



## Mortality risk factors and excess mortality in a cohort of cocaine users admitted to drug treatment in Spain ☆☆☆★

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### ABSTRACT

We assessed mortality risk factors and excess mortality compared to the general population in two Spanish sub-cohorts of 8,825 cocaine and heroin users (CHUs) and 11,905 only cocaine users (OCUs) aged 15–49 admitted to drug treatment. Heroin use (among all cocaine users), no-regular employment and drug injection (among CHUs and OCUs), daily cocaine use and previous drug treatment (among CUs), and death before 2005 and >10 years of heroin use (among CHUs) were clearly associated with higher mortality in Cox regression. Excess mortality was assessed by the directly standardized mortality rate ratio, which was higher in CHUs (14.3; 95% CI: 12.6–16.2) than CUs (5.1; 95% CI: 4.3–6.0) and in women than men, especially among OCUs (8.6; 95% CI: 7.5–10.0 vs. 3.5; 95% CI: 3.3–3.8); it decreased with age among CHUs, but did not decrease overall during 1997–2008. OCUs excess mortality was considerable and showed no signs of decline, suggesting the need for improved treatment and prevention interventions.

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### 1. Introduction

Cocaine use is widespread in many countries, mainly among young adults. In most countries cocaine is usually administered by sniffing, with smoking and injection generally restricted to heroin users and marginalized groups (United Nations Office on Drugs and Crime (UNODC), 2011; European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 2012; Substance Abuse & Mental Health Services Administration (SAMHSA), 2012a; Substance Abuse and Mental Health Services Administration (SAMHSA) (2012b)). Cocaine use has been associated with increased risk of cardiovascular, neurological, and psychiatric disorders, as well as unintentional

injuries, violent behaviours, and other health problems (European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 2007; Kaye & Darke, 2004a; Kuhns, Wilson, Maguire, Ainsworth, & Clodfelter, 2009; Macdonald et al., 2003; Maraj, Figueredo, & Lynn, 2010; Marzuk et al., 1995; Qureshi, Suri, Guterman, & Hopkins, 2001; Ryb et al., 2009; Santos et al., 2012; Schnitzer et al., 2010).

Cocaine accounts for a significant proportion of treatment admissions for illicit drugs in some countries. In addition, in the US and Spain it is the illicit drug related to the highest proportion of emergency room visits (United Nations Office on Drugs and Crime (UNODC), 2011; Delegación del Gobierno para el Plan Nacional sobre Drogas (DGPNSD), 2011; Substance Abuse and Mental Health Services Administration (SAMHSA) (2012b); European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), 2012). Thus, cocaine can be expected to contribute to a certain number of deaths in countries where it is used.

The role of cocaine in mortality can be assessed by quantifying the drug-induced deaths in which cocaine use is mentioned using special or general mortality registers (Bernstein et al., 2007; Coffin et al., 2003; Darke, Kaye, & Dufloy, 2005; Delegación del Gobierno para el Plan Nacional sobre Drogas (DGPNSD), 2011; Sanchez et al., 1995; Substance Abuse and Mental Health Services Administration, 2012), by investigating the presence of cocaine through toxicological analysis in some violent or sudden deaths (Kuhns et al., 2009; Lucena et al., 2010), or by studying mortality in cohorts of cocaine users over time

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(Arendt, Munk-Jorgensen, Sher, & Jensen, 2011; Barrio et al., 2013; Degenhardt et al., 2011b; Dias, Ribeiro, Dunn, Sesso, & Laranjeira, 2008; Pavarin, 2008; Ribeiro, Dunn, Laranjeira, & Sesso, 2004). All these have advantages and limitations, but this last approach makes it possible to quantify excess mortality in cocaine users compared to their age-sex peers in the general population, as well as to identify factors associated with a higher mortality risk (mortality risk factors).

Excess mortality is an indicator of the health needs of cocaine users in relation to the general population, and its time trends may reflect the influence of various factors, including changes in drug use patterns or the effectiveness of harm reduction interventions aimed at cocaine users (for example, drug abuse treatment).

The excess mortality for all causes among cohorts of cocaine users has been estimated as 4–12 times greater than in the general population (Arendt et al., 2011; Barrio et al., 2013; Degenhardt et al., 2011b; Dias et al., 2011). Most published estimates come from cohorts with over-representation of heroin users, drug injectors or crack/cocaine smokers, which are known or suspected to be associated with a higher risk of mortality (Barrio et al., 2013; Degenhardt et al., 2011a; Muhuri & Gfroerer, 2011). Thus, extrapolation of these estimates to all cocaine users in the general population could overestimate excess mortality. Moreover, most such estimates are based on standardized mortality ratios (SMRs); which allow comparison of the mortality risk of the cohort or cohort sub-groups with their age-sex peers in the general population, but not the excess mortality between different sub-groups, for example men and women. However, the latter comparisons would be possible using the direct method of standardization (Rothman, Greenland, & Lash, 2008).

