Differences in mortality in a cohort of cocaine use disorder patients with concurrent alcohol or opiates disorder

Running head: **Differences in mortality among cocaine users**

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Abstract

Aims. To study mortality in a cohort of cocaine use disorder patients, and compare results in those with concurrent alcohol or opiates disorder.

Design. Setting. Participants. A cohort of 10,539 cocaine use disorder individuals entering drug treatment in public outpatient centres in the city of Barcelona was followed from 1997 to 2011. Participants were divided at baseline into three groups: those with only cocaine use disorder (CUD), those with cocaine and alcohol use disorder, but not opioid (CAUD), and those with cocaine and opioid use disorder (COUD). Mortality was assessed through the Spanish National Mortality Register.

Measurements. Crude mortality rates (CMR), standardised mortality ratios (SMR), and rate ratios (RR) were calculated for each group. A multivariable Cox regression model was fitted to obtain adjusted mortality hazard ratios (aHR) of CAUD and COUD with respect to CUD. Specific mortality causes were also examined.

Findings. The total of 716 deaths registered resulted in a CMR=6.0/1000 person-year (PY); 95% confidence interval (CI): 5.1-7.0 for CUD, CMR=5.8/1000PY (95%CI:4.9-6.7) for CAUD, and CMR=20.7/1000PY (95%CI:18.8-22.8) for COUD, with no significant differences among sexes. Compared to the general population, mortality was four times higher (SMR=4.1, 95%CI:3.5-4.8) among CUD, more than three times among CAUD (SMR=3.4, 95%CI:2.9-3.9) and more than ten times among COUD (SMR=11.6, 95%CI:10.5-12.8), being always higher in women. External injuries, led by overdose, accumulated the biggest percentage of deaths among the three groups, but infectious diseases showed the highest excess mortality. Some differences regarding causes of death were observed between the three groups.

Conclusions. Cocaine use disorder patients present different profiles and mortality outcomes when concurrent disorder for alcohol or opiates is considered. Mortality risk and excess mortality are significantly greater among those with cocaine and opiates use disorder.

Keywords: Cocaine use disorder, mortality rate, excess mortality, cause of death

Introduction

Cocaine is the most commonly used illicit stimulant drug in Europe. Over two million people used cocaine in the last year in Europe, with Spain and the United Kingdom leading the ranking of prevalence of cocaine use [1]. Admission of cocaine users to specialised drug treatment centres started to grow in Spain in the 1990s, soon exceeding that of heroin users which was already declining. Currently, cocaine is responsible for the greatest proportion of admissions to treatment for illegal drugs with about 25% of all admissions [2]. In Barcelona, cocaine use increased up to 2006 when it reached a prevalence per 100 inhabitants of 2.50 (95%CI 1.54-4.13) among those aged 15-54 years old [3].

Despite the limited use of heroin and other opioids, these continue to be the drugs associated with most of the mortality related to illegal drug use in Europe, basically owing to drug overdose and infectious diseases [1,4,5]. Regarding cocaine, evidence suggests that its use increases the risk of injuries, cardiovascular disease, stroke and other health problems [6–10], but available mortality rates for cocaine vary widely. According to a systematic review of cohort studies [11], crude mortality rates among dependent cocaine users ranged from 0.53 to 6.1 per 100 person years, being four to eight times higher than their age and sex peers in the general population.

This variability in cocaine-related mortality could be attributed to the fact that cocaine users are not a homogeneous group and that the concomitant use of cocaine with other drugs, primarily opioids, would establish differences among cocaine users in the prevalence of injected use, HIV and other infectious diseases, and in the socioeconomic background that may distort mortality findings.

In order to address these issues, recent research in this field has made a distinction between socially integrated users who snort powder cocaine and who do not use heroin, and more marginalised users who use cocaine in conjunction with opiates [12–14], recording higher mortality risk among users of both cocaine and heroin and among those injecting drugs.

Besides, concurrent alcohol use disorder is common among those seeking treatment for cocaine dependence [15,16], with co-dependent patients presenting a wider array of health and social problems [16]. It has also been proposed that the synergistic effect of alcohol may potentiate acute adverse effects of cocaine [17,18], thus increasing mortality risks.

In order to contribute to the scant and inconclusive literature on cocaine-related mortality, the objective of this study was to estimate mortality rates and excess mortality overall and by

specific causes of death, in a cohort of cocaine users entering drug-dependence treatment and to compare the results in those with concurrent alcohol or opiates disorder.

