Health outcomes and use of harm reduction services in people who use drugs in Catalonia

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[...] havent-li dit un amic: "Tu, que creus que els déus no tenen presents les coses humanes, ¿no t'adones veient tantes pintures que molta gent es va salvar de les tempestes gràcies a les seves promeses i va arribar a port sana i estàlvia?", [Diagoras] va contestar: "El que passa és que els qui van naufragar i moriren en la mar no ho van poder pintar mai."

M. TUL·LI CICERÓ,

La naturalesa dels déus

Agraïments

En aquests moments en què la generositat amb el propi temps és difícil de trobar, vull agrair, primer de tot, la disposició de la Gabriela Barbaglia i en Jordi Alonso: una gran part del que he après en tot aquest procés prové dels primers articles que vaig poder escriure amb vosaltres. Aquesta tesi va néixer de l'entusiasme de l'Albert Espelt, que ha guiat tot el procés i ha sigut l'artífex d'alguns articles. En escriure els articles de la tesi he estat eficaçment acomboiat pels coautors i les coautores, especialment per la Cinta Folch. També he d'agrair a la Maica Rodríguez-Sanz haver acceptat ser la tutora de la tesi.

Dec un agraïment a totes les persones que han col·laborat en la tasca titànica de forjar el model de Barcelona. Cal destacar la lluita incansable de la Teresa Brugal, a qui dec bona part del que he après durant aquests anys. Aquest aprenentatge també ha sigut possible gràcies a tot l'equip del SEPAD (la Carmen Vecino, l'Ester Teixidó, la Marina Bosque, la Mercè Gotsens i l'Amaia Garrido potser són qui més m'han hagut d'aguantar). En Diego Aránega, l'Ester Aranda, la Noelia Girona, en Tomàs Balbas, la Lara Treviño i tot l'equip de Baluard, Robador, Garbivent i altres centres, també han sigut mestres i font de sentit per la meva feina, juntament amb les persones usuàries que he conegut i les que han participat en aquesta recerca.

A en Chema Gonzalez, primer autor de l'últim article de la tesi, espero haver sabut transmetre-li una part del que a mi em van ensenyar entre l'Albert, la Gabi i en Jordi. Vull agrair també a la Maribel Pasarin l'oportunitat de ser professor d'epidemiologia, que ha fet que m'adonés encara més de tot el que no sé.

També vull evocar aquí algunes persones que m'han guiat, sense saber-ho, en el meu camí per la investigació en les addiccions. Aquesta tesi té un deute amb el repositori d'evidència de l'EMCDDA i les persones que el fan possible, i també amb diverses investigadores que han format part insistentment del meu paisatge científic: Vendula Belackova, Samantha Colledge, Louisa Degenhardt, Sarah Wakeman...

Gràcies també als que hi sou sempre. La Laurie Birks, l'Elisabeth Salvo i l'Ashley Enning heu fet de revisores moltes vegades. Però, sobretot, juntament amb els vells amics de Banyoles, les medicines i els matemàtics, hi heu sigut sempre en els moments menys bons. Igualment, gràcies a la família Guàrdia-Munarriz, per la càlida acollida i pels dolcíssims treballs forçats dels divendres a la tarda. El darrer agraïment, i el més pregon, és a la meva família, la meva germana i els meus pares. Espero que seguireu omplint la buidor d'aquest mots. I a en Marcel Guàrdia per totes les raons que ell i jo ens sabem.

Abstract

Harm reduction is a set of programs and interventions that aim to reduce health and social harms of drug use. The Barcelona model aims to maximize access to harm reduction services and to integrate them with treatment programs.

This thesis objective is to describe the prevalence and associated factors of health outcomes - non-fatal overdose, HIV and Hepatitis C – in people who use harm reduction programs, and to evaluate the impact of extending the opening hours of a harm reduction program.

The thesis consists of three articles based on data from the REDAN study, a cross-sectional bio-behavioral study, and the Barcelona drug information system.

According to this thesis results, access to medical care and methadone treatment were the most significant factors preventing both non-fatal overdose and undiagnosed infections. Using a drug consumption room was associated with lower risk of undiagnosed HIV and Hepatitis C and was linked with increased awareness of overdose. Additionally, the night-time opening of a drug consumption room was associated with a higher service use among the most vulnerable clients and with an increase of the treated opioid overdoses.

In line with the aims of the Barcelona model, our results highlight the need to maximize access to harm reduction services.

Resum

La reducció de danys és un conjunt de programes i intervencions que tenen per objectiu reduir els efectes perjudicials en la salut i socials del consum de drogues. L'objectiu del model de Barcelona és maximitzar l'accés als serveis de reducció de danys i, alhora, integrar-los amb els programes de tractament.

Aquesta tesi té com a objectiu descriure la prevalença i els factors associats a la sobredosi no mortal, al VIH i a l'Hepatitis C en les persones que acudeixen als programes de reducció de danys, i avaluar l'impacte d'ampliar l'horari d'un programa de reducció de danys.

La tesi es compon de tres articles basats en les dades de l'estudi REDAN, un estudi bio-comportamental i transversal, i en les dades del sistema d'informació de drogues de Barcelona.

Atenent els resultats d'aquesta tesi, tenir accés a atenció sanitària i a tractament amb metadona són els factors més significatius per a prevenir tant les sobredosis no mortals com les infeccions per VIH o Hepatitis C no diagnosticades. L'ús d'una sala de consum de drogues s'associa a una disminució del risc de patir infeccions no diagnosticades i està lligat a un augment de la consciència d'haver patit una sobredosi. A més a més, l'obertura nocturna d'una sala de consum de drogues s'associa a un increment de l'ús del servei entre les persones usuàries més vulnerables i també a un augment de les sobredosis ateses.

En línia amb els objectius del model de Barcelona, els nostres resultats palesen la necessitat de maximitzar l'accés als serveis de reducció de danys.

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1. INTRODUCTION

1.1 Harm reduction overview

Harm reduction encompasses interventions, programs and policies that seek to reduce the health, social and economic harms of drug use to individuals, communities and societies (European Monitoring Center for Drugs and Drug Addiction 2010). Harm reduction is a combination of interventions including needle and syringe exchange, opioid maintenance treatment, drug consumption rooms, outreach and community teams, and public policies to protect the health of populations at risk (World Health Organization 2012a).

Harm reduction has had two main pillars. First, it has been driven by pragmatic public health approaches emphasizing the need for identifying specific harms, the need for interventions to be evidence based and targeted, and the need to adopt realistic goals—rather than pursue unattainable aspirational goals such as a drug free society. Second, it has been based in human rights, especially the rights of people who use drugs, to life and security, to health protection, to the provision of medical treatment and protection against harm from the community and state (Stimson 2007).

Harm reduction in the drug field has been traced back to the narcotic maintenance clinics in the United States in 1912 (European Monitoring Center for Drugs and Drug Addiction 2010) and the prescription of heroin and morphine to people dependent on opioids in the United Kingdom in the 1920s (Mars 2003). The World Health Organization recommended to take policy and actions to prevent harm to the individual or the society in 1974 (World Health Organization 1974), but

harm reduction came to prominence after the emergence of human immunodeficiency virus (HIV) in the 1980s (European Monitoring Center for Drugs and Drug Addiction 2010) and, more recently, after the emergency of opioid overdose deaths in different parts of the world in the early 2000's which has led to an exponential increase in harm reduction initiatives (Hawk, Vaca, and D'Onofrio 2015).

a) Harm reduction programs

Opioid agonist maintenance treatment

Opioid agonist maintenance treatment consists of the daily administration of an oral opioid agonist (methadone) or a partial agonist (buprenorphine) (World Health Organization 2009) with the aim to treat opioid dependence. Methadone and buprenorphine are listed as essential medicines by the World Health Organization (World Health Organization 2019). Other preparations, including pharmaceutical heroin (diamorphine) and slow-release morphine preparations, are also used in some countries (World Health Organization 2012a). To be most effective, it is important that maintenance treatment is provided at adequate doses (more than 60 mg in the case of methadone) and open ended as long as clinically indicated (World Health Organization 2009).

Methadone maintenance treatment is more effective than non-pharmacological approaches in retaining patients in treatment and in the suppression of heroin use as measured by self-report and urine or hair analysis (relative risk (RR) 0.66, 95% confidence interval (CI) 0.56-0.78, six randomized controlled trials) (Mattick et al. 2009). Studies consistently show that methadone or buprenorphine maintenance treatments are associated with statistically significant reductions in illicit

opioid use, injecting use and sharing of injecting equipment (Gowing et al. 2011). Maintenance treatment is associated with a 54% reduction in the risk of HIV infection (RR 0.46, 95% CI 0.32-0.67, 15 studies) (MacArthur et al. 2012), and with improving the effectiveness of anti-retro-viral treatment in people who use opioids and are HIV positive (Moore et al. 2019). It has also been found to be effective to reduce the risk of Hepatitis C acquisition by 50% (RR 0.50, 95% CI 0.40-0.63, 12 studies) (Platt et al. 2017).

Methadone or buprenorphine treatment are associated with substantial reductions in the risk for all-cause and overdose mortality in people dependent on opioids (Sordo et al. 2017). A systematic review (Mattick et al. 2009) found methadone treatment was associated with a reduction of overall mortality (RR 0.48, 95% CI 0.10-2.39, four randomized controlled trials) that was not statistically significant but is confirmed by observational evidence. According to observational evidence (Mathers et al. 2013), being in methadone treatment shows a strong significant protective effect (RR 0.37, 95% CI 0.29-0.48, five studies) towards mortality for any cause as compared to being out of treatment (either discharged or not in treatment). In a systematic review studying overdose mortality (Bargagli et al. 2007), all studies but one (RR 0.95, 95% CI 0.58, 1.54) reported significant protective effect ranging from 0.36 (95% CI 0.13-0.97) to 0.02 (95% CI 0.01-0.09).

A recent systematic review (Sordo et al. 2017) confirmed methadone maintenance treatment is associated with an average reduction of 25 deaths per 1000 person years (95% CI 14 -36). The all-cause mortality risk during treatment was much higher in the first four weeks than in the remainder of treatment. The review also found opioid substitution

treatment with buprenorphine could be associated with a reduction in mortality, with a similar risk across all time in treatment (about four deaths per 1000 person years) and a risk after cessation higher in the first four weeks than in the remainder of time out of treatment. Comparing maintenance treatment with other treatment pathways (nonintensive behavioral health, inpatient detoxification or residential services, intensive behavioral health, or treatment with naltrexone), only treatment with buprenorphine or methadone was associated with a reduced risk of overdose during 3-month follow-up (adjusted hazard ratio AHR 0.24, 95% CI 0.14-0.41) and 12-month follow-up (AHR 0.41, 95% CI 0.31-0.55) (Wakeman et al. 2020).

Maintenance treatment with methadone or buprenorphine is also associated with overall improvement of mental health (including, depression, anxiety or stress) even though improvements are greatest in the first six months (Fingleton, Matheson, and Jaffray 2015). Evidence-based international guidelines (World Health Organization 2009) strongly recommend maintenance treatment over detoxification for pregnant women who use opioids. Methadone treatment is also effective provided during incarceration to increase community treatment, and to reduce illicit opioid use, and injection drug use (Moore et al. 2019).

Needle Exchange programs

Needle exchange programs (also called syringe exchange programs or needle and syringe programs) are a health service that distributes needle and syringes and other paraphernalia at no cost to people who inject drugs (World Health Organization 2012b) with the aim to reduce the transmission of infectious diseases. Other paraphernalia may include filters, sterile water, alcohol swabs, cookers, acidifiers, tourniquets and needle-proof containers. Most needle exchange programs provide a variety of needles and syringes to cater for different types of drug use and for different preferences among people who inject drugs. There are three basic modes of delivering the services of needle and syringe programs: fixed sites, mobile services, and community-based outreach teams (World Health Organization 2007).

Needle exchange programs are associated with a reduction in injecting risk behavior (MacArthur et al. 2014), and HIV and Hepatitis C transmission among people who inject drugs. A systematic review (Aspinall et al. 2014) found needle exchange programs reduce the transmission of HIV among people who inject drugs with a pooled effect size of 0.66 (95% CI 0.43-1.01) across 12 studies and 0.42 (95% CI 0.22-0.81) across the six studies with higher quality. Another systematic review (Platt et al. 2017) found high needle exchange programs coverage in Europe is associated with a 76% reduction in Hepatitis C acquisition risk (RR 0.24, 95% CI 0.09 to 0.62). Needle exchange programs implemented in prison settings have also been found to be effective in reducing injecting risk behavior, and transmission of HIV and Hepatitis C (European Center for Disease Prevention and Control 2018).

Additionally, needle exchange programs may serve as an important point of entry to other health and social services (World Health Organization 2012b). Needle exchange programs should aim to engage people who use drugs on a regular basis and to facilitate access to other harm reduction programs, substance use or HIV treatment, care and support and to other health and welfare services. They may themselves offer basic health care and advice, such as wound care, addressing specific issues that may commonly affect people who inject drugs.

Drug consumption rooms

Drug consumption rooms are healthcare facilities where illicit drugs can be self-administered under hygienic conditions and the supervision of trained staff (definition adapted from (Hedrich, Kerr, and Dubois-Arber 2010)). Drug consumption rooms seek to attract hard-to-reach populations of people who inject drugs. The primary aim of these facilities is to reduce acute risks of infectious disease transmission and drug related overdose deaths, and to connect clients with treatment and other health and social services. At the same time, they seek to reduce drug use in public and improve public amenity in areas surrounding urban drug markets (European Monitoring Center for Drugs and Drug Addiction 2018). Drug consumption rooms may offer booths for injected drug use or spaces for inhaled drug use. Most drug consumption rooms offer various services including other harm reduction services, medical care and education and basic services such as warm meals or showers (Woods 2014).

Drug consumption rooms are efficacious in attracting the most marginalized people who use drugs (Potier, Laprévote, and Rolland

2014; Belackova and Salmon 2017). They reduce overdose-related harms and unsafe drug use behaviors, as well as facilitate uptake of addiction treatment and other health services (Kennedy, Karamouzian, and Kerr 2017). Further, they have been associated with improvements in public order and reductions in levels of public drug injections and dropped syringes (Potier, Laprévote, and Rolland 2014) without increasing drug-related crime (Kennedy, Karamouzian, and Kerr 2017). A systematic review (MacArthur et al. 2014) did not find sufficient evidence to support the effectiveness of drug consumption rooms in reducing HIV or Hepatitis C infections, while at the same time, other studies found drug consumptions rooms to be a cost-saving intervention because they prevent HIV and Hepatitis C infections (Bayoumi and Zaric 2008; Pinkerton 2010).

Frequent drug consumption room use is associated with increased access to drug treatment and lesser risk of injecting in public and sharing needles (Folch et al. 2018). According to a cohort study (Kennedy et al. 2019), individuals who report using drug consumption rooms on an at least weekly basis have a reduced risk of dying compared to those who report less than weekly or no use of this health service (adjusted hazard ratio 0.46, 95% CI 0.26–0.80, 112 participants). However, the context of this reduction is a high crude mortality rate in the cohort of people who use drugs of 22.7 (95% CI 18.7–27.4) deaths per 1,000 person-years and a median of 34 years of potential life lost (interquartile range 27–42) per death.

Other harm reduction programs

Harm reduction encompasses a wide range of health and social interventions and practices that include, but are not limited to, the interventions that have been described. Other important harm reduction interventions comprise overdose preventions programs, community-based outreach teams, non-abstinence-based housing and drug checking.

- **Naloxone distribution programs**

Overdose prevention programs or naloxone distribution programs usually include an education training on risk factors, signs and symptoms and strategies for preventing opiate overdoses and a skills training for administration of naloxone, rescue breathing and recovery position. After the trainings, participants are provided a naloxone kit (Tobin et al. 2009; Espelt et al. 2017). Naloxone is an opioid antagonist that can reverse the effects of opioids in the body, including respiratory depression, in a few minutes (European Monitoring Center for Drugs and Drug Addiction 2015; Clark, Wilder, and Winstanley 2014). An interrupted time-series analysis that compared communities and years where naloxone distribution was implemented with those where it was not, showed it was associated with lower rates of opioid related deaths (adjusted rate ratio 0.54, 95% CI 0.39 to 0.76) (Walley et al. 2013). This finding has been confirmed in Barcelona (Espelt et al. 2017) and Scotland (Bird et al. 2016).

- **Community-based outreach teams**

Community-based outreach teams engage populations of people who inject drugs in locations where they may spend time rather than through fixed-site services. In many contexts community-based outreach is a highly effective means of delivering HIV/AIDS prevention interventions, such as needle exchange programs, condom programs and targeted information, education and communication to people who inject drugs, as well as a useful access point for the referral of people who inject drugs to interventions such as opioid maintenance and HIV treatment (World Health Organization 2012b). Evidence is available indicating that when people who use drugs are referred by outreach workers to available, accessible and acceptable services such as counselling and drug dependence treatment, they are more likely to use these services and reduce their HIV risk behavior (World Health Organization 2004).

- **Housing**

A large proportion of people who use harm reduction services are homeless (Folch et al. 2018) or live in insecure accommodations (European Monitoring Center for Drugs and Drug Addiction 2018). There exist different approaches to ending homelessness, including emergency shelters, transitional housing or housing first. Housing first is a relatively new approach which consists in offering immediate access to independent housing without requiring sobriety or treatment initiation (Brooke 2011). Housing first has shown improvements in community functioning, quality of life, health-related quality of life and mental health symptoms of its participants. These effects are the same

for participants with and without a substance use disorder (Urbanoski et al. 2018).

- **Drug checking**

Drug checking, offered along information, personal advice and education, allows people who use drugs to identify the substance they want to use and to prevent harms associated with using an unknown substance. Drug checking services play an important role in the prevention of new psychoactive substances harms and informing users about new psychoactive substance related harm (Pirona et al. 2017). Results from drug checking services can also be used to monitor emerging drugs and trends over time from communities and hard-to reach markets, like crypto-markets (Vidal Giné et al. 2017). However, there is still a lack of evidence on the effectiveness of drug checking services in reducing harmful use or changing risk behaviors (Pirona et al. 2017).

b) Harm reduction programs in the international context

Injecting drug use is present in 179 of 206 countries throughout the world and an estimated 15.6 (10.2-23.7) million people among people aged 15-64 years use injected drugs (Degenhardt et al. 2017). Among them, the estimated HIV and Hepatitis C prevalence is 17.8% (10.8-24.8) and 52.3% (42.4-62.1), respectively. The estimated prevalence of depression diagnosis among people who inject drugs worldwide is 28.7% (20.8-36.6) and the lifetime prevalence of a suicide attempt is 22.1% (19.3-24.9) (Colledge et al. 2020). Some 585,000 people were estimated to have died as a result of drug use (excluding alcohol and

tobacco) in 2017 (United Nations Office on Drugs and Crime 2019). More than half of those deaths were the result of untreated Hepatitis C leading to liver cancer and cirrhosis. Two thirds of the deaths attributed to drug use disorders are related to opioid use. The greatest burden of disease is seen in East and South-East Asia, North America and South America, reflecting the large numbers of people who use opioids and people who inject drugs in those regions (United Nations Office on Drugs and Crime 2019). In recent years, a worrying increase in fatal drug-related overdose has been observed in some world regions, including North America and Australia (Harm Reduction International 2018).

Despite this heavy burden of disease, effective harm reduction interventions that can help prevent HIV and Hepatitis C spread in people who inject drugs are severely lacking in many countries. According to The Global State of Harm Reduction report (Harm Reduction International 2018), the number of countries providing needle and syringe programs and/or opioid maintenance therapy has more or less stagnated since 2014. Currently, only 86 countries (of the previously mentioned 179) implement needle and syringe programs to varying degrees (a drop from the 90 that did so in 2016) and 86 have opioid maintenance therapy (a moderate uptick of six countries compared to two years ago). Even in these countries, coverage varies widely, and is most often low according to the World Health Organization indicators, with less than 100 needle-syringes distributed per person who injects drugs per year or less than 20 opioid maintenance therapy recipients per 100 person who injects drugs per year (Larney et al. 2017). Globally, the article estimates that there are 33

(21–50) needle-syringes distributed via needle exchange programs per person who inject drugs annually, and 16 (10–24) opioid maintenance therapy recipients per 100 people who inject drugs. Less than 1% of people who inject drugs live in countries with a high coverage of both programs, meaning more than 200 needle distributed per person who inject drugs and more than 40 opioid maintenance therapy recipients per 100 people who inject drugs. A lack of specialized and accessible services for women and migrants also presents a barrier in all regions, as does stigma and discrimination towards people who use drugs (Harm Reduction International 2018).

