 (3.2–4.7)	3.9 (0.6–27.8)	2.0 (1.2–3.4)	5.8 (2.2–15.4)	3.0 (2.3–4.0)	15.3 (7.6–30.5)	3.3 (2.6–4.1)
Never used heroin, but sustained daily or near-daily extra-medical use of 1+ IRD	46.4 (9.9)	4.2 (3.2–5.6)	1.4 (1.2–1.5)	3.1 (2.2–4.4)	1.3 (1.2–1.5)	2.6 (1.9–3.5)	1.3 (1.2–1.4)	6.0 (4.5–8.0)	1.5 (1.4–1.6)
Never used heroin, with 'non-daily' use of 1+ IRD on 5+ occasions in the lifetime	47.5 (11.1)	3.5 (2.8–4.5)	1.1 (0.9–1.2)	2.2 (1.7–3.0)	1.0 (0.9–1.1)	2.0 (1.5–2.7)	1.0 (0.9–1.1)	4.2 (3.3–5.4)	1.1 (0.9–1.2)
Never used heroin, with 'non-daily' use of 1+ IRD on <6 occasions	50.5 (9.9)	3.2 (2.2–4.6)	0.7 (0.6–0.8)	2.5 (1.8–3.6)	1.0 (0.9–1.1)	2.3 (1.6–3.2)	1.0 (0.9–1.0)	4.2 (2.8–6.2)	0.8 (0.7–0.9)
Never used an IRD (reference)	55.9 (10.1)	5.7 (4.9–6.6)	1.0	3.8 (3.4–4.3)	1.0	3.7 (3.2–4.2)	1.0	5.6 (4.9–6.4)	1.0

[a] Differences in the mean age at death were not significant ($p > 0.5$) for both the "Any heroin use" and "Drug use status at baseline" variables.
[b] Models include covariate adjustment for age (centered to the lowest age value), and age (centered) squared.
[c] Models include covariate adjustment for sex, age (centered to the lowest age value), and age (centered) squared.
[d] This group included 15 individuals who used only heroin, but never daily, and 36 non-daily heroin users who also used 1+ IRD daily.

analysis would assign this death as a drug-caused death; otherwise, its omission would yield understatement of a drug's influence on premature mortality. We probed for a 'Len Bias bias' in our heroin estimates, looking for ICD 10 codes T40.1 (Poisoning by and adverse effect of heroin) and T40.2 (Poisoning by, adverse effect of and underdosing of other opioids), which would indicate heroin overdose death codes in NDI records on participants with no ECA-ascertained history of heroin use. We found none.

The possibility that some DIS-ascertained heroin users stopped or reduced heroin use should be noted (Calabria et al., 2010). In fact, NDI-recorded deaths for users might have nothing whatsoever to do with a person's heroin use in the 1980s. Observed deaths might be due to long-term consequences of correlated risky behaviors generally, such as nicotine use, unsafe sex practices, or criminal activities that pre-date heroin use (Ball et al., 1983; Harrell et al., 2012; Goldstein and Herrera, 1995). Interpreted in this fashion, this study's RR estimates clearly quantify heroin use history as a statistically independent predictor of survivorship and death under the statistical models we have used, even if there were to be no attempt to draw a firm causal inference from these heroin effect estimates. In addition, our NDI record trace stopped in 2007. We hope for new research grant support to update these estimates during recent years of dramatic increases in heroin-attributable mortality in the US, as noted elsewhere (e.g., Rudd et al., 2014).

Notwithstanding study limitations, these new estimates of heroin-predicted premature mortality in the US help to substantiate and extend what has been observed in more restricted samples, particularly in its estimates for heroin users who did not progress into sustained near-daily use. Counter-balanced with limitations, this epidemiological study has strengths that help lend credibility to its estimates, including its community sampling, standardized baseline assessments, and NDI follow-up for ascertainment of death.

We hope clinicians, public health workers and policy analysts will benefit from this new set of estimates on risk of premature death in an unrestricted community sample of heroin and other drug users in the community. Perhaps heroin estimates of this type can be communicated to young people who might be thinking about an initial trial use of heroin, with no expectation of sustained use. This new evidence also might have a more general utility in heroin prevention programs, other forms of public health outreach, new treatment innovations and drug policy interventions (Volkow et al., 2014b).

Financial disclosures

The authors are not aware of conflicts of interest. The financial support for the research is from the US National Institutes of Health National Institute on Drug Abuse [K05 award K05DA015799 (JCA); T32 award DA021129 (CLQ); R01 award DA026652 (WWE). Contents are the sole responsibility of the authors and do not necessarily represent official views of our university or the National Institute on Drug Abuse.

Contributors

Anthony JC designed the study; Roth K prepared the dataset, Lopez-Quintero C managed the literature searches, wrote the first draft of the manuscript and conducted the statistical analyses. All authors contributed to and have approved the final manuscript.

Conflict of interest

No conflict declared.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.drugalcdep.2015.08.030.

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