Methods

Design

A longitudinal study was designed with a dynamic cohort of 10,539 cocaine use disorder patients entering drug treatment between 1997 and 2011 in nine of the 14 public outpatient treatment centres in the city of Barcelona. These fully accessible public treatment centres with no waiting list are evenly distributed in the territory covering different socio-economic areas, and represent 73.8% of all cocaine treatment starts in the city. Treatment is universally provided free of charge, including opiate substitution treatment if needed. To estimate differences in mortality participants were divided in three groups considering their concomitant use of alcohol or opiates in addition to cocaine. The study had the approval of the Ethics Committee of Hospital del Mar and all participants signed an informed consent when entering the study.

Participants

The prime criterion for inclusion of participants in the study was the occurrence of cocaine use disorder, irrespective of the drug for which they initiated treatment. Participants were divided at baseline into three groups: those with only cocaine use disorder (CUD), those with alcohol disorder in addition to cocaine (CAUD), and those with cocaine and heroin or other opioids disorder (COUD). In cases where opioids and alcohol use disorder occurred together with cocaine, precedence was given to opioids.

Further information recorded at baseline was: sex, age, educational level, occupational status and whether they had a criminal record or not. Regarding health status, information on self-perceived health, a history of psychopathology and positive HIV status were also recorded. Drug use patterns such as years of cocaine use and use of injected drugs ever were also recorded.

Vital status of participants was obtained through confidential probabilistic record linkage with the Spanish National Mortality Register. In cases of death, date and cause of death were noted. Subjects not detected as dead were assumed to be still alive at the end of the study period (31 Dec. 2011).

Statistical analysis

All-cause crude mortality rates (CMR) and 95% confidence intervals (CI) were calculated separately for the three groups of cocaine users (CUD, CAUD and COUD) and by the different sociodemographic, health and drug use patterns variables. CMR were expressed in person-years of follow-up (PY). Each subject contributed to PY from baseline (date of treatment entry) until the date of death or 31 Dec. 2011 (end of study). Standardised mortality ratios (SMR) obtained using the indirect method and rate ratios (RR) by age groups were also computed in order to estimate excess mortality for the three user groups and by sex, using the general population of Barcelona in 2011 as the reference. SMR were also calculated taking into account only the first year after treatment entry. Specific mortality causes were registered using the International Classification of Diseases ninth revision (ICD-9) for 1997-1998 and ICD-10 thereafter. Causes of death were grouped into broad categories (external injuries, infectious diseases, circulatory diseases, respiratory diseases, neoplasms, digestive diseases, other diseases and ill-defined), each category except other diseases and ill-defined were further broken into sub-categories. Codes included in each category are shown as supplementary material (Table S1). Crude mortality rates and rate ratios were also calculated per cause of death for each group. Finally, a multivariable Cox regression model was fitted in order to obtain adjusted mortality hazard ratios (aHR) and 95% CI of CAUD and COUD with respect to CUD. The proportional hazard assumption, checked by examining Schoenfeld residuals, was not violated. Data were censored at 31 December 2011. The model was adjusted for sex, age, educational level, occupational status, HIV status (unknown HIV status considered as a category), and ever injector. All analyses were performed using STATA version 10.1.

Results

A total of 10,539 individuals (81% men) were followed from 1997 until their death or the end of 2011, generating a total of 71,924.5 person-years of follow-up.

Baseline characteristics

Table 1 shows participants' descriptive characteristics at treatment entry by group of drug use disorder. Cocaine-only (CUD) represented 34% of the total, cocaine and alcohol (CAUD) 43%, and cocaine and opioids (COUD) 23%. The proportions of women were 23%, 16% and 20%, respectively. Mean age at entry was 31.6 years (SD 8.1) for CUD, 33.2 (SD 7.9) for CAUD, and 32.3 (SD 7.2) for COUD. Approximately 55% of CUD and CAUD had only completed primary

education, while among COUD the figure was 72%. Furthermore, only 20% of COUD were working at baseline, compared to around 55% in the other two groups. Also, almost 60% of COUD had a criminal record, compared to 23% of CUD and 27% of CAUD. Regarding health status, about 60% of CUD and CAUD perceived their health as good, whereas among COUD the corresponding figure was 40%. Conversely, over 30% of CUD and CAUD had a record of psychopathology while among COUD the corresponding figure was only 18%. Differences concerning HIV infection were also substantial with only 2-3% of positive serostatus among CUD and CAUD compared to 17% among COUD. Regarding use patterns, the highest proportions of individuals with more than 10 years of cocaine use were recorded among CAUD and COUD (44% and 45%, respectively), while CUD had the highest percentage of individuals with less than five years of use (33%). Finally, 71% of COUD had a record of having used injected drugs compared to only 6% in the other groups.