In addition to needle and syringe programs and opioid maintenance therapy, drug consumption rooms operate in only 12 countries around the world, with Belgium implementing its first facility in 2018 and Portugal in 2019. Australia, Canada, France, Spain, Switzerland and Norway have also opened new sites since 2016, with at least two further countries expected to open new facilities (Ireland and Mexico) (Harm Reduction International 2018). In total, 117 sites operated in 2018, compared with 90 in 2016. The increase since 2016 is mainly due to 24 new sites opening in Canada. Regarding overdose prevention programs, only 12 countries in the world operate naloxone peer-distribution schemes, whereby individuals can pass on naloxone without each recipient requiring a personal prescription (Harm Reduction International 2018). Drug-checking services are reported to operate in five of the world regions (Eurasia, Latin America, North America, Oceania and Western Europe), however, most of them receive only private funding (Harm Reduction International 2018).

c) Harm reduction programs in the European context

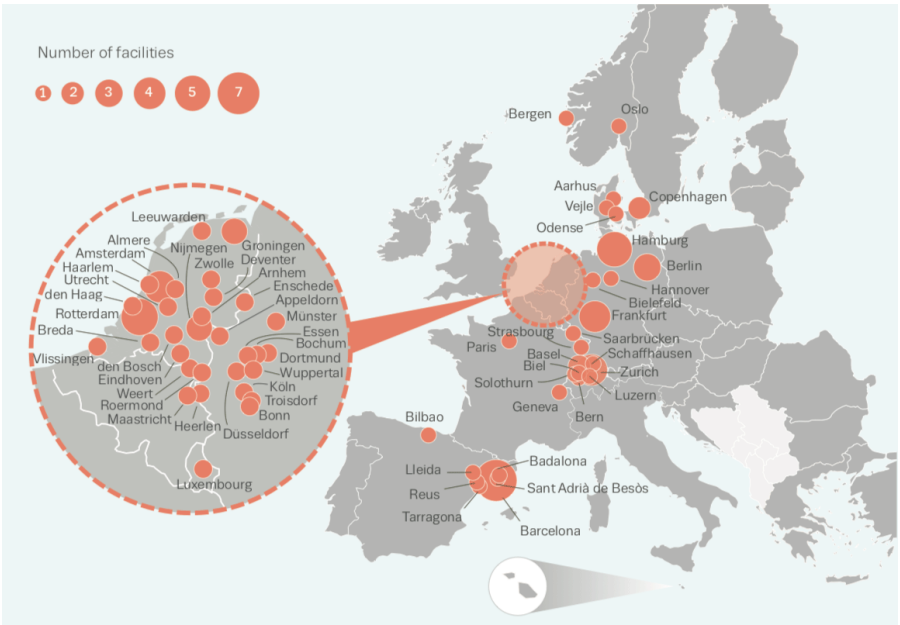
According to the 2019 European Drug Report (European Monitoring Center for Drugs and Drug Addiction 2019c) around 96 million or 29% of adults aged 15-64 in the European Union are estimated to have tried illicit drugs during their lives. The prevalence of high-risk opioid use (using opioids, including opioid medicines, weekly or more frequently for at least six months of the past 12 months, not according to a medical prescription) among adults is estimated at 0.4% of the EU population, the equivalent of 1.3 million people with high-risk opioid use in 2017. Even though the proportion of HIV diagnoses for which the route of transmission is attributable to injecting drug use is around 5% in Europe, this figure is much higher in some countries like Lithuania (62%) and Latvia (33%). Viral hepatitis, particularly infection caused by the Hepatitis C virus, is highly prevalent among people who inject drugs across Europe varying from 15% to 82% in different countries. It is estimated that at least 8,238 overdose deaths, involving one or more illicit drug, occurred in the European Union in 2017. This estimate has remained stable compared with the 2016 estimate.

All the countries in the European Union provide clean injecting equipment at specialised outlets free of charge (European Monitoring Center for Drugs and Drug Addiction 2019c). Besides sterile syringes and needles, pads to disinfect the skin, water to dissolve drugs, and clean mixing containers are often provided by harm reduction services in many countries, while non-injecting paraphernalia such as foil and pipes are less common. An estimated 654,000 people received maintenance treatment in the European Union in 2017 (European Monitoring Center for Drugs and Drug Addiction 2019c). A comparison with

current estimates of the number of people with high-risk opioid use in Europe would suggest that overall, about half receive maintenance treatment, but there are differences in coverage between countries. Methadone is the most commonly prescribed opioid substitution drug, received by almost two-thirds (63%) of substitution clients in Europe.

In 2018, 78 official drug consumption rooms operated in seven European Union countries (European Monitoring Center for Drugs and Drug Addiction 2018). Breaking this down further, as of April 2018 there were: 31 facilities in 25 cities in the Netherlands, 24 in 15 cities in Germany, 14 in seven cities in Spain, 12 in eight cities in Switzerland, five in four cities in Denmark, two in two cities in Norway, two in two cities in France, and one in Luxembourg. In 2019 Portugal opened two fixed and one mobile drug consumption rooms. Some cities such as Barcelona or Amsterdam (Rigoni, Breeksema, and Woods 2018) are implementing harm reduction programs for people who inhale stimulant drugs.

Figure 1. Map showing the location and number of drug consumption rooms throughout Europe in 2018



Source: Drug Consumption Rooms : An Overview of Provision and Evidence. (European Monitoring Center for Drugs and Drug Addiction 2018)

In 2018, community-based take-home naloxone programs were operating in 10 European countries. These programs are commonly run by drugs and health services, with the exception of Italy, where naloxone is an over-the-counter medication. Imprisoned people are included as a target population in take-home naloxone programs in Estonia, France, the United Kingdom and Norway (European Monitoring Center for Drugs and Drug Addiction 2019c).

d) Harm reduction programs in Spain and Catalonia

The prevalence of use of illicit substances in Spain has been relatively stable in recent years, with more than one third of the adult population reporting using an illicit substance at least once in their lifetime (European Monitoring Center for Drugs and Drug Addiction 2019d). The prevalence of lifetime heroin drug use among adults (15-64 years) was estimated at 0.6% of the Spain population in 2017 (Plan Nacional Sobre Drogas 2019a). In the same period and age-group, the lifetime prevalence of cocaine use was 1.3%. People with high-risk opioid use were estimated to be 68,297 (95% CI 46,014-90,579) among people aged 15-64 years in 2017 (European Monitoring Center for Drugs and Drug Addiction 2019d). In the last 20 years, HIV infection has represented one of the main health problems associated with drug use in Spain. However, since the end of the 1990s, a significant decrease has been observed in HIV infection associated with injecting drug use (European Monitoring Center for Drugs and Drug Addiction 2019d). In 2017 newly diagnosed cases of HIV attributed to injecting drug use were 3.0% while the prevalence of HIV among people who inject drugs was 30.8%. The prevalence of Hepatitis C among people who inject drugs in Spain has decreased in recent years from 68.9% in 2015 to 63.1% in 2017 (Plan Nacional Sobre Drogas 2019c). In 2017, 696 overdose deaths were reported in Spain (Plan Nacional Sobre Drogas 2019b). The overdose mortality rate among adults (15-64 years) was 15.7 cases per million. The drugs most commonly implicated in overdose deaths were opioids, followed by cocaine (European Monitoring Center for Drugs and Drug Addiction 2019d).

In Spain, 1,564,045 syringes were dispensed in 2017 (Plan Nacional Sobre Drogas 2017). Syringes are dispensed free of charge by different outlets including addiction treatment centers, harm reduction centers, mobile units, and drugstores. Besides sterile syringes and needles, pads to disinfect the skin, water to dissolve drugs, clean mixing containers and filters are routinely provided by all services. In Barcelona, 315,350 syringes were distributed and 249,426 were recuperated through the needle exchange program in 2019, which yields an 80% recuperation rate. Syringes were distributed in 16 harm reduction and treatment centers (called CAS, Centre d'Atenció i Seguiment or CRD, Centre de Reducció de Danys) but also in 78 drugstores and four primary care centers. Non-injecting paraphernalia such as foil and pipes are dispensed in one center (CAS Baluard), which includes a drug consumption room for inhaled use. A recent study (Nordt et al. 2020), estimated 4,693 (95% CI 4,066-5,319) people with high-risk opioid use in Barcelona. Using this estimation, 67 (between 59 and 78) syringes were dispensed per person per year, which is less than the World Health Organization recommended 200 syringes (World Health Organization 2012b).

Methadone maintenance treatment was made available by new laws in 1990 and 1996 that changed the approach to treatment from a drug-free approach to a harm reduction approach (Torrens, Fonseca, and Domingo-salvany 2013). In Spain, 59,857 people received maintenance treatment in 2017 (Plan Nacional Sobre Drogas 2017). A comparison with the 2017 estimates of the number of people with high-risk opioid use in Spain (European Monitoring Center for Drugs and Drug Addiction 2019d) would suggest that about 88% receive substitution

treatment, which is higher than the 2010 estimate of 60.3% (Barrio et al. 2012), and higher than the 50% European estimate in 2017. Methadone is the most commonly prescribed maintenance treatment drug, received by around 90% of substitution clients in Spain. In Catalonia, 7,290 people received maintenance treatment with methadone in 2017. Methadone maintenance treatment is offered in 55 centers, of which 41 also have buprenorphine/naloxone programs. Moreover, 156 drugstores, two mobile units and nine prisons in Catalonia offer methadone program (Plan Nacional Sobre Drogas 2017).

In 2017, 14 drug consumption rooms were in operation in Spain: 13 in Catalonia (Folch et al. 2018) and one in the Basque Country, serving a total of 3,568 people (Plan Nacional Sobre Drogas 2017). Barcelona has nine drug consumption rooms integrated in CAS, one drug consumption room in a mobile unit and one harm reduction drop-in center without drug consumption room. In 2019, these facilities served 4,216 clients which made a total of 230,377 visits to the centers. A total of 87,612 drug uses were supervised in drug consumption rooms, of which 36,005 (41%) were inhaled drug uses. Two centers have community-based outreach teams (23 professionals in 2019) with the aim of establishing contact with people who use drugs on the street and linking them with the centers and services. The community teams contacted 8,356 people in the streets in 2019. In 2009 overdose prevention trainings for professionals and people attending harm reduction and treatment centers were implemented in Catalonia. The trainings addressed risk factors, signs and symptoms, and management

of overdose episodes and distributed take-home naloxone kits to participants (Espelt et al. 2017).

- **Harm reduction programs and infectious diseases in Catalonia and Barcelona**

The number of new HIV cases in Catalonia has decreased from 165 new cases in 2001 to 27 new cases in 2018 (Figures 2 and 3). The availability of harm reduction programs has contributed to reductions in the prevalence of HIV in Catalonia (Folch et al. 2016). In Spain, the expansion of harm reduction interventions was delayed, although the concomitant decrease in heroin and injecting drug use led to reasonable coverage after 2000 (Barrio et al. 2012). However, data from samples of young people who inject drugs indicate ongoing transmission of HIV (Barrio et al. 2007; de la Fuente et al. 2006). According to a recent article (Folch et al. 2016), the HIV prevalence among people who have injected drugs for five years or less was 20.6% (95%CI 14.4%–56.9%), and among those who have done it for more than 10 years it was 40.5% (95% CI 36.1%–44.9%). The estimated HIV incidence in that article was 8.7 per 100 person-years. In Barcelona, the prevalence of HIV in people who inject drugs had decreased from 30.9% in 2008 to 25.1% in 2014 in men and from 43.4% to 31.4% in women (Brugal et al. 2017).

Figure 2. New HIV Infections by year and transmission group, and number of new HIV infections in the injection drug use group (Catalonia 2001-2008)

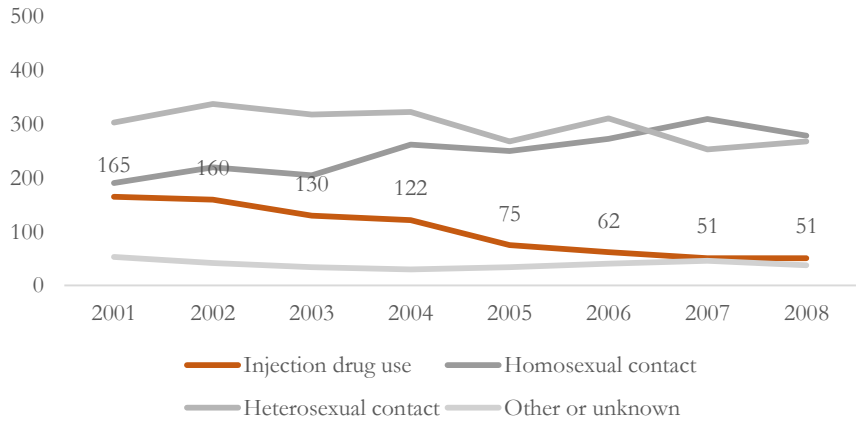


Figure source: Adapted from Sistema Integrat de Vigilància Epidemiològica de la SIDA/VIH/ITS a Catalunya 2010 (Centre d'Estudis Epidemiològics sobre les Infeccions de Transmissió Sexual i Sida de Catalunya (CEEISCAT) 2010)

Figure 3. New HIV Infections by year and transmission group, and number of new HIV infections in the injection drug use group (Catalonia 2009-2018)

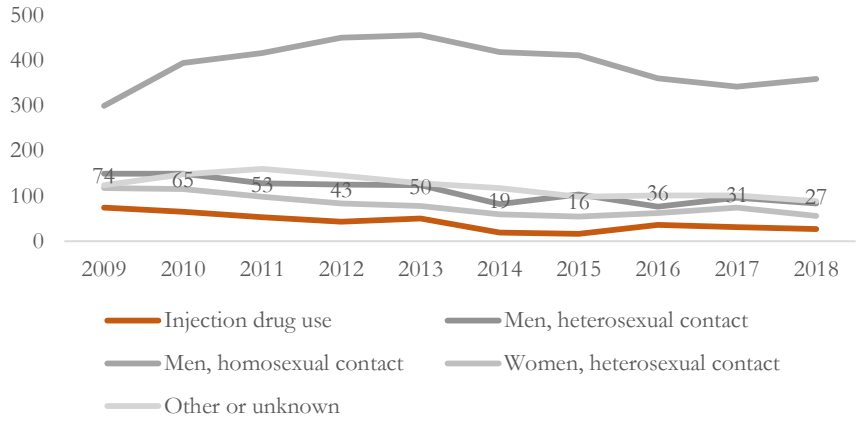


Figure source: Adapted from Vigilància Epidemiològica de la Infecció pel VIH i la SIDA a Catalunya. Informe Anual 2018 (Centre d'Estudis Epidemiològics sobre les Infeccions de Transmissió Sexual i Sida de Catalunya (CEEISCAT) 2019)

The prevalence of Hepatitis C in people who inject drugs in Catalonia remains high. The prevalence of Hepatitis C antibody in different cross-sections of the bio-behavioral study REDAN (contraction of REducció de DANys, harm reduction) was 72.0% (95% CI 68.8%–75.2%) in 2010-2011 (Folch et al. 2016) and 67.8% (95% CI not available) in 2014-2015 (Folch et al. 2018). Hepatitis C prevalence is significantly associated with time since first injection, increasing from 59.4% (95% CI 51.8– 67.0) in people who have injected drugs for five years or less to 77.1% (95% CI 73.4–80.9) in those with an injection history of more than 10 years (Folch et al. 2016). In Barcelona, the prevalence of Hepatitis C antibody in people who inject drugs had decreased from 73.1% in 2008 to 65.0% in 2014 in men and from 69.7% to 56.9% in

women (Brugal et al. 2017). Encouragingly, nowadays simple and well-tolerated direct-acting antiviral therapies for Hepatitis C infection are available and highly effective among people who use drugs (Grebely et al. 2019). However, there is still a need to address barriers to effective Hepatitis C care through increased testing, treatment and follow-up (Roncero et al. 2017).

- **Harm reduction programs and drug overdose in Catalonia and Barcelona**

A prospective study in Barcelona and Madrid estimated four out of 100 opioid overdoses are fatal (Espelt et al. 2015). The number of overdose deaths per year in Barcelona (Figures 4 and 5) has decreased from 140 deaths in men and 33 in women in 1989 to 48 deaths in men and 16 in women in 2017. The mean age at overdose death has increased from around 27 years in 1989 to around 45 years for both men and women in accordance with an ageing prevalent cohort of people who inject drugs in Barcelona. In 2009, overdose prevention trainings were implemented in Catalonia. Fewer fatal opioid overdoses than expected if the trainings had not been implemented were observed in the years after their implementation (Espelt et al. 2017).

Figure 4. Number of overdose deaths (bars) and mean age (line) in men by year, Barcelona 1989-2017

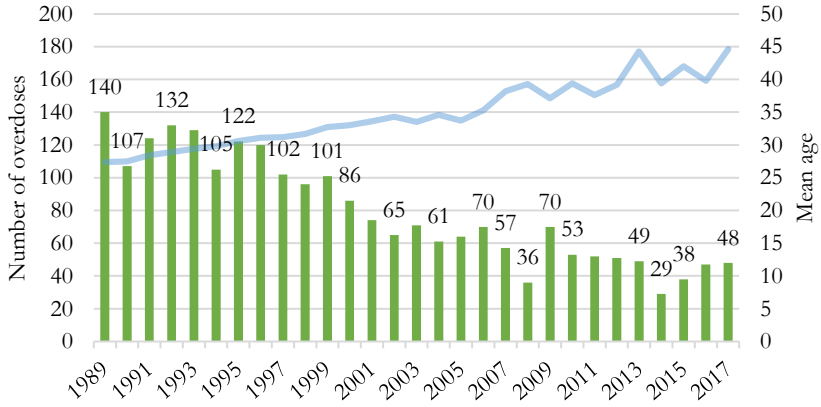


Figure source: Barcelona drug information system, Agència de Salut Pública de Barcelona.

Figure 5. Number of overdose deaths (bars) and mean age (line) in women by year, Barcelona 1989-2017

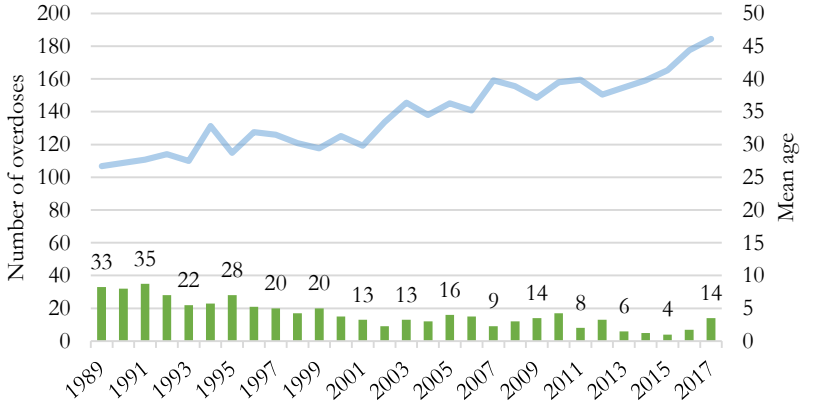


Figure source: Barcelona drug information system, Agència de Salut Pública de Barcelona.

1.2 The Barcelona model of substance use care

The final section of the introduction has been published as an editorial in the International Journal of Drug Policy.

Integration of harm reduction and treatment into care centers for substance use: the Barcelona model.

Oleguer Parés-Badell, Gabriela Barbaglia, Natanya Robinowitz, Xavier Majó, Marta Torrens, Albert Espelt, Montse Bartroli, Mercè Gotsens, and Maria Teresa Brugal.