Published data on mortality risk factors among cocaine users is scarce, due to limited cohort size or the difficulty of collecting information on relevant variables. Heroin or opioid use is suspected to be one of the main mortality risk factors, although its effect has not been quantified. This higher risk can be explained by the negative effects of the opioids themselves or a possible heightening of the negative effects of cocaine, especially on the cardiovascular system, when used concurrently with opioids, although this last remains a subject of debate (Bandettini et al., 2006; Goletiani, Mendelson, Sholar, Siegel, & Mello, 2009; Krantz, Baker, & Schmittner, 2006; Leri, Bruneau, & Stewart, 2003; Mello et al., 2005; Molina & Hargrove, 2011; Saland, Hillis, Lange, & Cigarroa, 2002; Schindler et al., 2007; United Nations Office on Drugs and Crime (UNODC), 2011). There is also a higher extent of crack/cocaine smoking and drug injection among cocaine users who also use heroin than among those who do not, which probably increases the risk of cardiovascular, respiratory, infectious, overdose and mental health problems (Baum et al., 2009; Cook et al., 2008; Devlin & Henry, 2008; Gossop, Manning, & Ridge, 2006; Hatsukami & Fischman, 1996; Shearer et al., 2007). In addition to opioid use and older age, other mortality risk factors are history of intravenous drug use (Arendt et al., 2011; Ribeiro et al., 2004), unemployment at baseline (Ribeiro et al., 2004), premature discharge from treatment or short time in treatment (Ribeiro et al., 2004; Yang, Huang, & Hser, 2006), early initiation of cocaine use (Yang et al., 2006), white ethnicity (Yang et al., 2006) or psychiatric comorbidity (Arendt et al., 2011). There are also some indications that the risk of death could be higher in males (Bernstein et al., 2007; Pavarin, 2008) and alcohol drinkers (Santos et al., 2012). Finally, excess mortality of cocaine users in comparison with the general population seems to be higher in females than males (Arendt et al., 2011; López, Martineau, & Palle, 2004), although the published results are not entirely conclusive.

In most mortality studies, cohorts of cocaine users are recruited in drug treatment facilities. In Spain in 1997–2009, an average of some 15,000 treatment admissions per year were reported for cocaine and 8,000 for heroin (in most of which the patient had also used cocaine in the 30 days prior to treatment). Thus, it is possible to recruit large cohorts of cocaine users for these studies. Treatment for cocaine abuse or dependence in Spain is generally based on individual or group therapy

with cognitive-behavioural orientation, with possible pharmacological support in case of psychiatric comorbidity (depression, anxiety, psychosis, etc.). Currently the most widespread treatment for heroin abuse or dependence is methadone maintenance, with buprenorphine maintenance used only rarely. It has been estimated that the coverage of heroin users by opioid substitution treatment (OST) in the whole country increased from 29% in 1997 to 61.9% in 2008, and that the increase occurred earlier in Barcelona than Madrid (Barrio et al., 2012).

The objectives of this study were: a) to estimate the mortality risk in a Spanish cohort of cocaine users, and to identify factors associated with a higher mortality risk, assessing especially the effect of heroin use, and b) to estimate excess mortality of two sub-cohorts defined by heroin use at baseline in comparison with the general population by sex and calendar-year of death.

## 2. Methods

### 2.1. Participants

A dynamic cohort of 20,730 cocaine users aged 15–49 was recruited in the cities of Madrid and Barcelona, Spain. Cocaine users who started drug treatment in 1997–2007 in publicly owned or funded centres in the two cities were included in the cohort regardless of whether they had been treated for drugs prior to 1997. Repeated admissions of the same subject were eliminated. All the treatment centres were outpatient centres that reported to the national drug information system and provided free care. Participants were initially separated in two subgroups, those who at baseline were cocaine and heroin users (CHUs), and those who were only cocaine users (OCUs). The criterion for cocaine use at baseline was being admitted for treatment to quit or reduce cocaine use or evidence in the clinical record of having used such drug within 30 days prior to treatment admission. The criterion for heroin use at baseline was similar, but obviously referring to heroin.

### 2.2. Baseline and follow up assessments

At the time of treatment admission an individual record was completed for each patient, including date of recruitment (which coincides with the date of treatment admission), existence of previous drug treatment, personal identifiers (first name, surname, date of birth and sex), socio-demographic variables (age, education, and employment), and drug use variables (lifetime drug injection, and frequency and length of cocaine and heroin use). Baseline measurements of socio-demographic variables and frequency of drug use referred to time of treatment admission or the previous 30 days. The proportion of missing values was less than 4% for all variables. Participants were followed until 31 December 2008. Vital status and date of death were obtained through record linkage with the Spanish National Mortality Register, which is virtually exhaustive, using the identifiers mentioned above. All individuals who were not identified as dead were considered to be alive at the end of follow-up. The rate of emigration abroad of the general population of the same age was estimated at 0.2% (Instituto Nacional de Estadística (INE), 2012), but this rate could be higher in cocaine users. Particular attention was paid to guaranteeing absolute confidentiality. In the cities of Madrid and Barcelona the data base with individual records from all drug treatment centres are centralized, registered in the Spanish Data Protection Agency, and subject to high security levels, as required by Spanish legislation on data protection for health data. The extraction of data for this study was performed in two different databases, one with personal identifiers and another with the epidemiological data. The record of the same patient in both bases included a meaningless identical code to link the information. In order to obtain mortality data, the database containing personal identifiers was sent to the Spanish National Mortality Register. The record linkage was performed in the register offices, obtaining a file without personal

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