Mortality

A total of 716 deaths were registered in the study period, with a mean age at death of 39.3 years. Crude mortality rates (CMR) were 6.0/1000 PY for CUD, 5.8/1000 PY for CAUD, and 20.7/1000 PY for COUD overall, with no significant differences between men and women (Table 1). Besides, higher CMR were found in all groups among those categorised as disabled/pensioner followed by unemployed, and those with a criminal record. CMR were also higher among those reporting poor health and, particularly, among those with a positive HIV test (18.7/1000 PY for CUD; 33.6/1000 PY for CAUD; and 42.4/1000 PY for COUD), and for those who had ever injected drugs (16.6/1000 PY for CUD; 18.3, for CAUD; and 24.0 for COUD). Among CAUD and COUD CMR were higher for those with more than 10 years of cocaine use.

Table 2 describes crude mortality rates and rate ratios per age group and standardised mortality ratios, by group of drug use disorder. Compared with the general population, mortality among CUD was four times higher (SMR 4.1), more than three times among CAUD (SMR 3.4) and more than ten times among COUD (SMR 11.6). Standardised mortality ratios for the first year after treatment entry were higher than those obtained for the entire period in the three groups (SMR 9.2, 95%CI: 5.5-12.9 for CUD, SMR 4.1, 95%CI: 2.0-6.2 for CAUD, and SMR 37.8, 95%CI: 28.6-46.9 for COUD). This excess mortality was always larger for women. Besides, results by age group indicate that the largest contribution to excess mortality corresponded to the youngest group. Mortality rate ratios among those aged 18-34 were 20.8 for CUD, 19.2 for CAUD and 114.8 for COUD.

The results of the Cox regression revealed that after adjusting for sociodemographic, health and use patterns variables, the risk of death among COUD was still two times higher than among CUD (aHR=2.14, 95%CI: 1.68-2.73). Conversely, differences between CUD and CAUD were not significant (aHR=0.85, 95%CI: 0.68-1.07). No differences by gender were observed.

Causes of death

Table 3 displays causes of death by categories for the total cohort and by group of drug use disorder. Of the 711 deaths with a valid recorded cause 20.7% corresponded to CUD, 22.2% to CAUD and 57.1% to COUD. The broad category accumulating the biggest percentage of deaths overall and among the three groups was external injuries (CUD: 41.5%, CAUD: 33.5%, and COUD: 36.2%), with overdose leading this category also in the three groups with 16.3%, 13.3% and 22.7% of all deaths, respectively. However, while other external injuries was the second most common specific cause of death for CUD and CAUD with 15% and 13.3% of all deaths respectively, AIDS was second in the ranking for COUD with 18% of all deaths within this group.

Excess mortality analysis per cause of death (Table 4) showed that, overall, infectious diseases had the highest ratio compared with the general population (RR=21.6), followed by external injuries (RR=18.8) and respiratory diseases (RR=12.4), not considering ill-defined causes. By groups of drug use disorder, infectious diseases led excess mortality among COUD (RR=64.6), followed by external injuries and respiratory diseases (RR=38.4 and RR=27.3, respectively). External injuries led excess mortality among both CUD and CAUD (RR=12.8 and RR=10.0, respectively), but while respiratory diseases was the second group among CUD with an excess mortality of almost eight times that of the general population for this cause (RR=7.8), in the case of CAUD it was Infectious diseases (RR=6.2), with respiratory (RR=5.7) and Digestive diseases (RR=4.9) following closely.

Discussion

Our results show higher mortality rates among individuals with concurrent cocaine and opiates use disorders, the risk of death being two times higher among this group compared to individuals with cocaine use disorder only. External injuries accounted for the highest share of deaths among the three groups, although infectious diseases showed the highest excess mortality overall. Patients with cocaine use disorder only and those with concurrent alcohol use disorder showed similar mortality rates, although they presented some differences regarding specific causes of death. The younger age group (18-34 years) had the highest mortality ratios, especially among those with cocaine and opiates use disorder, while

standardised mortality ratios were higher among women compared to men in the three groups.

As previously mentioned, heterogeneity among cocaine users could explain the wide range of mortality rates associated with cocaine use observed in the literature [11]. Differences in the characteristics at treatment entry between the three groups of patients in the present study would support the notion of different typologies of cocaine users. Other mortality studies have also considered concomitant use of opioids but not of alcohol [12–14]. In our study, those with cocaine and alcohol use disorder were older and there were fewer women, while fewer of those with cocaine and opiates use disorder were working compared with the other two groups. Differences in the health status were also notable. Those with cocaine only and cocaine and alcohol use disorder reported better health but were more likely to have a history of psychopathology than those with cocaine and opiates use disorder. Besides, the proportion of HIV infection, probably linked to injection use, was larger among the latter.