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Editorial

Integration of harm reduction and treatment into care centres for substance use: The Barcelona model

Introduction

The Barcelona model consists of offering harm reduction services – including drug consumption rooms (DCR) – hand-in-hand with substance use treatment programmes in care centres for substance use. The Barcelona model integrates different intervention options informed by a public health-based approach to drug use based on input from diverse stakeholders. Preliminary evidence suggest the Barcelona model has maximized access to harm reduction services, has eliminated many common barriers to treatment and is temporally associated with a decrease in the number of overdose deaths. The integration of harm reduction and treatment services has increased access to both programs without increasing relapse. The implementation of this model has been made possible by sustained political consensus reached through different technical and political committees and a quadrennial Action Plan on Drugs developed collaboratively by a diverse set of stakeholders.

History of substance use care in Barcelona

Like much of Western Europe, Barcelona has experienced a widespread increase in heroin use, beginning in the 1970s. This peaked at an incidence of 190 people who used heroin per 100,000 in the population aged 15–44 years in 1980, rising rapidly thereafter from less than 40 persons per 100,000 in 1971 and falling subsequently to about eight people per 100,000 in 2005 (Sanchez-Niubo et al., 2009) after the implementation of methadone maintenance treatment and harm reduction programs. Initially, treatment was provided by non-governmental organizations (NGOs) funded by the Social Services Department of the City Council. These treatment facilities were not part of the National Health System, they focused on abstinence and were poorly connected to medical services. In 1989, the City Council of Barcelona transferred the provision of substance use services from the Social Services Department to the Public Health Department. This department introduced a public health perspective on substance use, allowing a shift from an abstinence-only approach to a wider public health approach and involving the National Health System in substance use care. Between 1980 and 2000, 10 outpatient substance use centres (called CAS, Centres d'Atenció i Seguiment a drogodependències) opened in the city of Barcelona (Fig. 1). These centres incorporated methadone maintenance treatment since 1990 and have been the seed for the integration process, gradually incorporating harm reduction programmes.

Needle exchange programmes were set up in Barcelona in the early 1990s as a response to the HIV epidemic (Bosque-Prous & Brugal, 2016). Needle exchange was offered first in open drug scenes by community teams, and then incorporated as one of the programmes offered by the outreach centres. In 2001, an open air tent was set up to supervise drug use in Can Tunis, a large open drug scene situated in a disadvantaged neighbourhood next to the Barcelona harbour (Anoro, Ilundain, & Santisteban, 2003). In 2004, due to the growth of the harbour, Can Tunis was demolished, the neighbours were relocated, and the open drug scene was closed. The municipal government feared open drug use would move to the city centre and decided to open a DCR in downtown Barcelona. The next year, the first centre was opened that integrated harm reduction and treatment. In the 2000s the city of Barcelona started the process of integrating harm reduction facilities into existing treatment centres.

From political decision-making to technical implementation

Since 1987, policies and interventions on drugs in Barcelona have been guided by the City Council and the Action Plan on Drugs of the City of Barcelona (Brugal, Guitart, Espelt, Teixido-Compaño, & Bosque-Prous, 2017). This Plan aims to prioritize and evaluate drug policies in order to respond to the health and social impact of drug use, in partnership with all stakeholders in the city. The Plan started in response to the widespread increase in heroin use, but its comprehensive scope covers licit and illicit drugs and actions for a diversity of stakeholders, including public health and drug officials, politicians, security forces, and others.

The Plan is created in a participatory manner, with accountability to several stakeholders. The drafting of the Plan is launched every 4 years by a Directive Committee that includes all the political parties in the City Council. The Plan is drafted by the Barcelona Public Health Agency, taking into account the available scientific evidence. This process includes the participation of city district professionals, security forces and academics through a Technical Committee. A Social Committee includes the Technical Committee plus neighbourhood associations, NGOs, and people who use drugs associations. The Technical and Social committees meet bimonthly during the drafting of the Plan.

Political will and priorities are included in the proposal of the Plan through the Directive Committee. The political groups need to reach an agreement within the Committee in order to ask for modifications of the drafted Plan. For example, when new substance use care centres were planned to open, a political consensus was reached by agreeing to scatter harm reduction services throughout the 10 districts of the city in order to avoid a concentration of services. The Plan is debated and approved by the municipal plenary only after the Directive Committee (which is composed of one councilmember of each political group represented in the City Council) has accepted the Plan proposal. This participatory process has been effective: eight consecutive Plans have

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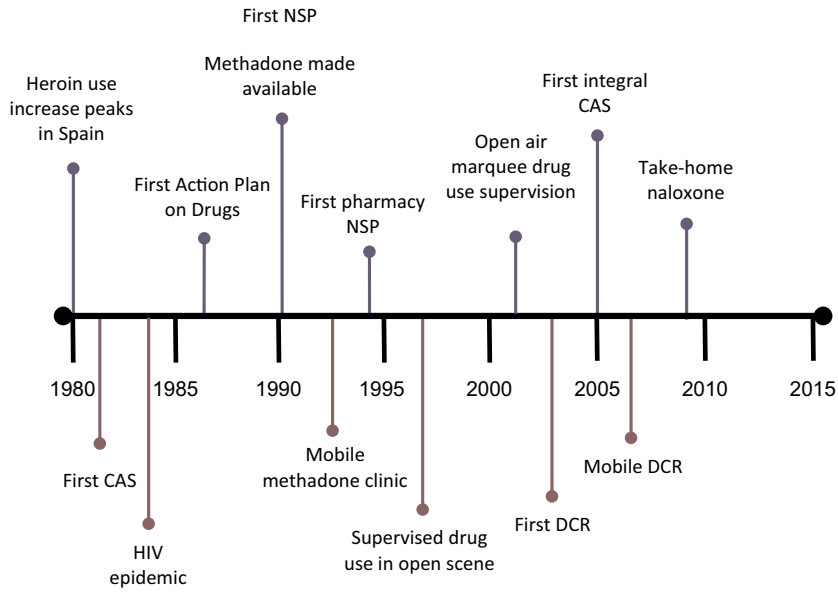

Fig. 1. Timeline of key moments for opioid use treatment and harm reduction provision in Barcelona from 1980 to 2015.
CAS: outpatient substance use centres; NSP: needle and syringe exchange programmes; DCR: drug consumption room

been approved and none has been voted against by a political party. The Directive Committee has made it easier to avoid the use of drugs and substance use as a political weapon since all political groups have a shared responsibility of the Plan and policies are debated every four years. Moreover, the Directive Committee has regular meetings to monitor the execution of the interventions during the implementation of the Plan and to safeguard the political consensus.

Unlike other countries where unsanctioned DCRs have been opened before legally sanctioned facilities (Kerr, Mitra, Kennedy, & McNeil, 2017), in Barcelona the political consensus enabled a municipal DCR to open in 2004 without the need for legislative changes. The opening of DCRs was also possible because, in Spain, possession of drugs for personal use and consumption is considered a minor offence that carries an administrative sanction, not a legal penalty (EMCDDA, 2018).

Description of the integrated outpatient centres for substance use

The objective of the Barcelona integrated centres is to provide seamless continuum of care pathways including harm reduction and treatment programmes to all people using drugs in the city of Barcelona regardless of their country of origin or citizenship status. Nine out of the 15 centres in the city offer harm reduction services – including DCR – hand-in-hand with treatment programs. Additionally, the city offers a harm reduction drop-in centre, a mobile DCR (Dietze et al., 2012) and a mobile methadone clinic. The centres are scattered across the districts of the city (Fig. 2). A total of eight out of ten districts already have an integrated centre, while two districts still have to incorporate harm reduction programmes into their centres.

The range of services in harm reduction programmes changes depending on the target population of each centre, since the number of clients of these programmes depends more on the proximity of drug trafficking and open drug scenes than on the size of their catchment area. All centres with harm reduction programmes offer a low-threshold methadone programme, needle exchange, DCR, take-home naloxone, overdose workshops and medical and social care. Some centres offer care for basic social needs (food, shower, laundry, lockers) in a drop-in space that enables clients to make contact with professionals (e.g., social workers, nurses), obtain support with financial and legal affairs, and participate in reintegration projects and recreational activities. The number of booths in the DCR ranges from one to five. Drug dealing is not allowed in the centres. One centre offers a DCR for inhaled drugs to foster change from injected to inhaled use. This has led to the implementation of a pipe exchange programme to provide safe pipes and inhaling paraphernalia for street use. In 2018 the most commonly used drugs in DCRs were: injected cocaine (33%), injected heroin (25%), injected combination of heroin and cocaine (10%), inhaled heroin (20%), inhaled cocaine (10%), inhaled methamphetamine (1%) and injected methadone (1%). According to an internal survey (data not shown) 90% of the DCRs clients were satisfied or very satisfied with the services provided in DCRs.

Information on needle exchange is provided in Fig. 3. In 2017, 331,619 syringes were provided to people who inject drugs in Barcelona. Harm reduction programmes identified 3788 clients in 2017, yielding a ratio of 87.5 syringes per client. However, some clients stay in the city for short periods of time and clients exchanging syringes in pharmacies or through the community team may not have been identified. Identifying clients who use needle exchange may be useful to offer them access to other programs and evaluating the program coverage. Around 10% of the provided syringes were used in a DCR while 90% were provided by needle exchange schemes. Of the latter, 75% were recovered through the syringe exchange while 11% had been discarded in the streets and were collected by outreach educators or the city cleaning services, and 14% were not recovered. Since 2014, the number of syringes exchanged has increased due to the emergence of new shooting galleries and drug houses in downtown Barcelona.

The treatment programmes offered by the Barcelona centres comprise outpatient treatment for alcohol, opiates, cocaine, cannabis, other drugs and dual diagnosis. For all substances, the treatment processes include healthcare (diagnosis and follow-up), psychological care and socio-educational care. Family support and emergency care are also

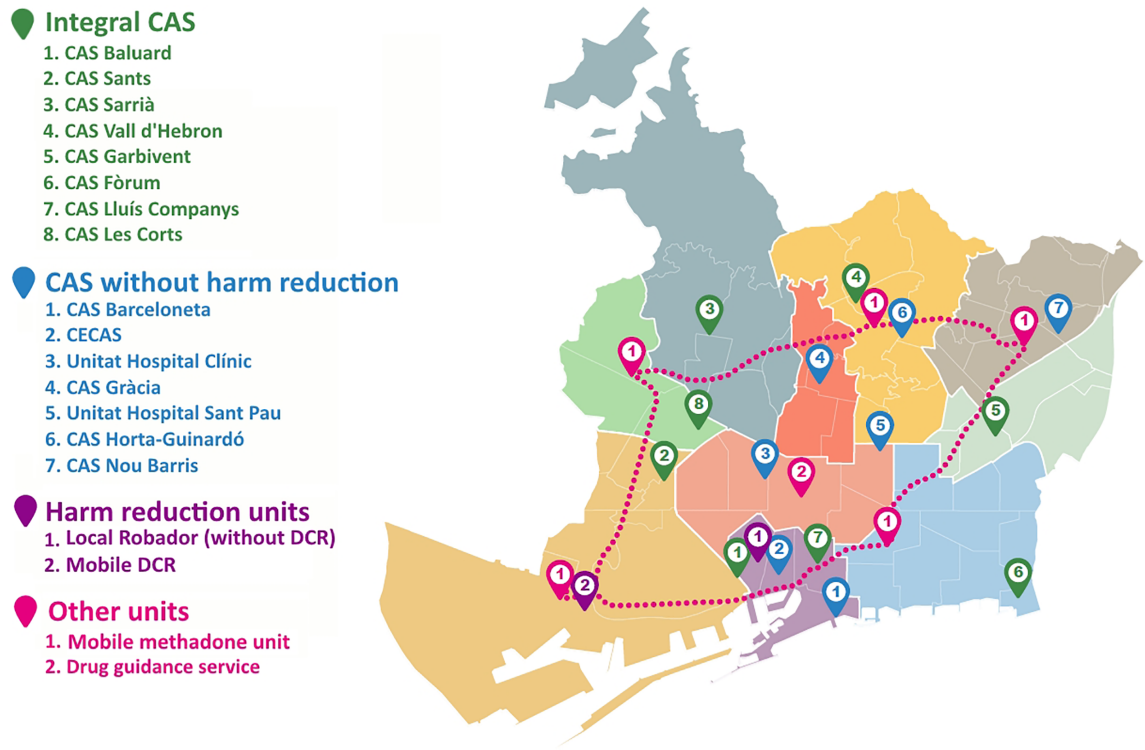

Fig. 2. Map of the outpatient substance use centres (CAS) and harm reduction units in Barcelona in 2017.

provided for patients who relapse and for former patients. Voluntary inpatient treatment is also available in dual diagnosis and detoxification units, which are located in general hospitals.

In the case of opiates, methadone maintenance treatment has been available in the centres since 1990, when a new law enabled a change from a drug-free approach to a harm reduction one (Torrens, Fonseca,

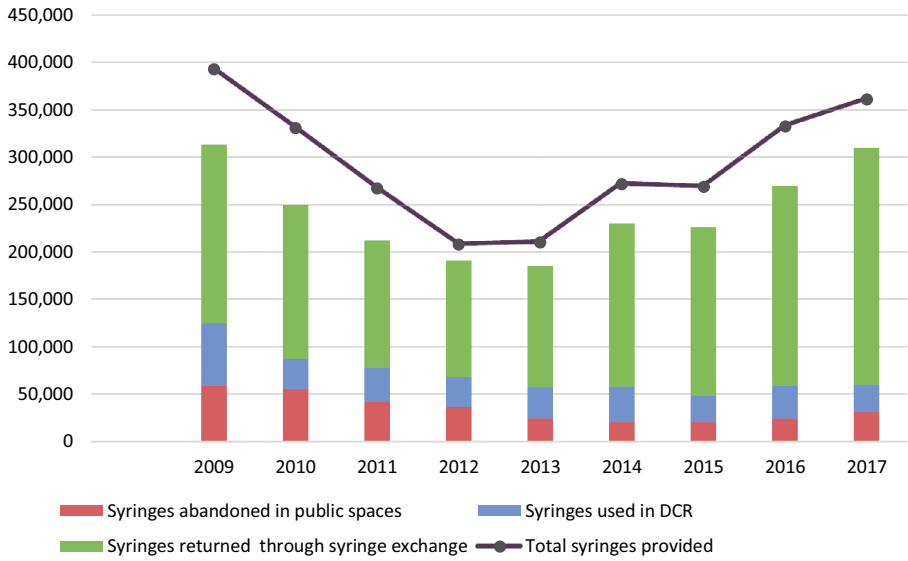

Fig. 3. Number of syringes provided through syringe exchange or DCR, and number of syringes abandoned in public spaces, returned through syringe exchange or used in DCR (2009–2017).

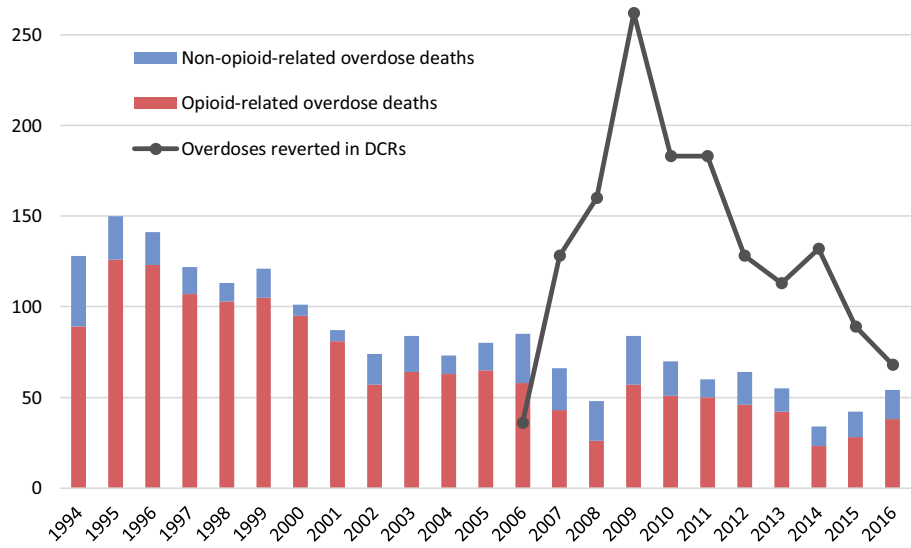

Fig. 4. Overdose deaths (opioid-related vs non-opioid-related) and number of overdoses reverted in DCRs in the city of Barcelona (1990–2016).

Castilloa, & Domingo-Salvanyb, 2013). Combination treatment with buprenorphine + naloxone was authorized in Spain in 2008, even though, unlike methadone, it is subject to patient copayment. Heroin maintenance treatment is unavailable, despite evidence of positive results in people with a chronic heroin use (Ferri, Davoli, & Perucci, 2011).

Barcelona's integrated approach has enabled the city to implement three essential interventions to tackle overdose deaths: methadone or buprenorphine + naloxone treatment, DCR and take-home naloxone. The take-home naloxone program was implemented in Barcelona in 2009 (Espelt et al., 2017). The number of overdose deaths (Fig. 4) has decreased from an average of 129 deaths per year between 1994 and 1999 to 52 deaths per year between 2011 and 2016. Around 95 overdoses per year have been reversed in DCRs in the last 3 years. The number of overdoses within DCRs has also decreased since professionals began to recommend dose splitting and the centres started to offer peer overdose prevention workshops. No overdose deaths have ever occurred in any DCR in Barcelona.

Rationale behind the Barcelona model

The Barcelona model ascribes to a definition of "substance use disorders" as a chronic and relapsing-remitting health problem characterized by compulsive drug seeking and use, despite harmful consequences (Baler & Volkow, 2006). Drawing on the Prochaska and Diclemente stages of change model (Prochaska & DiClemente, 1983) people who use drugs are seen to occupy different stages in relation to their drug use. In the Barcelona centres, harm reduction services are offered to people who use drugs and who may not have a clear intention to stop using them, engaging people who use drugs while they are in the pre-contemplation or contemplation stages (Fig. 5).

Access to harm reduction is maximized through outreach teams, DCR, and needle exchange programs. While facilitating entry to treatment is not the main objective of harm reduction programmes, it is a long-term objective that is facilitated by providing harm reduction and treatment in the same centre and by the same team of professionals. Harm reduction professionals are trained to foster positive behaviour change from pre-contemplation to preparation for treatment using brief interventions in those clients who may require substance use treatment. Offering harm reduction and treatment programs together makes it easier for harm reduction clients who may require treatment to prepare to take action (starting a treatment) because there are no breaks in the patient-professional relationship and the clients do not have to travel to another centre. Patients completing their treatment are offered a maintenance programme in which they receive a telephone call from professionals every six months. Furthermore, patients who drop out of treatment or relapse after treatment can use harm reduction services without fear of being penalized or they can restart their treatment through emergency care.

The stages of change model has been criticized because the stages may not be mutually exclusive and there is scant evidence of sequential movement through them (West, 2005). Another criticism is that the model leads to a failure to offer effective interventions to people in the early stages of change (Riemsma et al., 2002). This criticism is taken into account by the Barcelona model because, for example, methadone treatment is offered in the harm reduction programme. Offering low-threshold methadone treatment, which is offered even if consumption takes place, has been proven to reduce the frequency and associated risks of injection (Mattick, Breen, Kimber, & Davoli, 2009). Moreover, we acknowledge that drug treatment trajectories may involve the use of parallel services since people usually move forward and backward from one stage of change to another. And that harm reduction services need to be provided to all people who use drugs even if they do not need to start a treatment.

The Barcelona model highlights the aspects offered by both harm reduction and treatment programmes without establishing a hierarchy between them. Professionals focused on harm reduction may have different strengths to professionals focused on treatment. In 2005, the implementation of the model generated some resistance. Harm reduction professionals feared that patients who acknowledged using harm reduction services may be turned away from treatment programmes, while professionals focused on treatment programmes feared that the proximity of a DCR might encourage relapse. The opposite has occurred: the model has allowed professionals from both disciplines to work together. Annually, around 10% of harm reduction clients start an opioid treatment (data not shown), while relapses in treatment

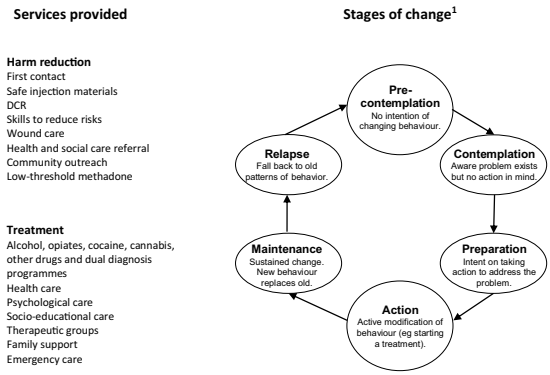

Fig. 5. Stages of change model by Prochaska and Di Clemente and services provided in the Barcelona model. Adapted from (Prochaska & DiClemente, 1983).

programmes have not increased since 2005 and patient satisfaction is high (Daigre et al., 2010). Harm reduction programmes in other settings, such as needle exchange programmes, have a treatment referral of around 5% in 3 years (Riley et al., 2002).

Further integration with other services

Effective policies on substance use must integrate a combination of approaches and interventions including preventive measures, healthcare interventions, social integration, housing and employment. Barcelona has had some success with this, as the Barcelona Public Health Agency has created relationships with health services, social services, city districts, pharmacies and prison administration.

In Barcelona's old town (the district with the highest impact of drug trafficking and homelessness) district officials, substance use professionals, security officials and social services professionals gather in monthly meetings (weekly during the summer) to discuss social problems (e.g., homelessness, open air drug use, drug trafficking, paraphernalia litter) in neighbourhood settings and to agree on the specific interventions each service can provide to address these issues. For example, in 2014, during the financial crisis, evictions went up due to payment defaults and some empty flats where used by dealers as shooting galleries or drug houses to avoid police pressure in the streets. Coordination with housing and security officials was needed to prevent family evictions resulting in empty flats in the neighbourhood and to close the shooting galleries. Harm reduction professionals provided needle exchange and naloxone to shooting galleries through peers, and DCRs provided an alternative and safer space for drug use, especially when shooting galleries were gradually closed by the police.

To expand the number of locations in Barcelona providing services, 65 pharmacies are part of the needle exchange programme and 34 are part of the take-home methadone programme. The substance use centres and penitentiary facilities in Barcelona coordinate when a person receiving treatment for a substance use is scheduled to leave prison. Moreover, monthly meetings between outpatient substance use centres and mental health centres allow for patient coordination.

Despite these advances, there is a need for further integration of services. Around 40% of harm reduction clients in Barcelona are homeless and do not have access to shelters or more permanent housing. Barcelona lacks housing resources for people who are actively using drugs and specialized shelter options for women, senior citizens who use drugs, people with concomitant diseases and people who have recently been discharged from hospital. The lack of these resources increases the stress on the centres and emergency room use and likely incurs a high economic cost. Moreover, the lack of shelter options has prevented the implementation of alcohol management and harm reduction programmes, such as those available in Canada (Pauly et al., 2013).

Declaration of Competing Interest

None.

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2. Justification

Harm reduction is a public policy inevitably linked to political and social debate. It is because of this, that it is important that harm reduction interventions are evaluated and health outcomes are monitored so that new interventions are developed upon sound scientific evidence. Even though most European countries have implemented harm reduction strategies, most of the evidence available on harm reduction interventions comes from interventions in Canada and Australia. While harm reduction strategies can be applied in different communities and have similarities in different countries, they also have to be adapted to unique country and local characteristics.

Barcelona relies on a range of harm reduction interventions that have allowed the city to curb the number of overdoses and the incidence of HIV among people who inject drugs (Espelt et al. 2017; Folch et al. 2016). However, further monitoring of the health outcomes and evaluation of harm reduction services in Barcelona is needed. An understanding of the harm reduction interventions provided in Barcelona and to what extent they have improved the health and social status of people who use drugs is critical to maintaining and improving existing harm reduction programs.

Around 30% to 50% of people living with HIV or Hepatitis C in Europe are unaware of their infection because they remain undiagnosed (Hamers and Phillips 2008; Wiessing et al. 2014). Previous studies in other settings indicate HIV and Hepatitis C self-report has a high specificity (around 90%) but lower sensitivity (around 20-40%) (Fisher et al. 2007; Origer 2012; Strauss et al. 2001; Schlicting et al. 2003).

People who acquire HIV through the use of injected drugs show late presentation to health services, delayed HIV diagnosis and antiretroviral therapy initiation, poorer immunological response to antiretroviral therapy and higher risk of progression to AIDS or death compared to patients with HIV infection acquired by sexual transmission (Suárez-García et al. 2016). However, HIV and Hepatitis C testing is still a non-routine procedure performed at patient request in the public health system. In order to design and implement strategies to tackle undiagnosed infections, we need to describe its prevalence and associated factors.

Regarding non-fatal overdose, a recent systematic review found that 41.5% (95% CI 34.6–48.4%) of people who inject drugs had experienced a non-fatal overdose in their lifetime and 20.5% (95% CI 15.0–26.1%) had experienced a non-fatal overdose episode in the last 12 months (Colledge et al. 2019). Non-fatal overdoses are linked to an increased risk of fatal overdose (Darke, Mattick, and Degenhardt 2003) and are associated with sequelae such as injuries, paralysis and chest infections (Colledge et al. 2019). Fatal drug overdoses have increased in recent years in several European countries (European Monitoring Center for Drugs and Drug Addiction 2019c), the United States (Hedegaard, Miniño, and Warner 2018) and Australia (Penington Institute 2018). On the contrary, in Spain, the number of fatal overdoses decreased between 1995 and 2010 and has remained stable at around 400 deaths per year since 2010 (European Monitoring Center for Drugs and Drug Addiction 2019b). A study in the early 2000s found that four out of 100 overdoses in people who inject drugs prove fatal (Espelt et al. 2015). Therefore, there is a need to know the prevalence of non-fatal

overdose in the Barcelona setting as has been assessed in other settings (Gossop et al. 1996). Moreover, the effect of overdose training, naloxone programs and other harm reduction programs on the prevalence of non-fatal overdose in Barcelona should be described.

Finally, using a drug consumption room has been linked to improvements in the health outcomes of people who use drugs and a reduction in the overdose frequency and overdose death (Kennedy, Karamouzian, and Kerr 2017; Marshall et al. 2011). Moreover, previous studies have not shown an increase in first time injections or drug dealing around drug consumption rooms after their opening (Kennedy, Karamouzian, and Kerr 2017; Potier, Laprévote, and Rolland 2014; Wood et al. 2006) even though half of the people who use drugs in public places would prefer to do it inside a facility (Stöver et al. 2015). The percentage of clients who report using drugs in public places is higher when the facilities are closed and opening hours are a barrier to drug consumption room use (Small et al. 2011; Stöver et al. 2015). However, no previous studies have evaluated the impact of extending the opening hours of a harm reduction program on the use of services and the overdoses attended.

3. Hypotheses and Objectives

3.1 Hypotheses

Article 1

1. The sensitivity of self-report of HIV and Hepatitis C is around 90% and the specificity around 20-40% in people who inject drugs in Catalonia
2. The proportion of undiagnosed HIV and Hepatitis C in people who inject drugs in Catalonia is around 30 to 50%
3. Being younger or foreign-born are factors associated with having an undiagnosed HIV or Hepatitis C in people who inject drugs in Catalonia

Article 2

1. The prevalence of non-fatal overdose in the last 12 months among people who inject drugs in Catalonia is around 20%
2. Overdose training and using a drug consumption room is associated with lower prevalence of non-fatal overdose in people who inject drugs in Catalonia

Article 3

1. The client profile of a drug consumption room during a 24-hour opening period is different than the client profile during a 15-hour opening period
2. The facility use, the drugs used, and the number of non-fatal overdose episodes is different in the 24-hour opening period compared to the 15-hour opening period
3. The daytime client profile of a drug consumption room is different than the night-time client profile in a 24-hour opening period
4. The facility use, the drugs used, and the number of non-fatal overdose episodes is different in the daytime compared to the night-time in the 24-hour opening period

3.2 Objectives

a) General objectives

The general objectives of the present thesis are (1) to describe the prevalence and associated factors of health outcomes - non-fatal overdose and undiagnosed HIV or Hepatitis C – in people who use harm reduction programs, and (2) to evaluate the impact of extending the opening hours of a harm reduction program.

b) Specific objectives

Article 1

1. To estimate the validity (sensitivity and specificity) of self-report of HIV and Hepatitis C infections in people who inject drugs in Catalonia
2. To estimate the proportion of undiagnosed HIV and Hepatitis C in people who inject drugs in Catalonia
3. To assess the risk factors associated with an undiagnosed HIV or Hepatitis C in people who inject drugs in Catalonia

Article 2

1. To describe the prevalence of non-fatal overdose among people who inject drugs in Catalonia
2. To assess the associated factors of non-fatal overdose in people who inject drugs in Catalonia

Article 3

1. To compare the CAS Baluard client profile during a 24-hour opening period and a 15-hour opening period
2. To compare the facility use, the drugs used, and the number of non-fatal overdose episodes between the 24-hour opening period and the 15-hour opening period

3. To compare CAS Baluard daytime client profile with night-time client profile in the 24-hour opening period
4. To compare the facility use, the drugs used, and the number of non-fatal overdose episodes during daytime and night-time in the 24-hour opening period

4. METHODS AND RESULTS

In order to achieve the objectives of the thesis, we present three articles:

Article 1. Undiagnosed HIV and Hepatitis C infection in people who inject drugs: From new evidence to better practice. **Oleguer Parés-Badell**, Albert Espelt, Cinta Folch, Xavier Majó, Victoria González, Jordi Casabona, Maria Teresa Brugal. Journal of Substance Abuse Treatment. 2017 Jun; 77:13-20. doi: 10.1016/j.jsat.2017.03.003

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Article 2. Prevalence and factors associated with non-fatal overdose among people who inject drugs in Catalonia. **Oleguer Pares-Badell**, Daniela Perez-Leon, Albert Espelt, Mercè Gotsens, Jordi Casabona, Xavier Majó, Joan Colom, Cinta Folch, REDAN study group.

Submitted to Addiction

Article 3. Impact of 24-hour schedule of a drug consumption room on service use and number of non-fatal overdoses. A quasiexperimental study in Barcelona. Jose María Montero-Moraga, Amaia Garrido-Albaina, Maria Gabriela Barbaglia, Mercè Gotsens, Diego Aranega, Albert Espelt, **Oleguer Parés-Badell**. International Journal of Drug Policy. 2020 Jul; 81:102772. doi: 10.1016/j.drugpo.2020.102772

Impact factor 4,444 (Quartile 1 in substance abuse)

Article 1

Undiagnosed HIV and Hepatitis C infection in people who inject drugs: From new evidence to better practice

Oleguer Parés-Badell, Albert Espelt, Cinta Folch, Xavier Majó, Victoria González, Jordi Casabona, Maria Teresa Brugal

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Undiagnosed HIV and Hepatitis C infection in people who inject drugs: From new evidence to better practice

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ABSTRACT

Background: The objective of this study was to estimate the proportion of undiagnosed HIV or Hepatitis C virus (HCV) infection and to assess the risk factors associated with an undiagnosed infection.
Methods: A questionnaire was distributed among people who inject drugs (PWID) in harm reduction centres in Catalonia, Spain 2008–2012 (n = 2243). Self-report of HIV and HCV was compared to oral fluid tests to calculate the proportion of undiagnosed infection. Associations of undiagnosed HIV and HCV with age, origin, risk and protective factors of infection and services use were calculated using a Poisson regression model with robust variance.
Results: The sensitivity of HIV self-report was 78.5% (75.2%–81.5%) and of HCV was 81.2% (79.1%–83.2%), being lower in younger and foreign-born PWID. Specificity for HCV was 55.9% (51.6%–60.1%). PWID who engaged in infection risk behaviors had lower risk of being undiagnosed. Being foreign-born and younger increased the risk of undiagnosed infection. PWID who had not accessed medical care in the last 6 months had 1.46 (1.10–1.93) times more risk of undiagnosed HIV and 1.37 (1.11–1.70) times more risk of undiagnosed HCV.
Conclusion: Outreach programmes are essential to provide PWID, specially foreign-born and younger PIWD, access to HIV and HCV test.

1. Background

About 30% of the people living with human immunodeficiency virus (HIV) in the European Union are unaware of their HIV infection (Hamers & Phillips, 2008). Among Hepatitis C virus (HCV) infected people in Europe, around 40% to 50% remain undiagnosed (Wiessing et al., 2014) whereas in the United States 45% to 85% are unaware of their HCV diagnosis (Smith et al., 2012). In Spain, HIV and HCV testing is a non-routine procedure performed when the health provider or the patient requests it at the public health system. HIV testing is also offered by in-pharmacy testing programmes and non-governmental organizations. However, recent regulatory changes may have limited access to testing to migrants with illegal administrative status (Belza et al., 2015).

Patients who acquired HIV infection through use of injected drugs show poorer health outcomes compared to patients with HIV infection acquired by sexual transmission (Suárez-García et al., 2016). They present late to health services, have delayed HIV diagnosis and antiretroviral therapy initiation, have poorer immunological response to antiretroviral therapy and have higher risk of progression to acquired immune deficiency syndrome (AIDS) or death. People who inject drugs (PWID) are extremely vulnerable to blood-borne infectious diseases through the sharing of syringes or other drug use material and through unprotected sex. Within Europe, 1.3 million people aged 15 to 64 are estimated to be problem opioid users, and about 1.700 people died of HIV/AIDS attributable to injection drug use in 2010 (EMCDDA, 2014). In Spain, the prevalence of HIV among PWID in 2012 was estimated to be 30.6% and the prevalence of HCV among PWID was between 80% in the year 2006

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and 66% in the year 2012 (SIVES, 2015). HIV-related mortality is the best documented indirect cause of death among people who use drugs, while HIV alone accounts for 14% of the known-cause deaths in people who use drugs in Europe (Giraudon, Buster, Espelt, Matias, & Vicente, 2015).

Professionals and researchers who work on outreach interventions aimed at PWID may have to rely on the self-reported HIV or HCV serostatus from PWID. Describing and assessing the presence of undiagnosed HIV, viral hepatitis and other infections is, therefore, an important objective for drug policies, especially in PWID populations. In order to design and implement new programmes or strategies to tackle undiagnosed infections, factors associated to remaining undiagnosed should be better known. The objectives of this research are (1) to estimate the validity (sensitivity and specificity) of self-report of HIV and HCV infections, (2) to estimate the proportion of undiagnosed HIV and HCV in PWID and (3) to assess the risk factors associated with an undiagnosed infection, using bio-behavioral surveys conducted in harm reduction centres in Catalonia, Spain.

2. Methods

2.1. Design of the study, setting and participants

This is a cross-sectional study on PWID who attended the network of state-owned harm reduction centres in Catalonia, Spain. The majority of the clients of this centres use illicit injected drugs, mainly heroin, cocaine and speedball (SIVES, 2015). Harm reduction centres' objective is to reduce health consequences associated with drugs use and to motivate and facilitate access to treatment through health, social and educational interventions (Bosque-Prous & Brugal, 2016). Interviews were performed in a biennial fashion in the years 2008, 2010 and 2012. A convenience stratified sample was considered in order to obtain an equal distribution of PWID by country of origin and by number of visits (see supplementary table). Individuals who reported having injected drugs in the previous six months and who had signed an informed consent were eligible to take part in the study (n = 2243). Participants were offered 10€ as an inducement. The protocol of this study received ethical approval from the Hospital Universitari Germans Trias i Pujol Ethics Committee.

Face to face interviews were conducted in each centre by paid and trained interviewers. Interviewers were external social workers that took a specific 4-hour course on the questionnaire and the PWID population. An anonymous structured questionnaire was adapted from that of the World Health Organization (WHO, 1994), and translated from English into four languages (Spanish, Romanian, Russian, and French). The questionnaire included questions on socio-demographic characteristics (place of origin, age, sex, educational status, and treatment status), drug use (frequency of injection, sharing of syringes and material, drugs used), sexual relationships, knowledge of HIV and HCV status and previous history of sexually transmitted infections, use of health and preventive services and incarceration. The interviews included 150 items taking about 30 to 40 min to answer. HIV and HCV point-of-care tests were taken anonymously using the OraSure instrument (Epitope Inc., UK) to collect the oral fluid that contains antibodies. Anti-HIV antibodies were detected using the screening kit Detect-HIV version 4 from Adaltis (Chohan et al., 2001); anti-HCV antibodies were detected using the screening kit HCV 3.0 SAVE ELISA (Ortho-Clinical Diagnostics) (González et al., 2008).

Our dependent variable was undiagnosed HIV or HCV infections. Participants who self-reported in the questionnaire not having or not knowing to have HIV but tested positive were identified as having an undiagnosed infection. In the questionnaire, three separate questions for HIV and HCV were asked to all the participants that acknowledged having been tested for HIV (n = 2074) or HCV (n = 2017) at least once in their life (Fig. 1): (1) "When was the last time you had an HIV/HCV test?" (2) "Do you mind telling us the results?" We used HIV and HCV oral fluid sample tests performed on all participants as gold standard. Two dichotomous variables were created in order to confront undiagnosed HIV and HCV infections with diagnosed infections.

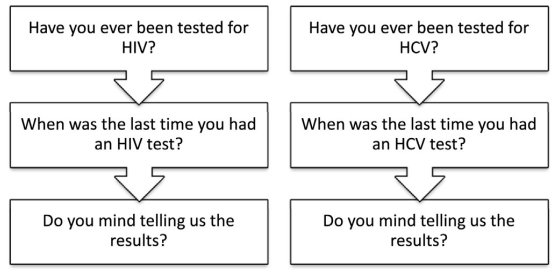

Fig. 1. Sequence of interview questions for disclosure of HIV and HCV status.

Independent variables included sex, age, place of origin, educational status, having taken an HIV test in the last 12 months, having had another sexually transmitted infection, having had Hepatitis B, having had a sexual relationship in the last 6 months, having had a regular partner who is HIV-positive in the last 6 months, the first drug injected, the use of shared syringes and material, having been treated for drug use, the use of drug consumption rooms, the access to medical care, and having ever been in prison. The place of origin was categorized into Spain, Eastern Europe (Eastern European countries as classified by the Multilingual Thesaurus of the European Union together with Latvia and Lithuania), Other European countries (Southern, Northern and Western European countries), North Africa and Middle East, and Other countries (including African, American and Oceanian countries). Educational status was categorized into no formal education, primary education or secondary education or more. The questionnaire included hepatitis A, pelvic inflammatory disease and the most common sexually transmitted infections: syphilis, gonorrhoea, genital warts, genital or anal herpes, chlamydial infection and trichomoniasis. Shared injection material comprises metal containers (also called cookers), filter, disinfectant wipe and water for injection. Sexual relationship in the last 6 months included vaginal, oral and anal sexual intercourse regardless of sexual orientation and condom usage. A regular partner was defined in the questionnaire as a partner that had been permanent or habitual in the last 6 months, even if the participant had sexual contact with other partners. Drug use treatment comprised medical detoxification, therapeutic community, methadone maintenance treatment or abstinence oriented treatment. A drug consumption room is a facility where illicit drugs can be used under supervision of trained staff. Participants were considered to have accessed medical care when they declared at least one visit to a primary health centre, a hospital or an emergency service in the last 6 months regardless of their insurance status.

2.2. Statistical analysis

The prevalence of HIV and HCV infection in the sample was calculated using 95% confidence intervals. The validity of self-reported HIV and HCV status was examined by comparing the answers to the questionnaire with the oral fluid sample test. Validity was assessed by the sensitivity (the proportion of individuals who self-reported having the infection and tested positive) and the specificity (the proportion of individuals who self-reported not having or not knowing to have the infection and tested negative) using 95% confidence intervals. Only participants who acknowledged having been tested at least once in their life were included. Validity analyses were run separately for foreign-born and native-born PWID.

The proportion of undiagnosed HIV and HCV infections was calculated by every independent variable. The proportion of undiagnosed HIV and HCV infections is the complementary value of self-report

sensitivity. We used a Poisson regression model with robust variance (Espelt, Mari-Dell'Olmo, Penelo, & Bosque-Prous, 2016) to estimate prevalence ratios and their 95% confidence interval for the independent factors associated with undiagnosed HIV and HCV. Bivariate analyses were performed to assess the association of variables with undiagnosed infection. Factors independently associated with the outcome in the bivariate analysis (using a p value under 0.2 as threshold) were included in the initial Poisson multivariate model with robust variance. The multivariate model was calculated by variable removal using the effect size and statistical significance, forcing the place of origin into the model. All the analyses were performed using the statistical software Stata (Version 13; StataCorp, College Station, TX).