Similar to other studies, our results show higher mortality rates among cocaine and opioids users compared to cocaine only users [12–14]. Furthermore, in our study mortality risk among those with cocaine and opiates use disorder is two times higher compared with cocaine only, even after considering sociodemographic, health and use patterns characteristics. This excess mortality could be explained by the high share of deaths for overdose and infectious diseases observed among this group. Overdose is the specific cause accumulating more deaths in the three groups, being markedly higher among those with cocaine and opiates use disorder. Overdose has been described as the major cause of death among opioids users [4] and it is therefore not surprising that overdose deaths among this group was outstandingly high. Besides, infectious diseases, specifically AIDS, are the other cause of death which is significantly higher among those with cocaine and opiates use disorder, and the one showing the highest excess mortality overall.

Conversely, those with cocaine only and cocaine and alcohol use disorder show similar mortality rates. In the same way, these two groups present considerable similarities at treatment entry except for the lower proportion of women, older age and a longer period of cocaine use among those with coexisting alcohol use disorder. However, we would highlight some differences regarding causes of death that would help to establish important distinctions between these two groups. The proportion of deaths due to external injuries (including overdose, suicide and other external injuries) is higher among those with cocaine use disorder only, while the share of infectious diseases, neoplasms and digestive diseases is larger among

those with cocaine and alcohol use disorder. Cocaine abstinence imposed at treatment entry frequently leads to depression which would in turn increase the probability of suicide in the first year. A higher risk for suicide has already been described among cocaine users linked to comorbid depression [19–21]. Besides, the burden of alcohol use on health would be manifest among those with concurrent alcohol use disorder in the higher mortality ratios for infectious and digestive diseases among this group compared to that of cocaine only, as described in other studies [22,23]. With respect to drug overdose deaths, some non-specific causes of death such as pulmonary edema and respiratory insufficiency, the leading cause within respiratory diseases in the three groups of our cohort, could further add to the final overdose figure. A study aimed at validating the underlying cause of death of the Mortality Register in Spain [24] found that over 20% of the deaths registered as caused by respiratory diseases were actually due to poisoning. It is also worth mentioning the high mortality rates for ill-defined causes in our cohort. In this regard, Gotsens et al. (24) concluded that a considerable number of ill-defined causes of death were in fact due to external injuries, mostly poisoning and suicides, which would signify a further increase of these deaths in the context of our study.

Even though opioid use disorder patients in our study were mostly heroin users, the widely documented increase of non-medical use of prescription opioids and its consequences, including drug overdose, prompts the need to improve data collection to favour the study and prevention of this cause of death [25–27]. Besides, as other studies have already pointed out [28] use patterns are important in order to target interventions to prevent drug overdose in particular subpopulations.

Comparing mortality in our cohort to that in the general population also shows that the highest excess mortality corresponds to the youngest with the only exception being women with cocaine and alcohol use disorder, probably due to the small number of young women in this group (lack of statistical power). The higher mortality observed during the first year after treatment entry in all groups can be explained because patients tend to delay seeking assistance and often reach treatment centres in a deteriorated health condition. This aspect can be very relevant to inform public health policies. The negative ratios obtained for neoplasm deaths could relate to the fact that in the general population this cause of death concentrates among those aged over 45 years, the age group showing the lowest excess mortality in our cohort. Besides, we have to bear in mind that deaths from external injuries or infectious diseases occurring earlier in life would compete with the risk of dying of other diseases at an older age. On the other hand, and contrary to the results of other studies with heroin users [29,30], mortality rates and hazard ratios do not differ between men and women

in our cohort of substance use disorder patients. The higher standardised mortality ratios of women compared to men can be explained by the lower mortality rates of women in all age-groups in the general population as in Guitart et al. [31].

We also have to consider that our study covers deaths occurring over a long period (from 1997 to 2011). Other studies analysing calendar-year of death in Spain have found a decrease in mortality risk in recent years among cocaine-heroin users [14] probably due to the decrease of fatal overdoses and HIV-related mortality following the implementation of opioid substitution therapy programs and the wide availability of antiretroviral therapy, as well as other recent harm reduction strategies (e.g. take-home naloxone). Therefore, it is possible that differences observed among those with concurrent cocaine and opioids use disorder and the other two groups in our study would diminish if we were to consider recent years only, though looking for differences over time was not an objective of our study.

Establishing different typologies of users and examining mortality indicators and causes of death has proven to be a helpful way to shed some light on the mortality associated with cocaine use. However, some other limitations have to be mentioned. The groupings used in this study were defined on the basis of the patient's drug use disorder at baseline and changes regarding the drug of choice or other characteristics such as route of administration or HIV serostatus that may affect mortality risk were not assessed. For instance, some of the overdose deaths registered in the groups of cocaine only and cocaine and alcohol use disorder would not necessarily be cocaine overdoses as the individual may have switched to sporadic or permanent opioid use later. Similarly, no information was collected regarding cocaine use during follow-up. Also, it could be that treatment centres differed in their assessment of substance use disorder and this may have had an impact on the classification of patients for our groups of use disorder; for instance, alcohol use disorder might not have been registered if cocaine use was a major concern.