3. Results

A total of 2243 PWID were interviewed, 748 in the year 2008, 761 in 2010 and 734 in 2012. The vast majority of the participants admitted to having been tested and having received the results for HIV and HCV (92.5% and 89.9% respectively) at least once in their life. 57.6% had been tested for HIV in the last year. Table 1 summarizes the characteristics of the sample, differentiating HIV-positive (n = 732), HCV-positive (n = 1578) and HIV/HCV co-infected individuals (n = 567). The majority of the sample consisted of men (82.5%) born in Spain (60.1%) that had formal education (90.0%).

As shown in Table 2, the prevalence of HIV in the sample was 33% (95% CI: 31%–35.5%), while the prevalence of HCV was 73% (95% CI 71.0%–74.5%). The prevalence of HIV varied widely by origin: native-born (41%) and foreign-born from North Africa and Middle East (39%) showed higher prevalences than PWID born in European countries (lower than 20%). Conversely, HCV prevalence in foreign-born, especially in Eastern Europeans (80% (95% CI: 76%–83.6%)) was higher than in native-born participants (72% (95% CI: 69%–74.5%)). The prevalence of HIV/HCV co-infection in the sample was 25%, as 567 individuals were infected with both diseases.

Self-reporting of HIV yielded a sensitivity of 78.5% (95% CI 75.2%-81.5). Eastern Europeans presented the lowest sensitivity (49.8% (95% CI: 37.6%–60.1%)) while great differences were shown between foreign-born and native-born PWID and between age groups. In contrast, specificity was over 90% in all groups. Sensitivity of self-reporting of HCV was 81.2% (95% CI: 79.1%–83.2%), lower in foreign-born PWID (71.9% (95% CI 67.9%–75.6%)). In contrast, the lowest specificity for HCV self-report was found in native-born Spaniards (49% (95% CI: 43.6%–54.4%)) and participants over 45 years ((32.3% (95% CI 22.9%–42.7%)).

Table 3 (HIV) and Table 4 (HCV) show the risk factors of having an undiagnosed infection. 21.5% of all HIV-positive participants were unaware of their status. In regard to HCV, 18.9% of participants who tested positive were previously undiagnosed. Female PWID had a lower risk of being undiagnosed (APR: 0.57 (95% CI 0.38–0.85)) than their male counterparts. Likewise, older PWID tended to have lower risk of being undiagnosed both for HIV and HCV. Not having had a sexually transmitted infection or Hepatitis B and not having used shared syringes in the last 6 months increased the risk of undiagnosed infection. North African and Middle East immigrants had 1.66 (95% CI 1.10–2.50) times higher risk of being unaware of their HCV, compared to native-born Spaniards.

Not having accessed medical care in the last 6 months increased the risk of undiagnosed HIV by 1.46 (95% CI 1.10–1.93) and of undiagnosed HCV by 1.37 (95% CI 1.11–1.70). Being currently in treatment for drug use is a protective factor of undiagnosed HIV and HCV, while having used drug consumption rooms in the last 6 months was a protective factor for undiagnosed HIV.

Figs. 2 and 3 show the proportion of undiagnosed HIV and HCV among participants who tested positive in the saliva test, showing the interaction between place of origin and age group. The proportion of undiagnosed infection was higher among immigrants in all age groups, both in HIV and HCV-positive participants. When a multivariate model

Table 1
Distribution of the independent variables studied among all participants, HIV-positive participants, HCV-positive participants and HIV/HCV co-infected participants (saliva test).[a]

	Total sample (n = 2243)		HIV-positive (n = 732)		HCV-positive (n = 1578)		HIV/HCV co-infection (n = 567)	
Independent variable	n	%	n	%	n	%	n	%
Sex								
Male	1850	82.5%	588	80.3%	1319	83.6%	463	81.7%
Female	390	17.4%	142	19.4%	257	16.3%	103	18.2%
Age								
17–29	429	19.1%	66	9.0%	255	16.2%	51	9.0%
30–34	424	18.9%	111	15.2%	291	18.4%	91	16.0%
35–44	978	43.6%	378	51.6%	727	46.1%	303	53.4%
>45	412	18.4%	177	24.2%	305	19.3%	122	21.5%
Place of origin								
Spain	1347	60.1%	536	73.2%	943	59.8%	403	71.1%
Eastern Europe	498	22.2%	101	13.8%	387	24.5%	92	16.2%
Europe, others	233	10.4%	40	5.5%	146	9.3%	28	4.9%
North Africa and Middle East	115	5.1%	45	6.1%	79	5.0%	39	6.9%
Other	50	2.2%	10	1.4%	23	1.5%	5	0.9%
Educational status								
No formal education	219	9.8%	93	12.7%	155	9.8%	64	11.3%
Primary education	1206	53.8%	452	61.7%	847	53.7%	353	62.3%
Secondary education or more	813	36.2%	186	25.4%	573	36.3%	149	26.3%
HIV test in the last 12 months								
Yes	1293	57.6%	302	41.3%	914	57.9%	238	42.0%
No	891	39.7%	402	54.9%	623	39.5%	308	54.3%
Ever had another STI								
Yes	569	25.4%	257	35.1%	422	26.7%	194	34.2%
No	1629	72.6%	460	62.8%	1128	71.5%	359	63.3%
Ever had Hepatitis B								
Yes	448	20.0%	231	31.6%	360	22.8%	188	33.2%
No	1759	78.4%	492	67.2%	1199	76.0%	373	65.8%
Sexual relationship in the last 6 months								
Yes	1721	76.7%	500	68.3%	1192	75.5%	381	67.2%
No	522	23.3%	232	31.7%	386	24.5%	186	32.8%
Regular partner who is HIV-positive in the last 6 months								
Yes	158	7.0%	100	13.7%	120	7.6%	71	12.5%
No	2085	93.0%	632	86.3%	1458	92.4%	496	87.5%
First drug injected								
Heroin	1534	68.4%	531	72.5%	1112	70.5%	419	73.9%
Other drugs	594	26.5%	168	23.0%	395	25.0%	130	22.9%
Use of shared syringes in the last 6 months								
Yes	1156	51.5%	531	72.5%	887	56.2%	412	72.7%
No	1083	48.3%	200	27.3%	688	43.6%	154	27.2%
Use of shared material in the last 6 months								
Yes	995	44.4%	301	41.1%	681	43.2%	232	40.9%
No	1196	53.3%	405	55.3%	855	54.2%	313	55.2%
Ever in treatment for drug use								
Yes, nowadays	1153	51.4%	440	60.1%	846	53.6%	336	59.3%
Yes, but not now	340	15.2%	57	7.8%	208	13.2%	43	7.6%
No, never	749	33.4%	235	32.1%	523	33.1%	188	33.2%
Use of drug consumption room in the last 6 months								
Yes	1139	50.8%	374	51.1%	838	53.1%	290	51.1%
No	1050	46.8%	341	46.6%	711	45.1%	265	46.7%
Access to medical care in the last 6 months								
Yes	1527	68.1%	561	76.6%	1090	69.1%	428	75.5%
No	712	31.7%	170	23.2%	485	30.7%	138	24.3%
Ever in prison								
Yes	1486	66.3%	604	82.5%	1094	69.3%	469	82.7%
No	756	33.7%	127	17.3%	484	30.7%	98	17.3%

[a] Percentages may not add up to 100% because of DK/NA/REF answers.

Table 2
Prevalence of HIV and HCV in harm reduction centres of Catalonia and validity of self-report.

	HIV						HCV					
	Prevalence[a]		Sensitivity[b]		Specificity[c]		Prevalence[a]		Sensitivity[b]		Specificity[c]	
	%	95% CI (%)	%	95% CI (%)	%	95% CI (%)	%	95% CI (%)	%	95% CI (%)	%	95% CI (%)
Sex												
Male	32	30.0 to 34.7	77.2	73.4 to 80.7	97.2	96.0 to 98.1	74	71.0 to 75.7	81.7	79.4 to 83.8	57.7	52.9 to 62.4
Female	38	33.0 to 43.1	83.2	75.9 to 89.0	98.2	95.5 to 99.5	68	63.0 to 72.9	79.1	73.4 to 84.1	49.1	39.5 to 58.7
Place of origin												
Foreign-born	21	18 to 24.3	59.1	51.2 to 66.7	97.4	95.8 to 98.5	74	70.0 to 76.6	71.9	67.9 to 75.6	67.7	60.7 to 74.1
East Europe	20	16.0 to 23.9	49.8	37.6 to 60.1	98.2	96.1 to 99.3	80	76.0 to 83.6	71.2	66.0 to 76.0	66.7	55.5 to 76.6
Europe (other)	17	12.0 to 22.3	69.4	51.9 to 83.7	97.8	94.4 to 99.4	65	58.0 to 71.5	76.5	68.4 to 83.3	72.6	60.9 to 82.4
North Africa and Middle East	39	29.0 to 49.4	72.2	54.8 to 85.8	93	83.0 to 98.1	76	66.0 to 83.8	69	56.9 to 79.5	43.5	23.2 to 65.5
Other countries	21	10.0 to 35.0	60	26.2 to 87.8	94.7	82.3 to 99.4	46	30.0 to 62.8	61.1	35.7 to 82.7	81	58.1 to 94.6
Spain	41	38.0 to 43.6	84.6	81.2 to 87.6	97.3	95.9 to 98.4	72	69.0 to 74.5	87	84.7 to 89.2	49	43.6 to 54.4
Age												
17–29	16	12.0 to 19.7	37.5	24.9 to 51.5	97	94.5 to 98.6	64	58.0 to 68.7	67.7	61.1 to 73.9	74.6	66.1 to 81.9
30–34	27	23.0 to 31.8	71.2	61.4 to 79.6	99.3	97.4 to 99.9	70	65.0 to 74.7	77.6	72.0 to 82.5	67	57.4 to 75.6
35–44	38	35.0 to 41.5	80.9	76.4 to 84.9	97.2	95.4 to 98.4	76	73.0 to 78.8	83.7	80.7 to 86.4	49.3	42.4 to 56.2
>45	45	40.0 to 49.9	91.3	86.0 to 95.0	95.8	92.1 to 98.0	75	70.0 to 79.4	89	84.7 to 92.4	32.3	22.9 to 42.7
HIV test in the last 12 months												
Yes	23	21.0 to 25.6	67.5	61.8 to 72.8	98.2	97.1 to 98.9	72	69.0 to 74.5	80	77.2 to 82.6	62.9	57.5 to 68.0
No	50	47.0 to 54.1	86.5	82.6 to 89.9	95.5	92.2 to 97.4	74	70.0 to 76.8	83	79.5 to 86.1	44.7	37.5 to 52.1
Use of shared syringes in the last 6 months												
Yes	47	44.0 to 50.0	87.7	84.5 to 90.4	96	94.0 to 97.4	78	75.0 to 80.4	89.3	86.4 to 91.3	30.6	24.8 to 37
No	18	16.0 to 21.0	52.2	44.6 to 59.8	98.4	97.2 to 99.1	66	63.0 to 69.5	70.6	66.8 to 74.1	75.2	70.0 to 79.9
Ever in treatment for drug use												
Yes, nowadays	38	35.0 to 41.2	84.4	80.6 to 87.8	97.8	96.4 to 98.8	75	72.0 to 77.6	86.4	83.9 to 88.7	43.4	37.4 to 49.6
Yes, but not now	17	12.0 to 21.7	45.5	30.4 to 61.2	96.4	93.0 to 98.4	64	58.0 to 70.2	53.1	45.1 to 61.0	75.6	65.4 to 84.0
No, never	32	29.0 to 35.9	73.8	67.4 to 79.4	97.2	95.3 to 98.5	72	68.0 to 75.1	81.9	56.7 to 70.9	64	56.7 to 70.9
Access to medical care in the last 6 months												
Yes	38	35.0 to 40.1	82.3	78.8 to 85.4	96.9	95.5 to 97.9	74	71.0 to 76.1	85	82.7 to 87.2	52.7	47.5 to 58.0
No	24	20.0 to 27.3	65.1	56.7 to 72.8	98.3	96.7 to 99.3	70	66.0 to 73.5	71.9	67.3 to 76.2	61.9	54.4 to 69.0
Ever in prison												
Yes	41	39.0 to 44.1	82.8	79.5 to 85.9	96.7	95.3 to 97.9	76	73.0 to 77.9	84.4	82.0 to 86.6	45.9	40.4 to 51.4
No	17	14.0 to 20.3	58.1	48.6 to 67.2	98.2	96.8 to 99.1	66	63.0 to 70.1	73.6	69.2 to 77.7	71.1	64.6 to 77.0
Total	33	31.0 to 35.5	78.5	75.2 to 81.5	97.4	96.4 to 98.1	73	71.0 to 74.5	81.2	79.1 to 83.2	55.9	51.6 to 60.1

[a] Prevalence: proportion of the sample found to have the condition.
[b] Sensitivity: proportion of infected individuals that are identified by self-report.
[c] Specificity: proportion of non-infected individuals correctly identified by self-report.

was built without the variable age, place of origin reached statistical significance. Being an immigrant was a risk factor of undiagnosed HIV, reaching statistical significance for all places of origin (data not shown).

4. Discussion

About 90% of PWID who attended the network of harm reduction centres had been tested for HIV and HCV at least once in their lifetime. The sensitivity of self-report was around 79% and 81% in PWID infected with HIV and HCV, respectively. While the sensitivity of self-repot of Spanish-born PWID was 85%, it was 50% in HIV-positive Eastern European immigrants. Regarding HCV, the specificity of self-report was around 56% in PWID. Having an undiagnosed infection in both diseases was associated with being younger and having a lower perception of infection risk due to the lack of risk practices, such as sharing syringes or having had previous sexually transmitted infections. Being foreign-born increased the risk of undiagnosed infection in all age groups. In contrast, enhanced access to testing through the use of health and preventive services or by having been in prison protected PWID against being undiagnosed. The use of health and preventive services, such as access to medical care and treatment or use of drug consumption rooms, was the most significant modifiable factor predicting an undiagnosed infection.

4.1. Strengths and limitations

The results of this study may be extrapolated to PWID who use harm reduction facilities, as we used a convenience sample in order to have access to a hard-to-reach population. PWID are a hidden population from whom information is usually only obtained when they are in contact with health services, law enforcement or social services (Rossi, 1999; Wirth & Tchetgen Tchetgen, 2014). Harm reduction centres are an opportunity for early contact with PWID. The acceptability of rapid test for HIV and HCV is high among PWID enrolled in harm reduction programmes (Fernàndez-López, Folch, Majó, Gasulla, & Casabona, 2016). However, results may not be generalized to other PWID populations.

On the one hand, risk behaviors may have been underestimated in our study even though self-reported risk behaviors have been found to be valid and not influenced by social desirability bias (Darke, 1998). Interviewers attempted to create an anonymous nonjudgmental atmosphere and used simple and understandable language in order to minimize this limitation. However, some HIV or Hepatitis C individuals who were aware of their status could have hidden their known status in their self-report. On the other hand, the oral fluid tests used in our study as gold standard for HIV and HCV had a high validity. According to manufacturer's instructions, the sensitivity of the oral fluid test for HIV, Detect-HIV version 4 from ADALTIS, was 100% and the specificity was 99.7% (ADALTIS, 2014). According to the Food and Drug Administration package insert, the oral fluid test for HCV, HCV 3.0 SAVE ELISA (Ortho-Clinical Diagnostics), had a sensitivity of 100% (95% CI 92.9%–100%) and a specificity of 99.95% (Hepatitis C Virus Encoded Antigen (Recombinant c22-3, c200 and NS5) ORTHO® HCV Version 3.0 ELISA Test System, 2009).

The sample size of this study enabled us to analyze risk factors with statistical robustness even when the sample was stratified. The sample included interviews from three different years. Despite a diminishing prevalence of HIV over time, particularly in native-born PWID, no

Table 3
Undiagnosed HIV proportion and adjusted prevalence ratio estimated with multi-level Poisson regression models with robust variance.

	Undiagnosed HIV							
	%	Bivariate models HIV				Multivariate model HIV			
		PR[a]	95% CI		p value	APR[b]	95% CI		p value
Sex									
Male	22.8%	1.0				1.0			
Female	16.8%	0.7	0.5	1.1	0.138	0.6	0.4	0.9	0.006
Age									
17–29	62.5%	1.0				1.0			
30–34	28.8%	0.5	0.3	0.7	<0.001	0.7	0.5	0.9	0.023
35–44	19.1%	0.3	0.2	0.4	<0.001	0.7	0.5	1.0	0.026
>45	8.7%	0.1	0.1	0.2	<0.001	0.4	0.2	0.7	0.002
Place of origin									
Spain	15.4%	1.0				1.0			
Eastern Europe	51.2%	3.3	2.5	4.5	<0.001	1.3	0.9	1.8	0.110
Europe, others	30.6%	2.0	1.2	3.4	0.012	1.3	0.8	2.1	0.225
North Africa and Middle East	27.8%	1.8	1.0	3.2	0.041	0.8	0.4	1.5	0.413
Other	40.0%	2.6	1.2	5.7	0.017	0.8	0.5	1.3	0.340
Educational status									
No formal education	17.6%	1.0							
Primary education	19.1%	1.1	0.7	1.8	0.750				
Secondary education or more	28.7%	1.6	1.0	2.7	0.060				
HIV test in the last 12 months									
Yes	32.5%	1.0				1.0			
No	13.5%	0.4	0.3	0.6	<0.001	0.5	0.4	0.7	<0.001
Ever had another STI									
Yes	9.3%	1.0				1.0			
No	28.1%	3.0	2.0	4.6	<0.001	1.7	1.1	2.5	0.018
Ever had Hepatitis B									
Yes	9.9%	1.0				1.0			
No	27.2%	2.7	1.8	4.2	<0.001	1.6	1.0	2.4	0.033
Sexual relationship in the last 6 months									
Yes	23.3%	1.00							
No	17.5%	0.75	0.54	1.05	0.097				
Regular partner who is HIV-positive in the last 6 months									
Yes	13.1%	1.0							
No	22.9%	1.8	1.0	3.0	0.038				
First drug injected									
Heroine	20.3%	1.00							
Other drugs	24.7%	1.21	0.88	1.68	0.244				
Use of shared syringes in the last 6 months									
Yes	12.3%	1.0				1.0			
No	47.8%	3.9	2.9	5.1	<0.001	2.3	1.7	3.1	<0.001
Use of shared materials in the last 6 months									
Yes	22.9%	1.00							
No	20.9%	0.91	0.68	1.22	0.531				
Ever in treatment for drug use									
Yes, nowadays	15.6%	1.0				1.0			
Yes, but not now	54.5%	3.5	2.5	5.0	<0.001	1.8	1.1	2.7	0.011
No, never	26.2%	1.7	1.2	2.3	0.001	1.4	1.0	1.8	0.029
Use of drug consumption room in the last 6 months									
Yes	19.1%	1.0				1.0			
No	24.7%	1.3	1.0	1.7	0.081	1.5	1.2	2.0	0.001
Access to medical care in the last 6 months									
Yes	17.7%	1.0				1.0			
No	34.9%	2.0	1.5	2.6	<0.001	1.5	1.1	1.9	0.008
Ever in prison									
Yes	17.2%	1.0				1.0			
No	41.9%	2.4	1.8	3.2	<0.001	1.8	1.3	2.5	<0.001

[a] Prevalence ratio.
[b] Adjusted prevalence ratio.

differences were found between different years (2008, 2010 and 2012) in the validity of self-report, which is why all interviews performed during the different years were analyzed together. However, we could not perform separate analysis by sex because only 17% of our sample was female and the majority of them were Spanish-born. To the best of our knowledge this is the first study that explores the risk factors of undiagnosed HIV infection. The high proportion of undiagnosed HIV in PWID limits the validity of self-report. In light of our results, self-report limitations could be more acute depending on the PWID risk behaviors and barriers to health and preventive services. A recent study in San Diego, California (Collier et al., 2015), found that older age and drug treatment were factors associated with knowing about HCV infection. These findings are consistent with our results, even when in our study age and treatment are controlled by other risk factors taken into account in a multivariate model.

4.2. Prevalence, sensitivity and specificity of HIV and HCV

The prevalence of HIV among PWID in Spain was between 30.6% and 39.7% in the years 2006 and 2012 and the prevalence of HCV was found to be between 66% and 88% in the year 2008 (SIVES, 2015). These figures are consistent with the prevalences found in our study (33% for HIV and

Table 4
Undiagnosed HCV proportion and adjusted prevalence ratio estimated with multi-level Poisson regression models with robust variance.

	Undiagnosed HCV								
	%	Bivariate models HCV				Multivariate model HCV			
		PR[a]	95% CI		p value	APR[b]	95% CI		p value
Sex									
Male	18.4%	1.0				1.0			
Female	21.3%	1.3	1.0	1.7	0.045	1.3	1.0	1.7	0.056
Age									
17–29	32.9%	1.0				1.0			
30–34	22.3%	0.7	0.5	0.9	0.01	0.8	0.6	1.1	0.101
35–44	16.3%	0.5	0.4	0.6	0.00	0.7	0.5	0.9	0.001
>45	11.0%	0.3	0.2	0.5	0.00	0.5	0.3	0.8	0.001
Place of origin									
Spain	13.0%	1.0				1.0			
Eastern Europe	29.0%	1.1	0.8	1.5	0.557	1.1	0.9	1.5	0.427
Europe, others	23.4%	1.2	0.8	1.7	0.435	1.2	0.8	1.6	0.411
North Africa and Middle East	31.0%	1.4	0.9	2.2	0.201	1.7	1.1	2.5	0.017
Other	38.9%	1.3	0.8	2.4	0.310	1.6	1.0	2.5	0.064
Educational status									
No formal education	23.1%	1.0							
Primary education	15.4%	0.7	0.5	0.9	0.013				
Secondary education or more	23.0%	0.7	0.5	1.0	0.047				
HIV/HCV co-infection									
Yes	12.5%	1.0							
No	22.6%	1.8	1.4	2.4	<0.001				
Ever had another STI									
Yes	13.4%	1.0							
No	21.1%	1.3	0.9	1.7	0.137				
Ever had Hepatitis B									
Yes	12.1%	1.0							
No	20.9%	1.2	0.8	1.7	0.325				
Sexual relationship in the last 6 months									
Yes	20.1%	1.0							
No	15.1%	0.8	0.6	1.1	0.197				
Regular partner who is HIV-positive in the last 6 months									
Yes	6.1%	1.0				1.0			
No	20.0%	2.4	1.1	5.1	0.030	2.1	1.0	4.3	0.047
First drug injected									
Heroin	17.6%	1.0							
Other drugs	23.9%	1.2	1.0	1.5	0.070				
Use of shared syringes in the last 6 months									
Yes	10.8%	1.0				1.0			
No	29.5%	2.1	1.6	2.7	<0.001	2.2	1.7	2.7	<0.001
Use of shared materials in the last 6 months									
Yes	21.4%	1.0							
No	17.4%	0.9	0.7	1.1	0.140				
Ever in treatment for drug use									
Yes, nowadays	13.5%	1.0				1.0			
Yes, but not now	47.2%	1.9	1.4	2.4	<0.001	2.0	1.6	2.6	<0.001
No, never	18.3%	1.0	0.8	1.3	0.830	1.1	0.9	1.5	0.302
Use of drug consumption room in the last 6 months									
Yes	19.8%	1.0							
No	17.8%	1.1	0.9	1.4	0.461				
Access to medical care in the last 6 months									
Yes	15.1%	1.0				1.0			
No	28.1%	1.4	1.1	1.8	0.002	1.4	1.1	1.7	0.004
Ever in prison									
Yes	15.6%	1.0				1.0			
No	26.6%	1.3	1.0	1.6	0.050	1.3	1.0	1.6	0.023

[a] Prevalence ratio.
[b] Adjusted prevalence ratio.

73% for HCV) for the years 2008 to 2012. Previous studies indicate self-report of HIV status in PWID shows a high specificity (around 99.3% according to Strauss, Rindskopf, Deren, & Falkin, 2001 and 99.5% according to Fisher, Reynolds, Jaffe, & Johnson, 2007) whereas sensitivity is lower (43.8% according to Strauss et al., 2001 and 31.5% (95% CI 29.4%–33.8%) according to Fisher et al., 2007), a trend consistent with our findings. On the contrary, prior studies on the validity of HCV self-report have found higher specificity (around 100% according to Origer, 2012 and 98.1% according to Schlicting et al., 2003) than the specificity found in our study (55.9% (95% CI 51.6%–60.1%)). We performed HCV antibody test but we could not perform HCV RNA test. Therefore, we identified exposure to HCV infection, but not current infection. A positive result for HCV antibodies may indicate an acute infection, chronic hepatitis, or even a past HCV infection. Participants that have been under treatment for HCV and have been told that the virus was no longer detected in the blood may have reported to be HCV negative when the oral fluid test was positive. Even though the prevalence of HIV/HCV co-infection was high in our sample, the vast majority of HIV/HCV co-infected individuals were aware of their HIV and HCV infections, hence, co-infection had to be dropped from the multivariate analysis.

4.3. Risk factors associated to undiagnosed HIV and HCV

In light of our results, around 21% of PWID who were HIV infected were undiagnosed. The corresponding figure was 19% for HCV infection. Undiagnosed infections were more prevalent among younger and foreign-born PWID and those who have lower access to health and preventive services, that is, the most vulnerable groups within the PWID population. Foreign-born PWID face lower socioeconomic status, communication difficulties, lower knowledge of the health system and drug poly-consumption patterns (Saigí et al., 2014). All these factors play a role both in immigrants' poor health outcomes and their access to healthcare and HIV or HCV testing. Undocumented migrants face particular barriers to accessing HIV testing and other health services, due to lack of legal status and health insurance. Younger people make less use of health services, hence there are fewer opportunities for them to enquire about their risk factors and symptomatology, and fewer opportunities to perform medical tests.

Contrary to intuition, the absence of risk factors for acquiring an infection (such as sharing syringes or having had previous sexually transmitted infections or Hepatitis B) enhances the risk that if an HIV or HCV infection occurs, it remains undiagnosed. Individuals who present less risk behaviors may not perceive the need of testing regularly and may not be aware of their actual serostatus (Ha et al., 2014; Stein, Maksad, & Clarke, 2001). What's more, in our sample, having taken an HIV test in the last 12 months increases the risk of undiagnosed infection. This could be explained by the fact that HIV-positive individuals diagnosed in the past do not retake HIV tests, as they already know their status. The prevalence of HIV among the participants who had taken an HIV test in the last 12 months was 23.3%, whereas among participants who had not taken the test the prevalence was 45.1%. Otherwise, some HIV-positive participants may have used the test to come into terms with an unaccepted previous diagnosis or may have felt revealing their status was stigmatizing (Chambers et al., 2015). However, given the high incidence of HIV in our study population, seroconversion during the inter-test interval may have occurred.

4.4. Implications for clinicians and policymakers

Current guidance from the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) recommends regular offering of rapid tests of HIV and HCV to PWID at least once every 6 to 12 months. The per-person cost of counseling, testing and referral of HCV was $25 per patient tested in 2006 (Honeycutt et al., 2007). Regarding HIV, the mean cost of rapid HIV testing was $48 for a negative test and $64 for a preliminary-positive result in 2006 (Pinkerton et al., 2010). The

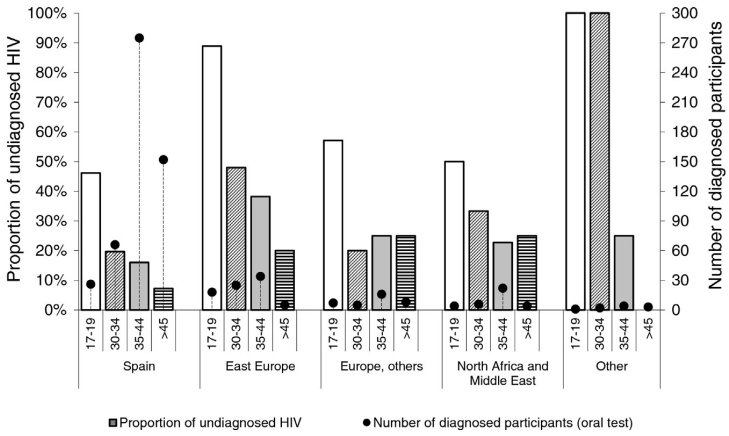

Fig. 2. Proportion of undiagnosed HIV and number of participants who tested positive (saliva test) by place of origin and age group.

relatively low cost per tester who returns for results supports recommendations for routine testing of PWID. Knowledge of one's status may represent a first step for starting treatment and may prevent HIV-positive PWID from engaging in risk behaviors, therefore reducing the likelihood of infecting others (Kwiatkowski, Fortuin Corsi, & Booth, 2002). PWID who are HIV positive have higher risk of delayed diagnosis, progression to AIDS and death compared to HIV-positive people who do not inject drugs (Suárez-García et al., 2016). In addition, given an opioid overdose lethality of 4.2% in Spain (Espelt et al., 2015), it is essential to identify HIV-infected PWID as they have a 74% greater risk of opioid overdose and a 99% greater risk of opioid overdose lethality than their counterparts who are not HIV infected (Green, McGowan, Yokell, Pouget, & Rich, 2012).

Our results highlight the necessity of testing higher risk groups such as foreign-born and younger people who inject drugs. The use of health and preventive services has been proven to play a major role in the access to testing for HIV and HCV. The exclusion of irregular immigrants from the National Healthcare system in Spain since September 2012 (Pérez-Molina & Pulido Ortega, 2012) may jeopardize foreign-born PWID access to treatment and medical care, making tests less available (Hoyos et al., 2013) and discouraging PWID from seeking medical care for fear of legal consequences of drug use. That's why harm reduction resources, such as supervised injecting facilities and needle exchange programmes, are essential points of contact with foreign-born PWID (Barrio et al., 2012).

Our results indicate the necessity of providing HIV and HCV tests as part of the enrolment process in outreach services to out-of-treatment PWID. In the case of HCV, tests should be performed even when PWID self-report having passed the infection, given the low specificity of self-report. A comprehensive approach that engages public health programmes, health care providers and non-governmental organizations is required. Outreach-based interventions that include rapid HIV and HCV tests can play an important role in increasing the rate of early diagnosis, particularly in populations who do not seek conventional medical care.

Contributors

OPB and AE designed the study and took overall responsibility of the project. OP and AE wrote the manuscript. OP, AE, CF and MTB did the analysis and interpretation of data. XM, VG and JC critically revised the manuscript, contributed important intellectual content and participated in the acquisition of data.

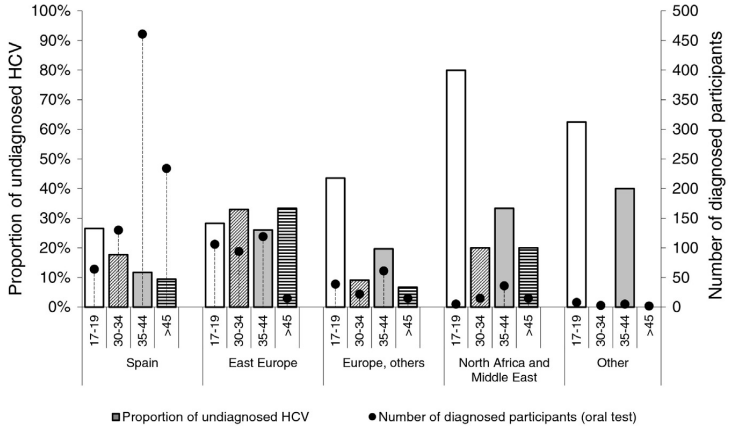

Fig. 3. Proportion of undiagnosed HCV and number of participants who tested positive (saliva test) by place of origin and age group.

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Competing interests

None to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jsat.2017.03.003.

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Article 2

Prevalence and factors associated with non-fatal overdose among people who inject drugs in Catalonia

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Prevalence and factors associated with non-fatal overdose among people who inject drugs in Catalonia

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Abstract

Aims: to describe the prevalence and factors associated with non-fatal overdose among people who inject drugs (PWID).

Design: Cross-sectional surveys performed in the years 2008-09, 2010-11, 2012-13 and 2014-15. Setting: Catalonia, Spain. Participants: 2,396 PWID recruited in harm reduction facilities.

Measurements: Participants completed an interview-administered questionnaire on sociodemographic characteristics, drug use and services use. HIV and hepatitis C tests were performed. Primary outcomes: lifetime and self-reported non-fatal overdose in the last 12 months.

Findings: The prevalence of lifetime non-fatal overdose was 54.3% and the prevalence of non-fatal overdose in the last 12 months was 17.2%. Self-reported non-fatal overdose in the last 12 months was more prevalent among PWID who had used heroin or tranquilizers in the previous 6 months. Other factors associated with non-fatal overdose were the presence of hepatitis C antibodies and syringe sharing. A protective factor against non-fatal overdose was having used methadone. The prevalence of non-fatal overdose was higher in participants more frequently using drug consumption rooms and in those who had received overdose training, possibly due to greater awareness of overdose signs and symptoms and higher self-reporting.

Conclusions: Overdose prevention efforts should focus on PWID who use heroin and have hepatitis C. Future research should address the association between the use of drug consumption rooms and non-fatal overdose by using prospective study designs.

Introduction

Heroin overdoses are an acute reaction that can be easily reversed with naloxone [1], an opiate antagonist administered through injection or a nasal spray. However, a Spanish study in the early 2000s found that 4 out of 100 overdoses in PWID prove fatal [2]. Fatal drug overdoses have increased in recent years in several countries, including the United Kingdom, the Netherlands, Sweden, Finland [3], the United States [4] and Australia [5]. In Spain, the number of fatal overdoses decreased between 1995 and 2010 and has remained stable at around 400 deaths per year since 2010 [6].

A recent systematic review found that 41.5% of PWID has experienced a non-fatal overdose in their lifetime [7]. Non-fatal overdose is more frequent in persons with a prior history of non-fatal overdose, in homeless people, in people sharing syringes [8–10], in those injecting heroin along with other depressants [11], and after prison release [12]. Non-fatal overdoses are linked to an increased risk of fatal overdose [13] and are associated with sequelae such as injuries, paralysis and chest infections [7].

The aims of this study were to describe the prevalence and factors associated with non-fatal overdose among PWID recruited in harm reduction facilities in Catalonia.

Methods

This bio-behavioral surveillance study was conducted in PWID attending the network of 17 harm reduction facilities in Catalonia, Spain [14, 15]. Interviews were performed in the years 2008-09, 2010-11, 2012-13 and 2014-15. We used a stratified convenience sample to obtain an equal distribution of PWID by country of origin and by number of visits to each facility. Individuals who reported injecting drugs in the previous 6 months and who had signed an informed consent form were eligible to take part in the study (n=2,966). To ensure independence of samples, we excluded 570 participants who reported they had completed a questionnaire in previous surveys. We included 2,396 participants (748 in 2008-09, 597 in 2010-11, 536 in 2012-13 and 515 in 2014-15). Participants were offered €10-12 as an inducement. The study protocol was approved by the Hospital Universitari Germans Trias i Pujol Ethics Committee.

Face-to-face interviews were conducted by trained interviewers in each facility using an anonymous structured questionnaire adapted from the ITINERE project [16] and the "Multi-city study on drug injecting and risk of HIV infection" project [17]. The interview lasted approximately 35 minutes and the questionnaire was translated into Spanish, Romanian, Russian, English and French.

Our dependent variables were self-reported lifetime non-fatal overdose and non-fatal overdose in the last 12 months. The interview defined an overdose as the occurrence of difficulty in breathing, collapse or loss of consciousness, difficulty waking up, or blue skin or lips.

The interview gathered information on sociodemographic characteristics (age, sex, country of origin, educational attainment, main income source, place of residence), drug use (time since first injection, frequency of injection, substances used, sharing of syringes), accessing healthcare services (facilities for drug use care, primary health facilities, treatment for drug addiction) and prison history. Most questions on behaviors referred to the previous 6 months. The subcategories of the independent variables are listed in Tables 1 and 2.

We obtained oral fluid samples to determine HIV and hepatitis C status. HIV antibodies were detected using Genscreen HIV-1/2 Version 2.0 assay from Bio-Rad. Hepatitis C antibodies were detected using HCV 3·0 SAVe ELISA.

Statistical analysis

We calculated the prevalence of non-fatal overdose by each independent variable. Differences in overdose prevalence between groups were assessed using chi-square tests for categorical variables and the nonparametric equality-of-medians test for continuous variables. We obtained bivariate prevalence ratios using Poisson models with robust variance [18].

All variables were included in a multivariate Poisson model with robust variance to obtain adjusted prevalence ratios (APR) and 95% confidence intervals. The multivariate model was adjusted by survey year. We performed a collinearity test before including continuous variables in the model. Since naloxone kits are made available after overdose training, we included only overdose training in the

multivariate model. Separate analyses were performed for lifetime non-fatal overdose and non-fatal overdose in the last 12 months. To analyze non-fatal overdose in the last 12 months, we included variables on behaviors in the previous 6 months.

Results

The prevalence of lifetime non-fatal overdose among PWID recruited in harm reduction facilities was 54.3% (95%CI 52.3%-56.3%) (Table 1). The prevalence in different survey years was 54.0% (95%CI 50.4%-57.6%) in 2008-09, 57.5% (95%CI 53.4%-61.4%) in 2010-11, 54.7% (95%CI 50.4%-58.8%) in 2012-13, and 50.9% (95%CI 46.5%-55.2%) in 2014-15. Compared with PWID not reporting overdose, those reporting a non-fatal overdose were older (38 versus 37 years) and had a longer history of injecting use (18 versus 11 years). In the multivariate analysis, the adjusted prevalence ratio of years of injection was 1.03 (95%CI 1.02-1.03). The prevalence of lifetime non-fatal overdose was higher in PWID who had received overdose training, those who were receiving treatment and those who had been in prison.

--- Table 1 ---

The prevalence of non-fatal overdose in the last 12 months among PWID was 17.2% (95%CI 15.7%-18.7%) (Table 2). The prevalence in different survey years was 18.6% (95%CI 15.9%-21.5%) in 2008-09, 18.6% (95%CI 15.7%-21.9%) in 2010-11, 13.3% (95%CI 10.6%-

16.4%) in 2012-13, and 17.5% (95%CI 14.4%-21.0%) in 2014-15. The median age and years of injecting in PWID reporting an overdose in the last 12 months were similar to those in PWID not reporting overdose.

The prevalence of overdose in the last 12 months was 19.1% in PWID using heroin in the last 6 months compared with 8.9% in those not using heroin (APR 1.72 95%CI 1.20-2.46). A higher prevalence of overdose in the last 12 months was also associated with tranquilizer use and syringe sharing. The prevalence of non-fatal overdose in the last 12 months was lower in PWID using methadone in the last 6 months than in those not using methadone (APR 0.80 95%CI 0.64-0.99).

A higher prevalence of overdose self-report was associated with use of a drug consumption room (DCR) in more than 50% of the injections and with receiving overdose training (APR 1.42 95%CI 1.16-1.73 and APR 1.56 95%CI 1.29-1.88, respectively). A higher prevalence of non-fatal overdose in the last 12 months was associated with the presence of hepatitis C antibodies.

--- Table 2 ---

Discussion

PWID attending harm reduction facilities in Catalonia had a lifetime non-fatal overdose prevalence of 54.3% and a prevalence in the previous 12 months of 17.2%. Self-reported lifetime non-fatal overdose was more prevalent among PWID with a longer history of injecting drug use, those who had received overdose training, had been enrolled in treatment, or had been in prison. Self-reported non-fatal overdose in the last 12 months was more prevalent among PWID who had shared syringes or who had hepatitis C antibodies. PWID using heroin in the last 6 months had a 72% higher prevalence of non-fatal overdose than those not using heroin. In contrast, having used methadone was a protective factor against non-fatal overdose. Contrary to our hypothesis, the prevalence of self-reported non-fatal overdose in the last 12 months was higher in participants more frequently using DCRs and in those who had received overdose training.