Finally, our study cohort was formed by patients from public treatment centres and this may have led to an underrepresentation of patients from more advantaged socioeconomic background attending private treatment services. This cohort may also lack representativeness regarding people with cocaine use disorder in the general population with lighter forms of cocaine use disorder not seeking treatment and given the relative lack of effective treatment options. In this respect, mortality among cocaine use disorder patients in general may be over-estimated in this study.

Our results indicate that excess mortality and mortality risk are significantly higher among patients with cocaine and opiates use disorder compared with the other two groups. However, our analyses have also revealed some differences between those with cocaine only and those with cocaine and alcohol use disorder regarding leading causes of death. Overdose deaths are a major concern among the three groups and point to the need to target prevention policies for specific subpopulations of users.

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Table 1. Descriptive characteristics at treatment entry and crude mortality rates (CMR) of a cohort of cocaine users by group of drug use disorder. Barcelona, 1997-2011.

	Cocaine Use Disorder only (CUD)					Cocaine and Alcohol Use Disorder (CAUD)					Cocaine and Opioids Use Disorder (COUD)				
	N	(%)	deaths	person-years	CMR/1000 PY (95%CI)*	N	(%)	deaths	person-years	CMR/1000 PY (95%CI)*	N	(%)	deaths	person-years	CMR/1000 PY (95%CI)*
Total	3590	(34)	147	24645.7	6.0 (5.1-7.0)	4509	(43)	158	27442.6	5.8 (4.9-6.7)	2440	(23)	411	19836.1	20.7 (18.8-22.8)
Sociodemographic															
Mean age (Std. Dev.)	31.6 (SD 8.1)					33.2 (SD 7.9)					32.3 (SD 7.2)				
Male	2765	(77)	110	19015.0	5.8 (4.8-7.0)	3777	(84)	137	23230.3	5.9 (5.0-7.0)	1949	(80)	340	15801.4	21.5 (19.3-23.9)
Female	825	(23)	37	5630.8	6.6 (4.6-9.1)	732	(16)	21	4212.3	5.0 (3.1-7.7)	491	(20)	71	4034.7	17.6 (13.8-22.4)
Education															
Primary	1969	(55)	97	13651.2	7.1 (5.8-8.7)	2541	(56)	97	15843.5	6.1 (5.0-7.5)	1756	(72)	303	14582.0	20.8 (18.5-23.3)
Secondary	1211	(34)	32	8673.7	3.7 (2.5-5.3)	1512	(34)	52	9322.2	5.6 (4.1-7.4)	512	(21)	88	4050.3	21.7 (17.6-26.9)
University	389	(11)	14	2176.7	6.4 (3.5-10.8)	448	(10)	9	2220.8	4.1 (1.9-7.7)	143	(6)	15	952.4	15.8 (8.8-26.0)
Occupational status															
Working	1922	(54)	53	13865.2	3.8 (2.5-5.1)	2525	(56)	73	16195.9	4.5 (3.5-5.7)	493	(20)	64	4196.3	15.3 (11.7-19.6)
Unemployed	1091	(30)	55	6962.2	7.9 (6.0-10.3)	1436	(32)	58	8000.9	7.2 (5.6-9.4)	1375	(56)	226	11356.4	19.9 (17.4-22.7)
Disabled/pensioner	148	(4)	16	872.1	18.3 (10.5-29.7)	164	(4)	15	854.3	17.6 (9.8-29.0)	160	(7)	55	1073.0	51.3 (38.8-67.2)
Other	397	(11)	20	2767.4	7.2 (4.4-11.1)	370	(8)	11	2312.8	4.8 (2.4-8.5)	349	(14)	61	2719.1	22.4 (20.2-25.0)
Criminal record															
Yes	823	(23)	49	5396.0	9.1 (6.7-12.0)	1212	(27)	56	7164.6	7.8 (6.0-10.2)	1449	(59)	270	12137.4	22.3 (19.7-25.1)
No	2694	(75)	94	18764.3	5.0 (4.1-6.2)	3189	(71)	99	19589.4	5.1 (4.1-6.2)	879	(36)	125	7084.3	17.6 (14.7-21.2)
Health status															
Self-perceived health															
Poor	1238	(34)	71	8380.3	8.5 (6.7-10.8)	1583	(35)	69	9490.2	7.3 (5.7-9.2)	1414	(58)	253	11270.2	22.4 (19.8-25.5)
Good	2308	(64)	74	16146.2	4.6 (3.6-5.8)	2791	(62)	82	17124.4	4.8 (3.8-6.0)	972	(40)	154	8439.4	18.2 (15.6-21.4)
Psychopathology															
Yes	1166	(32)	47	6807.7	6.9 (5.1-9.2)	1631	(36)	54	8587.9	6.3 (4.7-8.2)	435	(18)	71	3223.3	22.0 (17.3-28.0)
No	2264	(63)	86	16534.6	5.2 (4.2-6.5)	2792	(62)	90	18074.1	5.0 (4.0-6.2)	1706	(70)	286	13747.4	20.8 (18.5-23.4)
HIV+															
Yes	110	(3)	12	641.5	18.7 (9.7-32.7)	71	(2)	14	416.6	33.6 (18.4-56.4)	410	(17)	145	3417.7	42.4 (35.9-50.2)
No	1474	(41)	70	10007.7	7.0 (5.5-8.9)	1700	(38)	54	9813.6	5.5 (4.2-7.2)	967	(40)	129	7990.3	16.1 (13.5-19.2)
Unknown	2006	(56)	65	13996.5	4.6 (3.6-5.9)	2738	(61)	90	17212.4	5.2 (4.2-6.5)	1063	(44)	137	8428.1	16.3 (13.7-19.3)
Use patterns															
Years of cocaine use															
< 5 years	1184	(33)	43	9545.2	4.5 (3.3-6.1)	1098	(24)	35	7779.3	4.5 (3.1-6.3)	541	(22)	73	4520.0	16.2 (12.8-20.3)
6 to 10 years	1082	(30)	50	7580.2	6.6 (4.9-8.7)	1201	(27)	40	7744.8	5.2 (3.7-7.0)	577	(24)	85	5232.6	16.2 (13.1-20.2)