This is a cross-sectional study using surveys carried out in different years. To ensure independence of samples, we excluded participants reporting they had completed the questionnaire in previous surveys. However, this resulted in fewer participants than in recent surveys. Additionally, differences in overdose prevalence between survey years were not statistically significant. The results are representative of individuals attending DCRs, who tend to be male, and in older PWID with unstable housing and a long-term history of drug use [19]. Because we were unable to assess factors associated with fatal overdose and the individuals in our study population tend to have long histories of drug use, we may have missed important factors associated with high fatality. Moreover, both non-fatal overdose and the factors analyzed in this

study were self-reported data that could have been underreported. However, a study using the same sample found low HIV underreporting [20].

Cross-sectional studies can fall into reverse causality bias. In our study, participants reporting frequent DCR use and attendance at overdose training had a higher prevalence of non-fatal overdose. The first objective of overdose training is to help PWID recognize the signs and symptoms of this event [21]. Likewise, if an overdose occurs within a DCR, the staff will treat the acute symptoms and will give advice to avoid a new overdose. Therefore, our results may point to greater awareness of non-fatal overdose and the probability of self-reporting an overdose rather than to an increase in the number of overdoses after frequent DCR use or overdose training. Ecological data have shown that opioid overdose deaths are reduced in communities implementing opioid education and naloxone distribution [21, 22]. A recent cohort study reported that frequent DCR use was associated with a lower risk of all-cause mortality [23].

The lifetime prevalence of non-fatal overdose and the prevalence in the past 12 months among PWID identified in this study is consistent with the results of an international systematic review reporting prevalences of 41.5% and 20.5%, respectively [7]. Another review found medians of 47% and 17% among people who use drugs [24]. Some studies have found an association between the risk of non-fatal overdose and younger age [25, 26] and having been to prison [24]. We found these associations in the lifetime prevalence of non-fatal overdose but not in the prevalence in the last 12 months. Unlike other studies [10, 25, 27],

in our multivariate analysis, non-fatal overdose was not associated with unstable accommodation.

In our study, the factor most closely associated with non-fatal overdose was recent heroin use. We also found an association with tranquilizer use. This pattern is consistent with findings in other studies [26, 28, 29]. However, some studies have also found an association with other substances such as cocaine [27] and alcohol [28]. In contrast, we found that methadone use was a protective factor against non-fatal overdose. While one study [10] found a positive association between methadone detoxification and non-fatal overdose, we and other authors observed the opposite when assessing methadone maintenance treatment [25, 26]. This protective effect may be due to the long half-life of methadone, allowing for accumulation in the body and steady-state plasma levels [30]. Hence, it does not have the pronounced narcotic effects of shorter-acting opioids such as heroin [31].

HIV and hepatitis C are known risk factors for overdose death [32]. However, ours and other studies [33] failed to find an association between HIV status and risk of non-fatal overdose. We did find an association, however, between hepatitis C antibody positive status and the prevalence of non-fatal overdose. Although evidence is limited, reduced opiate metabolism in damaged livers may prolong the period of heavy intoxication and increase the risk of overdose [34]. Other studies have found increased risks of non-fatal overdose associated with factors we have not been able to assess, such as cardiovascular disease, mental health problems, suicidal ideation and suicide attempts [35], fear of police arrest [36], and sex trade work [29].

Overdose is a preventable cause of death and injury. In light of our results, overdose prevention efforts should focus on PWID who use heroin and have hepatitis C. This is the first study to review the association between the frequency of use of DCR and overdose training with non-fatal overdose. However, our results seem to be affected by reverse causality bias. Future research should address this issue using study designs able to identify timing of the exposure and overdose.

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Figures and tables with legends

Table 1. Prevalence, bivariate models and multivariate model of **lifetime non-fatal overdose** by demographic, drug use and service attendance characteristics

Variable	Non-fatal overdose n (1302)	% (54.3)	Total 2396	p value	PR	95% CI		p value	APR	95% CI		p value
Sex												
Male	1093	55.3%	1976	**<0.001**	1.00				1.00			
Female	208	50.4%	413		0.91	0.82	1.01	0.076	0.99	0.90	1.10	0.868
Age (years)												
Median (IQR)	38 (32-44)			**<0.001**	**1.02**	**1.01**	**1.02**	**<0.001**	**0.99**	**0.98**	**1.00**	**0.001**
18 to 29	208	43.3%	480	**<0.001**								
30 to 34	237	50.9%	466									
35 to 44	574	57.5%	998									
45 or older	283	63.5%	446									
Country of origin												
Spain	846	60.0%	1411	**<0.001**	**1.29**	**1.19**	**1.39**	**<0.001**	1.03	0.95	1.13	0.450
Other	456	46.6%	979		1.00				1.00			
Educational attainment												
No schooling	142	54.8%	259	**0.025**	1.00				1.00			
Primary studies	697	57.0%	1223		1.04	0.92	1.17	0.53	1.02	0.91	1.15	0.692
Secondary or more	461	51.1%	903		0.93	0.82	1.06	0.274	1.08	0.95	1.22	0.253
First injected drug												
Heroin	956	57.7%	1658	**<0.001**	1.00				1.00			
Other	299	46.8%	639		**0.81**	**0.74**	**0.89**	**<0.001**	0.92	0.84	1.01	0.089
No response	47	50.5%	93		0.88	0.71	1.08	0.208	0.95	0.78	1.17	0.644
Years injecting												
Median (IQR)	18 (10-25)			**<0.001**	**1.02**	**1.02**	**1.03**	**<0.001**	**1.03**	**1.02**	**1.03**	**<0.001**
0 to 5	162	33.1%	489	**<0.001**								
6 to 10	175	49.3%	355									
11 or more	958	62.7%	1529									

Variable	Non-fatal overdose n (1302)	% (54.3)	Total 2396	p value	PR	95% CI		p value	APR	95% CI		p value
Has recieved overdose training												
Yes	576	65.6%	878	**<0.001**	**1.37**	**1.27**	**1.47**	**<0.001**	**1.24**	**1.16**	**1.34**	**<0.001**
No	720	48.0%	1499		1.00				1.00			
Has recieved a naloxone kit												
Yes	358	69.0%	519	**<0.001**	**1.37**	**1.27**	**1.48**	**<0.001**				
No	924	50.3%	1838		1.00							
Treatment status												
Yes, currently	711	60.7%	1172	**<0.001**	**1.70**	**1.48**	**1.95**	**<0.001**	**1.32**	**1.15**	**1.53**	**<0.001**
Previous treatment	443	54.8%	808		**1.54**	**1.34**	**1.78**	**<0.001**	**1.28**	**1.11**	**1.48**	**0.001**
No, never	148	35.7%	414		1.00				1.00			
Ever in prison												
Yes	947	60.6%	1562	**<0.001**	**1.42**	**1.30**	**1.55**	**<0.001**	**1.23**	**1.13**	**1.35**	**<0.001**
No	354	42.8%	827		1.00				1.00			

Table 2. Prevalence, bivariate models and multivariate model of **non-fatal overdose in the last 12 months** by demographic, drug use and service attendance characteristics

Variable	Non-fatal overdose n (411)	% (17.2)	Total 2396	p value	PR	95% CI		p value	APR	95% CI		p value
Sex												
Male	342	17.3%	1973	0.774	1.00				1.00			
Female	69	16.7%	412		0.97	0.76	1.22	0.775	0.93	0.73	1.20	0.585
Age												
Median (IQR)	36 (30-42)			0.063	**0.99**	**0.98**	**1.00**	**0.017**	0.98	0.97	1.00	0.086
18 to 29	100	20.9%	479	0.056								
30 to 34	79	17.0%	465									
35 to 44	169	17.0%	996									
45 or more	63	14.1%	446									

Variable	Non-fatal overdose n (411)	% (17.2)	Total 2396	p value	PR	95% CI		p value	APR	95% CI		p value
Country of origin												
Spain	235	16.7%	1408	0.406	0.93	0.78	1.11	0.406	0.85	0.67	1.07	0.160
Other	176	18.0%	978		1.00				1.00			
Educational attainment												
No schooling	44	17.1%	258	0.813	1.00				1.00			
Primary school	216	17.7%	1221		1.04	0.77	1.39	0.808	1.05	0.78	1.41	0.750
Secondary or more	150	16.6%	902		0.98	0.72	1.32	0.872	1.02	0.74	1.39	0.922
Main source of income												
Employed	60	13.3%	452	**0.045**	1.00				1.00			
Unemployed with social security benefit	94	18.7%	504		**1.41**	**1.04**	**1.89**	**0.025**	1.27	0.93	1.74	0.139
Unemployed without social benefit	255	18.0%	1419		**1.35**	**1.04**	**1.76**	**0.023**	1.06	0.81	1.40	0.651
Accommodation												
Stable accommodation	203	14.2%	1433	**<0.001**	1.00				1.00			
Unstable or no accommodation	208	21.8%	953		**1.54**	**1.29**	**1.84**	**<0.001**	1.14	0.93	1.40	0.213
Lives alone												
Yes	156	20.5%	760	**0.004**	**1.31**	**1.09**	**1.57**	**0.003**	1.08	0.89	1.31	0.444
No	255	15.7%	1626		1.00				1.00			
HIV status												
Positive	139	20.2%	687	**0.012**	**1.27**	**1.06**	**1.53**	**0.011**	1.11	0.90	1.36	0.321
Negative	268	15.9%	1681		1.00				1.00			
Hepatitis C antibody status												
Positive	302	18.7%	1612	**0.004**	**1.35**	**1.10**	**1.65**	**0.004**	**1.32**	**1.05**	**1.65**	**0.017**
Negative	105	13.9%	755		1.00				1.00			
Most frequent injected drug last 6 months												
Heroin	228	20.6%	1107	**<0.001**	**1.40**	**1.13**	**1.73**	**0.002**	**1.38**	**1.09**	**1.75**	**0.008**
Heroin and cocaine	102	14.7%	692		0.90	0.68	1.18	0.441	0.99	0.73	1.34	0.937
Cocaine	74	13.2%	560		1.00				1.00			
First injected drug												
Heroin	283	17.1%	1655	0.609	1.00				1.00			
Other	115	18.0%	638		1.05	0.87	1.28	0.599	1.19	0.96	1.47	0.106
No answer	13	14.0%	93		0.82	0.49	1.37	0.443	0.94	0.56	1.57	0.802

Variable	Non-fatal overdose n (411)	% (17.2)	Total 2396	p value	PR	95% CI		p value	APR	95% CI		p value
Years injecting												
Median (IQR)	15 (6-23)			0.759	1.00	0.99	1.01	0.946	1.00	0.99	1.02	0.797
0 to 5	97	19.9%	488	0.221								
6 to 10	57	16.1%	355									
11 or more	255	16.7%	1526									
Having used a used syringe last 6 months												
Yes	241	20.6%	1169	**0.001**	**1.48**	**1.24**	**1.77**	**<0.001**	**1.28**	**1.04**	**1.58**	**0.018**
No	169	13.9%	1215		1.00				1.00			
Daily injection												
Yes	222	19.5%	1138	**0.005**	**1.29**	**1.08**	**1.54**	**0.005**	1.08	0.90	1.29	0.427
No	188	15.1%	1244		1.00				1.00			
Having used cocaine in the last 6 months												
Yes	331	18.5%	1788	**0.005**	**1.38**	**1.10**	**1.73**	**0.006**	1.13	0.87	1.46	0.355
No	80	13.4%	595		1.00				1.00			
Having used heroin in the last 6 months												
Yes	373	19.1%	1952	**<0.001**	**2.16**	**1.57**	**2.96**	**<0.001**	**1.72**	**1.20**	**2.46**	**0.003**
No	38	8.9%	429		1.00				1.00			
Having used heroine and cocaine mix in the last 6 months												
Yes	260	18.6%	1398	**0.042**	**1.21**	**1.01**	**1.45**	**0.043**	1.07	0.86	1.32	0.557
No	151	15.4%	981		1.00				1.00			
Having used tranquilizers in the last 6 months												
Yes	273	20.8%	1310	**<0.001**	**1.62**	**1.34**	**1.96**	**<0.001**	**1.45**	**1.16**	**1.81**	**0.001**
No	138	12.9%	1073		1.00				1.00			
Having used methadone in the last 6 months												
Yes	234	16.3%	1437	0.128	0.87	0.73	1.04	0.127	**0.80**	**0.64**	**0.99**	**0.041**
No	177	18.7%	947		1.00				1.00			
Having used other opiates in the last 6 months												
Yes	68	25.5%	267	**<0.001**	**1.57**	**1.25**	**1.97**	**<0.001**	1.08	0.84	1.40	0.536
No	343	16.2%	2117		1.00				1.00			
Having used MDMA in the last 6 months												
Yes	74	26.2%	282	**<0.001**	**1.64**	**1.32**	**2.04**	**<0.001**	1.12	0.85	1.47	0.410
No	337	16.0%	2102		1.00				1.00			

Variable	Non-fatal overdose n (411)	% (17.2)	Total 2396	p value	PR	95% CI		p value	APR	95% CI		p value
Having used amphetamines in the last 6 months												
Yes	80	25.0%	320	**<0.001**	**1.56**	**1.26**	**1.93**	**<0.001**	1.20	0.93	1.55	0.163
No	331	16.1%	2059		1.00				1.00			
Having used cannabis in the last 6 months												
Yes	310	18.6%	1664	**0.004**	**1.35**	**1.10**	**1.67**	**0.005**	1.08	0.85	1.36	0.531
No	99	13.8%	719		1.00				1.00			
Using DCR >50% injections												
Yes	246	20.4%	1203	**<0.001**	**1.49**	**1.23**	**1.80**	**<0.001**	**1.42**	**1.16**	**1.73**	**0.001**
No	137	13.8%	995		1.00				1.00			
No answer	28	14.9%	188		1.08	0.74	1.57	0.682	1.25	0.84	1.87	0.261
Has recieved overdose training												
Yes	202	23.1%	874	**<0.001**	**1.67**	**1.40**	**1.98**	**<0.001**	**1.56**	**1.29**	**1.88**	**<0.001**
No	208	13.9%	1499		1.00				1.00			
Has recieved a naloxone kit												
Yes	139	26.9%	517	**<0.001**	**1.86**	**1.55**	**2.23**	**<0.001**				
No	265	14.4%	1836		1.00							
Used health services in the last 6 months												
Yes	301	18.6%	1616	**0.006**	**1.32**	**1.08**	**1.62**	**0.007**	1.18	0.96	1.46	0.114
No	108	14.1%	766		1.00				1.00			
Treatment status												
Yes, currently	183	15.7%	1167	**0.02**	1.00	0.77	1.30	0.993	0.81	0.60	1.11	0.186
Previous treatment	163	20.3%	804		1.29	0.99	1.68	0.056	0.96	0.73	1.26	0.753
No, never	65	15.7%	414		1.00				1.00			
Ever in prison												
Yes	302	19.4%	1560	**<0.001**	**1.47**	**1.20**	**1.79**	**<0.001**	1.22	0.98	1.52	0.079
No	109	13.2%	825		1.00				1.00			

Article 3

Impact of 24-hour schedule of a drug consumption room on service use and number of non-fatal overdoses. A quasiexperimental study in Barcelona

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Impact of 24-hour schedule of a drug consumption room on service use and number of non-fatal overdoses. A quasiexperimental study in Barcelona

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ABSTRACT

Background: The opening hours of drug consumption rooms could constitute a barrier to access among people who use drugs (PWUD). CAS Baluard is an outpatient substance use care center in Barcelona, which provides a drug consumption room in Barcelona among other services. The objectives of our study were to compare the client profile, the facility use, the drugs used, and the number of non-fatal overdose episodes between (1) a 15-hour opening period of a drug consumption room versus a 24-hour opening period; and (2) between daytime and nighttime during the 24-hour period.

Methods: Data from CAS Baluard was obtained from March-June (15-hour opening period) and July-October (24-hour opening period), 2018. The sociodemographic characteristics of clients were gathered in both periods and in the daytime and nighttime client groups in the 24-hour period. Finally, associations were estimated between facility use and period and between facility use and opening hours.

Results: There were 1,089 clients in the 15-hour period and 1,262 in the 24-hour period. There were no sociodemographic differences in the clients between periods. During nighttime, there was a higher proportion of women (17%) and homeless people (47%) than during daytime (12% and 30%, respectively). Injected cocaine use was more frequent during nighttime (34%) than during daytime (25%) and injected heroin use was less frequent during nighttime (17%) than during daytime (24%). There was a non-significant increase in non-fatal overdose risk during nighttime (PR 3.9 95%CI 0.98-15.64). However, when we analyzed heroin use alone, the increase in non-fatal overdose risk was significant (PR 4.69 95%CI 1.17-18.75).

Conclusion: During nighttime, attendance at the facility was higher among women, homeless people, and people who used stimulants. Our results point to a possible increase in overdose risk during nighttime, when most drug consumption rooms are closed.

Introduction

Drug consumption rooms (DCR) are facilities where people who use drugs (PWUD) can use drugs in safe and hygienic conditions (Rhodes & Hedrich, 2010). These facilities may also refer PWUD and accompany them to other social and health services (EMCDDA, 2018). There are DCRs in several countries in Europe, Canada and Australia (EMCDDA, 2018; Kennedy, Karamouzian & Kerr, 2017; Kerr, Mitra, Kennedy & McNeil, 2017). There are currently nine DCRs in Barcelona, with one mobile unit and one DCR for inhaled use.

DCRs have been linked to improvements in the health of PWUD. DCRs use has been associated with a reduction in overdose frequency and overdose death (Kennedy et al., 2017; Marshall, Milloy, Wood, Montaner & Kerr, 2011). Additionally, after the opening of DCRs, substance use treatment and the use of other health services increases among clients (Kennedy et al., 2017; Wood, Tyndall, Zhang, Montaner

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& Kerr, 2007). However, there is no conclusive evidence that DCRs reduce HIV and HCV transmission among clients (Rhodes & Hedrich, 2010).

In addition, DCRs are not always welcomed by residents, even though they reduce public drug use and the number of syringes and other injecting materials found in the street after their opening (Belackova & Salmon, 2017; Espelt et al., 2017a; Kerr et al., 2017; Potier, Laprévote, Dubois-Arber, Cottencin & Rolland, 2014; Sepúlveda, Báez & Montenegro, 2008; Vecino et al., 2013). Equally, previous studies have not shown an increase in first time injections or drug dealing around DCRs after their opening (Kennedy et al., 2017; Potier et al., 2014; Wood, Tyndall, Lai, Montaner & Kerr, 2006). In fact, their clients report similar or lower drug use after DCRs opening (Kerr, Kimber, Debeck & Wood, 2007; Kinnard, Howe, Kerr, Skjødt Hass & Marshall, 2014). DCRs are valuable, as public drug use is related to syringe sharing and a lower frequency of injection site cleaning after injection (Marshall, Kerr, Qi, Montaner & Wood, 2010; Mazhnaya, Tobin & Owczarzak, 2018).

Previous research has found opening hours to be a barrier to DCRs use for some PWUDs (Small, Ainsworth, Wood & Kerr, 2011; Stoever, Förster, Hornig & Theisen, 2015). The percentage of PWUD who report using drugs in public places is higher when the facilities are closed. Half of PWUD who use drugs in public places would prefer to do so inside a facility (Stoever et al., 2015).

In Europe, DCRs opening hours can vary from 3 to 20 hours per day depending on the facility (Woods, 2014). There are experiences in Madrid and Vancouver where, for different reasons, opening hours were extended to 24 hours per day during specific periods. In Copenhagen, there is a center that closes for only 3 hours (Hedrich, 2004; Otterstatter, Amlani, Guan, Richardson & Buxton, 2016). The Baluard outpatient substance use care center (CAS Baluard) in Barcelona, is a comprehensive center that offers treatment and harm reduction services from a bio-psycho-social perspective and has a multidisciplinary team. Harm reduction programs include syringe sharing, DCRs for injected and inhaled drug use, overdose prevention and medical, psychological and educational consultations. A residents' petition to address public drug use, which was on the rise in the neighborhood where the CAS Baluard is situated, influenced the political decision to extend its opening hours, from the regular 7 a.m. to 10 p.m. schedule, to 24 hours a day, from July until November 2018.