> 10 years	1262	(35)	50	7197.9	6.9	(5.2-9.2)	1963	(44)	76	10562.5	7.2	(5.7-9.1)	1109	(45)	227	8808.1	25.8	(22.6-29.4)
Ever injector																		
Yes	215	(6)	28	1686.8	16.6	(11.0-24.1)	274	(6)	35	1913.1	18.3	(12.8-25.4)	1727	(71)	338	14108.9	24.0	(21.5-26.6)
No	3323	(93)	119	22805.8	5.2	(4.4-6.3)	4212	(93)	122	25474.7	4.8	(4.0-5.7)	706	(29)	72	5706.4	12.6	(9.9-16.0)

* Crude Mortality Rates per 1000 person-years and 95% Confidence Interval.

Table 2. Mortality indicators in a cohort of cocaine users by age and group of drug use disorder in men and women. Barcelona 1997-2011.

	Age groups	Total			Males			Females		
		CMR/1000PY (95%CI) (a)	RR (95%CI) (b)	SMR (95%CI) (c)	CMR/1000PY (95%CI) (a)	RR (95%CI) (b)	SMR (95%CI) (c)	CMR/1000PY (95%CI) (a)	RR (95%CI) (b)	SMR (95%CI) (c)
Cocaine only (CUD)	18-34	7.5 (5.7-9.8)	20.8 (15.8-27.2)		7.4 (5.3-10.1)	14.8 (10.6-20.3)		7.7 (4.3-12.4)	35.5 (19.8-57.2)	
	35-44	5.1 (3.9-6.7)	6.3 (4.8-8.3)		4.7 (3.4-6.4)	4.8 (3.5-6.6)		6.5 (3.6-10.7)	10.2 (5.7-16.9)	
	45-64	5.7 (4.0-7.9)	1.5 (1.0-2.0)		5.8 (3.9-8.5)	1.1 (0.7-1.6)		5.1 (2.0-10.5)	2.0 (0.8-4.1)	
				4.1 (3.5-4.8)			3.0 (2.4-3.5)			6.8 (4.6-9.0)
Cocaine and alcohol (CAUD)	18-34	6.9 (5.0-9.3)	19.2 (13.9-25.8)		8.1 (5.9-10.9)	16.3 (11.8-21.9)		1.6 (0.2-5.9)	7.4 (0.9-27.2)	
	35-44	4.5 (3.3-5.9)	5.6 (4.3-7.3)		4.3 (3.1-5.8)	4.4 (3.2-5.9)		5.3 (2.4-10.1)	8.4 (3.8-15.9)	
	45-64	6.6 (5.1-8.6)	1.7 (1.3-2.2)		6.5 (4.8-8.5)	1.2 (0.9-1.6)		7.7 (3.7-14.1)	3.0 (1.4-5.5)	
				3.4 (2.9-3.9)			2.6 (2.1-3.0)			4.5 (2.6-6.4)
Cocaine and opiates (COUD)	18-34	41.3 (34.9-48.9)	114.8 (97.0-135.9)		49.1 (40.9-59.0)	98.5 (82.1-118.4)		22.4 (14.0-25.8)	103.3 (64.6-119.0)	
	35-44	18.7 (16.1-21.7)	23.1 (19.9-26.8)		17.7 (14.9-20.9)	18.1 (15.3-21.4)		23.0 (16.4-31.3)	36.2 (25.8-49.3)	
	45-64	13.4 (10.9-16.7)	3.5 (2.8-4.3)		15.1 (12.2-18.8)	2.8 (2.3-3.5)		5.7 (2.3-11.8)	2.2 (0.9-4.6)	
				11.6 (10.5-12.8)			8.8 (7.9-9.8)			15.7 (12.0-19.3)

(a) Crude Mortality Rate per 1000 person-years and 95% confidence interval.

(b) Rate Ratio and 95% confidence interval calculated using Barcelona 2011 population as the reference.

(c) Standardised Mortality Ratio and 95% confidence interval using Barcelona 2011 population as the reference.

Table 3. Causes of death among a cohort of cocaine users by groups of drug use disorder. Barcelona 1997-2011

	Total		Cocaine only (CUD)		Cocaine and alcohol (CAUD)		Cocaine and opiates (COUD)	
	Deaths	%	Deaths	%	Deaths	%	Deaths	%
External injuries	261	36.7	61	41.5	53	33.5	147	36.2
Overdose	137	19.3	24	16.3	21	13.3	92	22.7
Suicide	40	5.6	15	10.2	11	7.0	14	3.4
Other ext. Inj.	84	11.8	22	15.0	21	13.3	41	10.1
Infectious diseases	109	15.3	7	4.8	12	7.6	90	22.2
AIDS	87	12.2	4	2.7	10	6.3	73	18.0
Viral hepatitis	12	1.7	1	0.7	1	0.6	10	2.5
Other infectious dis.	10	1.4	2	1.4	1	0.6	7	1.7
Circulatory diseases	87	12.2	24	16.3	25	15.8	38	9.4
Ischaemic heart dis.	30	4.2	9	6.1	10	6.3	11	2.7
Other forms of heart dis.	35	4.9	12	8.2	9	5.7	14	3.4
Other circulatory dis.	22	3.1	3	2.0	6	3.8	13	3.2
Respiratory diseases	74	10.4	16	10.9	13	8.2	45	11.1
Pulmonary edema & resp. insuffic.	51	7.2	12	8.2	10	6.3	29	7.1
Pneumonia	9	1.3	2	1.4	0	0.0	7	1.7
Other respiratory diseases	14	2.0	2	1.4	3	1.9	9	2.2
Neoplasms	68	9.6	15	10.2	26	16.5	27	6.7
Digestive	21	3.0	3	2.0	8	5.1	10	2.5
Respiratory	28	3.9	6	4.1	13	8.2	9	2.2
Other neoplasms	19	2.7	6	4.1	5	3.2	8	2.0
Digestive diseases	50	7.0	7	4.8	14	8.9	29	7.1
Diseases of the liver	43	6.0	5	3.4	11	7.0	27	6.7
Other digestive diseases	7	1.0	2	1.4	3	1.9	2	0.5
Other diseases	35	4.9	10	6.8	9	5.7	16	3.9
Ill-defined	27	3.8	7	4.8	6	3.8	14	3.4
TOTAL	711	100	147	20.7	158	22.2	406	57.1

Table 4. Mortality indicators per main causes of death in a cohort of cocaine users by groups of drug use disorder. Barcelona 1997-2011

	Barcelona 2011	Cohort											
		Total			Cocaine only (CUD)			Cocaine and alcohol (CAUD)			Cocaine and opiates (COUD)		
		Deaths	CMR/1000PY (95%CI)(b)	RR (95%CI)(c)	Deaths	CMR/1000PY (95%CI) (b)	RR (95%CI) (c)	Deaths	CMR/1000PY (95%CI) (b)	RR (95%CI) (c)	Deaths	CMR/1000PY (95%CI) (b)	RR (95%CI) (c)
External injuries	0.2	261	3.6 (3.2-4.1)	18.8 (16.6-21.2)	61	2.5 (1.9-3.2)	12.8 (9.9-16.7)	53	1.9 (1.5-2.5)	10.0 (7.5-13.1)	147	7.4 (6.3-8.7)	38.4 (32.6-45.2)
Infectious diseases	0.1	109	1.5 (1.3-1.8)	21.6 (17.8-26.1)	7	0.3 (0.1-0.6)	4.0 (1.6-8.3)	12	0.4 (0.2-0.8)	6.2 (3.2-10.9)	90	4.5 (3.7-5.6)	64.6 (52.3-80.1)
Circulatory diseases	0.3	87	1.2 (1.0-1.5)	4.4 (3.6-5.4)	24	1.0 (0.6-1.5)	3.5 (2.3-5.3)	25	0.9 (0.6-1.3)	3.3 (2.1-4.9)	38	1.9 (1.4-2.6)	7.0 (4.9-9.6)
Respiratory diseases	0.1	74	1.0 (0.8-1.3)	12.4 (9.8-15.6)	16	0.6 (0.4-1.0)	7.8 (4.5-12.6)	13	0.5 (0.3-0.8)	5.7 (3.0-9.7)	45	2.3 (1.7-3.0)	27.3 (19.9-36.6)
Neoplasm	4.2	68	0.9 (0.7-1.2)	0.2 (0.2-0.3)	15	0.6 (0.4-1.0)	0.2 (0.1-0.2)	26	0.9 (0.6-1.4)	0.2 (0.1-0.3)	27	1.4 (0.9-2.0)	0.3 (0.2-0.5)
Digestive diseases	0.1	50	0.7 (0.5-0.8)	6.7 (5.0-8.9)	7	0.3 (0.1-0.6)	2.7 (1.1-5.7)	14	0.5 (0.3-0.9)	4.9 (2.7-8.2)	29	1.5 (1.0-2.1)	14.1 (9.5-20.3)
Ill-defined	0.02	27	0.4 (0.2-0.5)	16.3 (10.7-23.7)	7	0.3 (0.1-0.6)	12.3 (4.9-25.3)	6	0.2 (0.1-0.5)	9.4 (3.5-20.5)	14	0.7 (0.4-1.2)	30.6 (16.7-51.3)

(a) Crude Mortality Rate per 1000 persons.

(b) Crude Mortality Rate per 1000 person-years and 95% confidence interval.

(c) Rate Ratio and 95% confidence interval calculated using Barcelona 2011 population as the reference.

Table S1. International Classification of Diseases (ICD-9 and ICD-10) codes used to classify cause of death in a cohort of cocaine users. Barcelona 1997-2011

	Deaths	Codes
External inj.	261	
Overdose	137	E8500, E8501, E8589, E8590, E8591, X410, X42, X420, X424, X425, X429, X44, X440, X441, X442, X444, X446, X449, X49, X490, X499
Suicide	40	E9554, X640, X649, X690, X70, X700, X701, X706, X709, X719, X740, X749, X80, X800, X804, X809, X818, X819, X840, X844, X849
Other ext. Injuries	84	E8192, E9289, F102, F112, F142, F190, F192, F199, V041, V050, V055, V09, V092, V239, V274, V445, V459, V475, V485, V489, V576, V892, W139, W17, W174, W179, W199, W698, W708, W749, W78, W795, W809, W840, W841, W849, X099, X599, X910, X942, X99, X999, Y099, Y12, Y120, Y30, Y33, Y830, Y831
Infectious diseases	109	
AIDS	87	2795, B20, B200, B202, B203, B205, B206, B207, B208, B209, B21, B212, B213, B218, B220, B222, B227, B238, B24
Viral hepatitis	12	B182, B199
Other infectious dis.	10	A09, A86, A412, A419
Circulatory diseases	87	
Ischaemic heart dis.	30	I21, I214, I219, I248, I249, I259
Other forms of hearth dis.	35	I33, I330, I38, I42, I420, I422, I461, I499, I50, I500, I509, I51, I514, I517, I519
Other circulatory dis.	22	430, I110, I269, I27, I270, I279, I60, I615, I619, I71, I710
Respiratory diseases	74	
Pulmonary edema & Resp. insuf.	51	J81, J96, J960, J969
Pneumonia	9	J13, J18, J189
Other respiratory dis.	14	496, J09, J209, J439, J441, J449, J841, J850, J90, J988
Neoplasms	68	
Digestive	21	C159, C169, C169, C189, C19, C20, C22, C220, C252, C259
Respiratory	28	C321, C349, C381
Other neoplasms.	19	C439, C509, C539, C549, C64, C689, C80, C81, C837, C859, C920, C97, D414, D487
Digestive diseases	50	
Diseases of the liver	43	K701, K703, K729, K739, K74, K746, K769
Other digestive dis.	7	K254, K400, K409, K559, K859, K860, K92
Other diseases	35	3589, D849, G039, G122, G409, G473, G710, G931, G934, L89, M009, M726, N10, N12, N179, N19, Q283, R092, R570, R571, R58, R688
Ill defined.	27	7860, 7958, 7998, 9999, R98, R98X, R99