There could be differences in DCRs use and clients' profile between daytime and nighttime, which may require the adjustment of the services offered during night hours. As far as we know, no published study has evaluated whether a 24-hour opening schedule involves differences in DCRs use or variations in clients' profile or drug use. Therefore, the objectives of our study were [1] to compare the CAS Baluard client profile during the 24 hour opening period and the previous 15-hour opening period, [2] to compare the facility use, the drugs used, and the number of non-fatal overdose episodes between the 24-hour opening period and the 15-hour opening period, [3] to compare CAS Baluard daytime client profile with nighttime client profile in the 24-hour opening period and [4] to compare the facility use, the drugs used, and the number of non-fatal overdose episodes use during daytime and nighttime in the 24-hour opening period.

Methods

We performed a quasi-experimental pre-post study without a comparison group using data from the Public Health Agency of Barcelona harm reduction information system. The 'pre' period consisted of the 15-hour period, in which the CAS Baluard opened for 15 hours a day, from March 1st to June 30th, 2018. The 'post' period consisted of the 24-hour period, in which the center opened for 24 hours a day from July 1st to October 31st, 2018. The CAS Baluard client profile and service use was compared between the 15-hour period and the 24-hour period, and between daytime and nighttime in the 24-hour period.

Study variables

Every time a client visits the center for the first time, an initial screening is performed in which information on sociodemographic characteristics is registered. Then, each time the client uses a service (e.g. the DCR, social worker's office), the client answers a standardized questionnaire, which is different for each service. If the client wishes to use the DCR, the client is asked what substance will be used, if it will be injected or inhaled, among other questions. Furthermore, additional information is registered, for example: if a hygienic advice is given, or if the client suffers from an overdose.

The main independent variable was the study period: the 15-hour opening period of the CAS Baluard and the 24-hour opening period. In the second analysis, which was restricted to the 24-hour period, the independent variable was opening hours: daytime from 7 a.m. to 9:59 p.m. and nighttime from 10 p.m. to 6:59 a.m. We considered 7 a.m. to 9:59 p.m. as daytime since it is the regular opening hours of CAS Baluard.

The dependent sociodemographic variables were age, gender, country of birth, and residential situation. The dependent variables regarding CAS Baluard use were drug use episodes (the number of times a drug was used in the DCR), the substance used (recoded according to type and route of drug use), injecting site (part of the body where the drug was injected), and if an overdose occurred during a drug use episode. The injecting site was included in the study to assess the proportion of high-risk injections (inguinal/jugular injections).

The number of syringes distributed by the syringe exchange program and the syringes collected by the city cleaning services and the harm reduction programs of Barcelona were also gathered.

Statistical analysis

To study the client profile, an anonymized database was created with single clients and their sociodemographic characteristics. To study CAS Baluard use, another database was created with information from visits to the center. A visit to the center consists of an activity performed in the CAS Baluard, so a client can make several visits in the same day. Visits were linked with the characteristics of the person making the visit.

First, a descriptive analysis was performed to show sociodemographic characteristics and the frequency of visits among single clients in the 15- and 24-hour periods. Then, sociodemographic characteristics of the visits were studied and compared between periods. In this analysis, visits were the analysis unit, so the sociodemographic characteristics of several visits could refer to the same individual. Differences between periods were assessed with the chi-square test, Fisher's exact test, Student's t test or Wilcoxon-Mann-Whitney test, whenever appropriate.

Afterward, CAS Baluard use was compared between the 15- and 24-hour periods. Visits were, once again, the analysis unit in this analysis so different drug use episodes could refer to the same client. Prevalence Ratios (PR) and their 95% confidence intervals (95% CI) were calculated using Poisson regression models with robust variance to estimate the association between DCR use variables (drug use episodes, substance used, injecting site and overdoses) and the study period (Espelt, Mari-Dell'Olmo, Penelo & Bosque-Prous, 2017b). Models were first performed unadjusted, and then adjusted by sociodemographic variables that were related to the study period in the descriptive analyses, or that were possible confounders: gender, age, country of birth and residential situation A sub analysis was done that included only visits involving heroin use. Other opioids were excluded from the sub-analysis because the majority of clients who use opioids in CAS Baluard use heroin, and use of other opioids is residual.

In a second analysis, client profile analysis was replicated for daytime and nighttime client groups in the 24-hour period. The nighttime client group were those clients who visited the facility at least once

Table 1
Description of CAS Baluard single clients by study period.

	15-h		24-h		
	n	%	n	%	p-value
Gender					0.455
Men	909	83.6	1,076	85.4	
Women	176	16.2	181	14.4	
Trans women	2	0.2	3	0.2	
Age (mean and SD)	39.5	8.9	39.4	8.7	0.694
Country of birth					0.468
Spain	425	39.4	463	36.9	
Rest of Europe	418	38.7	502	40.0	
Other	237	21.9	290	23.1	
Residence					0.523
Home, apartments	211	31.4	249	33.6	
Unstable residence	179	26.6	203	27.4	
Homeless	282	42.0	290	39.0	
Visits per person (median and range)	3	1-874	4	1-625	0.317
Number of visits					0.538
Single visit	340	31.2	409	32.4	
Two or more visits	749	68.8	853	67.6	
Total	1,089		1,262		

CAS Baluard: Baluard outpatient substance use care center. SD: Standard deviation. Missing values in the 15-hour period: 2 for gender, 9 for country of birth and 417 for residence; in the 24-hour period: 2 for gender, 7 country of birth and 520 for residence.

during the nighttime (10 p.m. to 6 a.m.) in the 24-hour period. The daytime client group were those clients who visited the facility only during the daytime (7 a.m. to 9 p.m.) in the 24-hour period. Facility use analysis was also replicated but with comparison of daytime visits with nighttime visits, and estimation of the association between CAS Baluard use with opening hours.

National directives (ethical and deontological codes of the professional associations) and international directives (Helsinki declaration, Fortaleza, Brazil, October 2013) were followed. Data was treated as confidential, following the personal data protection law of Spain (Organic Law 3/2018 of 5 December on the Protection of Personal Data and the Guarantee of Digital Rights).

Results

During the study period, the CAS Baluard was visited by 1,994 persons. There were 1,089 clients in the 15-hour period and 1,262 in the 24-hour period (Table 1). In both periods, distribution regarding client's profile was similar in terms of gender; about 85% of clients were men, 15% were women and 0.2% were trans women. There were no differences in the other sociodemographic variables between periods. Clients had a mean age of 39 years, between 35% and 40% were born in Spain and about 40% were homeless (Table 1).

Figure 1 represents the number of visits per hour for each study period. In both periods, there were two time-points with a higher number of visits, around 8 a.m. and at 4 p.m. In the 24-hour period, there were a considerable number of visits at 10 pm, which decreased during the night.

Regarding the CAS Baluard use, a total of 35,023 visits were made in the 15-hour period and 47,494 in the 24-hour period (Table 2), representing an increment of 36%. Most (85%) visits were made by men, but in the 24-hour period there was a 0.8% increase in the proportion of visits made by women. The percentage of visits among people born in Europe also increased in the 24-hour period.

There were 8,654 drug use episodes during the 15-hour period and 14,713 during the 24-hour period (Table 3). The percentage of visits in which the DCR was used increased from 24.7% of the total visits to the CAS Baluard in the 15-hour period to 31.0% in the 24-hour period. The probability of use of the DCR and injected cocaine use was higher in the 24-hour period than in the 15-hour period. The results do not suggest a higher risk of overdose in this period than in the previous one (PR 1.76 95%CI 0.48-6.52). The results were similar in the sub-analyses that included only heroin use (PR 1.67 95%CI 0.45-6.15).

Regarding client's profile in the 24-hour period, the proportion of women in the nighttime client group was 17.0%, higher than in the daytime client group (11.6%) (Table 4). There was also a higher proportion of people from the rest of Europe in the nighttime client group than in the daytime client group. The proportion of homeless people was higher in the nighttime client group (46.5%) than in the daytime client group (30%). In the nighttime client group, 85% of people visited the facility more than once during the 24-hour period. Meanwhile, in the daytime client group, 50.8% of clients visited the facility only once during that period.

Looking at the visits made in the 24-hour period, there were 35,773 visits during the day and 11,721 during the night (Table 5). The proportion of visits made by women was higher during nighttime (16.9%) than during daytime (15.3%). The proportion of visits of people born outside of Spain increased during nighttime. Most of the visits were made by homeless people.

A total of 9,732 drug use episodes occurred during daytime and 4,891 during nighttime in the 24-hour period (Table 6). During nighttime, drug use episodes among the total number of visits increased from 27.2% during daytime to 42.5% during nighttime. In this period, there were three overdoses during the day and six during nighttime, all of them after heroin use. The risk of suffering an overdose was four times higher during the nighttime than during daytime (PR 3.9 95%CI 0.94-15.62), but the confidence interval was wide and not significant. However, when we included only heroin use, there was a statistically significant increased risk (PR 4.69 95%CI 1.17-18.75). The pattern of drug use also differed. During night opening hours, the proportion of injected and inhaled cocaine use increased (from 24.7% and 11.4% to 33.5% and 13.7%, respectively). The probability of injected cocaine use was 36% higher and that of inhaled cocaine use was 20% higher during nighttime than during daytime. However, heroin use decreased during the night, reaching 17.4% for injected heroin and 12.6% for inhaled heroin. During nighttime, the probability that the drug consumed was heroin was 25% lower, both for injected and inhaled heroin use.

Injected heroin use progressively increased from 7-8pm, when it represented 19% of the total drug use episodes, until reaching 39% of the total drug use episodes between 5-6 a.m. (Figure 2). Injected heroin use had two time-points of higher use, around 9-10 a.m. and around 19-20 p.m. Injected cocaine use was greater during nighttime, with 39% of the total drug use episodes around 5-6 a.m.

Discussion

Cocaine injection and visits among women in the CAS Baluard were higher in the 24-hour period than in the 15-hour period. Visits of clients and drug use episodes were also higher in the 24-hour period. Furthermore, in this period there was higher use of the DCR compared with other services during nighttime (42.5% of visits) than during daytime (27.2% of the visits), as well as greater cocaine use and less heroin use. The proportion of women was higher in the nighttime client group (17%) than in the daytime client group (11.6%). The proportion of frequent clients was also higher in the nighttime client group, and visits by women were also higher during nighttime. The results suggest a possible increased risk of overdose in visits during nighttime in the 24-hour period (PR 3.9 95%CI 0.98-15.62), despite lower heroin use. Taking into account only heroin use, we found a higher risk of overdose during nighttime than during daytime (PR 4.69 95%CI 1.17-18.75).

Although several studies support extending the opening hours of some DCRs during the night (Otterstatter et al., 2016; Peacey, 2014; Small et al., 2011; Stoever et al., 2015), our study is, as far as we know, the first with a quasi-experimental pre-post design that compares the use of the DCR between day and night.

A pre-post study design without a comparison group has limitations

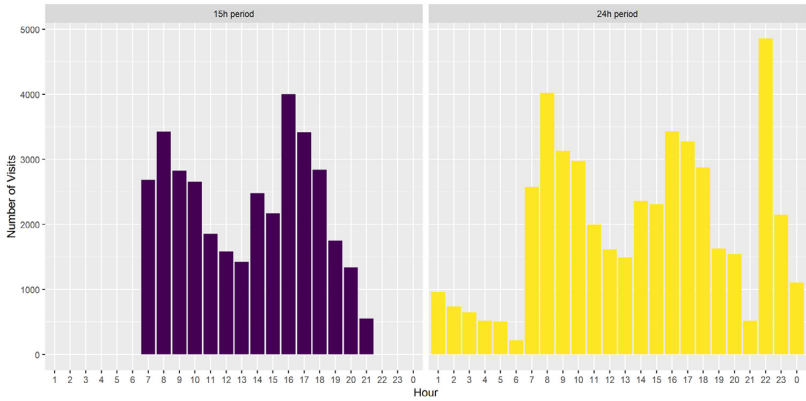

Figure 1. Number of CAS Baluard visits per hour in the 15-hour period and in the 24-hour period.

Table 2
CAS Baluard visits' client profile comparison by study period.

	15-h		24-h		
	n	%	n	%	p-value
Gender					0.002
Men	29,752	85.0	39,950	84.3	
Women	5,199	14.9	7,448	15.7	
Trans women	22	0.1	19	0.0	
Age (mean and SD)	39.5	8.2	40.1	8.6	<0.001
Country of birth					<0.001
Spain	12,570	36.0	16,834	35.6	
Rest of Europe	15,376	44.0	22,009	46.5	
Other	7,009	20.0	8,472	17.9	
Residence					<0.001
Home, flat, apartments	5,866	21.7	8,877	24.2	
Unstable residence	5,067	18.8	6,073	16.6	
Homeless	16,085	59.5	21,680	59.2	
Total visits	35,023		47,494		

CAS Baluard: Baluard outpatient substance use care center. SD: Standard deviation. Missing values in the 15-h period: 50 for gender, 11,381 for country of birth, and 8,005 for residence; in the 24-h period: 77 for gender, 179 for country of birth and 10,864 for residence.

regarding internal validity. Factors not taken into account in the study could have affected the observed results. However, we have no record of interventions implemented during the study period that could have had an impact in the study outcomes. While a comparison group may have controlled some limitations, there is no comparable center to CAS Baluard in Barcelona. Other DCRs in Barcelona do not offer the same services that CAS Baluard does and they do not have as many single clients and visits. Furthermore, a study in six European cities found great variability in the drugs used between cities, but also within cities (EMCDDA, 2019). Therefore, comparing results between DCR and between cities could also be subject to limitations.

We did not assess if seasonality had any influence in the results of the study. The time of the year could potentially affect the number of visits to the center. However, when we compared the 15-hour period and the 24-hour period, no differences were observed in the sociodemographic characteristics of clients between periods. This could indicate that seasonality may not have had a great impact on the profile of clients who visit the center.

Another limitation could be that the type of drug use in CAS Baluard may differ from that in other DCRs. In this facility, unlike other centers, there is a specific room for inhaled drugs. These issues, in addition with the limitations of the study design, could limit the ability to extrapolate the results of this study to other smaller DCRs, or which do not have a

Table 3
CAS Baluard and its drug consumption room use comparison by study period.

		15-h		24-h							
	n	%	n	%	p-value	PR		CI (95%)	aPR*		CI (95%)
Drug use episodes	8,654	24.7	14,713	31.0	<0.001	1.25	1.23	1.28	1.23	1.20	1.27
Substance used											
Injected heroin.	1,829	21.1	3,212	21.8	0.109	1.03	0.98	1.09	1.13	1.06	1.20
Inhaled heroin	1,647	19.0	2,230	15.2	<0.001	0.80	0.75	0.84	0.83	0.78	0.89
Injected heroin and cocaine	1,743	20.1	2,935	20.0	0.367	0.99	0.94	1.04	0.81	0.76	0.86
Injected cocaine	2,062	23.8	4,071	27.7	<0.001	1.16	1.11	1.22	1.10	1.05	1.16
Inhaled cocaine	1,175	13.6	1,792	12.2	0.001	0.90	0.84	0.96	1.03	0.95	1.11
Others	198	2.3	473	3.2	<0.001	1.41	1.19	1.66	1.97	1.63	2.4
Injecting site											
Upper extremities	5,261	93.3	9,560	93.4	<0.001	1.00	0.99	1.01	1.01	1.00	1.03
Lower extremities	197	3.5	393	3.8	0.034	1.10	0.93	1.30	0.93	0.77	1.14
Inguinal/jugular	183	3.2	279	2.7	0.134	0.84	0.70	1.01	0.76	0.62	0.92
Overdoses for all substance use	3	0.0	9	0.1	0.553	1.76	0.48	6.52			
Overdoses for heroin use**	3	0.0	9	0.1	0.113	1.67	0.45	6.15			
Syringes distributed by PIX	87,676		116,830								
Syringes collected on the street	1,516		1,789								

CAS Baluard: Baluard outpatient substance use care center. PR: Prevalence ratio. CI: Confidence interval. aPR: adjusted Prevalence Ratio. PIX: Syringe Exchange Program. *Adjusted by gender, age, country of birth and residential situation. **Only takes into account cases in which the drug used was heroin.

Table 4
Description of CAS Baluard single clients by daytime and nighttime group in the 24-hour period.

	Daytime		Nighttime		
	n	%	n	%	p-value
Gender					0.003
Men	539	87.9	537	83.0	
Women	71	11.6	110	17.0	
Trans women	3	0.5	0	0.0	
Age (mean and SD)	39.7	8.7	39.1	8.8	0.204
Country of birth					0.034
Spain	225	36.6	238	37.1	
Rest of Europe	229	37.3	273	42.6	
Other	160	26.1	130	20.3	
Residence					<0.001
Home, apartments	132	39.6	117	28.6	
Unstable residence	101	30.3	102	24.9	
Homeless	100	30.1	190	46.5	
Visits per person (median and range)	1	1-312	20	1-874	<0.0001
Number of visits					<0.001
Single visit	312	50.8	97	15.0	
Two or more visits	302	49.2	551	85.0	
Total	614	48.7	648	51.3	

CAS Baluard: Baluard outpatient substance use care center. Missing values in daytime client group: 1 for gender and 281 for residence; in nighttime client group: 1 for gender, 7 for country of birth and 239 for residence.

Table 5
CAS Baluard visits' client profile comparison by daytime and nighttime visits in the 24-hour period.

	Daytime		Nighttime		
	n	%	n	%	p-value
Gender					<0.001
Men	30,223	84.6	9,727	83.1	
Women	5,471	15.3	1,977	16.9	
Trans women	19	0.1	0	0	
Age (mean and SD)	40.2	8.6	40.1	8.5	0.217
Country of birth					<0.001
Spain	12,408	34.8	4,426	37.9	
Rest of Europe	16,799	47.2	5,210	44.6	
Other	6,425	18.0	2,047	17.5	
Residence					<0.001
Home, flat, apartments	6,435	23.4	2,442	26.7	
Unstable residence	4,544	16.5	1,529	16.7	
Homeless	16,488	60.1	5,192	56.6	
Total visits	35,773	75.3	11,721	24.7	

CAS Baluard: Baluard outpatient substance use care center. Missing values in daytime visits: 60 for gender, 141 for country of birth and 8,306 for residence; in nighttime visits: 17 for gender, 4,727 for country of birth and 2,558 for residence.

room for inhaled drugs. This is supported by a recent study that found a great variability in the drugs used between and within cities (EMCDDA, 2019).

The different use of CAS Baluard in the 24-hour period could have several explanations. The increase in clients and drug use episodes in the 24-hour period could be explained by the differences observed between daytime and nighttime use. In this period, we found a higher proportion of total visits to the DCR overnight, as the DCR was almost the only service available for clients during the night. Throughout the longer operating hours of the center, this could explain the higher number of visits and drug use episodes compared with the 15-hour period. It is unlikely that opening for 24 hours a day led to higher drug use by clients, as several previous studies did not support the idea that DCRs increase substance use (Folch et al., 2018; Kerr et al., 2007; Kinnard et al., 2014).

The differences in the drug use patterns between periods, and more obviously between day and night in the 24-hour period could be explained by the cocaine use pattern. It has been observed that the number of injections per day are higher in people who use injected cocaine than in those who use heroin, although the days that they consume tend to be more sporadic (Leri, Stewart, Tremblay & Bruneau, 2004). The higher proportion of cocaine use observed in night visits could be a result of having captured the repeated and continuous use of this substance, while regular heroin use was already captured during daytime. Another possibility could be the different proportion of frequent clients between the daytime and nighttime client groups. A DCR in Germany also found a higher percentage of frequent clients during nighttime. In that DCR, 31% of clients only visited the center once during the year (Stoever et al., 2015). A study carried out in Catalonia's network of harm reduction centers found that for frequent clients the DCR was the main place of injection, while infrequent clients used drugs mostly at home (Folch et al., 2018). Therefore, it is possible that frequent clients make different use of DCRs, thus explaining the differences in drug use between day and night in the 24-hour period.

Greater severity of overdoses have been observed overnight, indicating the possible existence of a circadian rhythm in which there is increased susceptibility to opioids during the night (Gallerani et al., 2001). This higher susceptibility could explain the greater risk of overdose during nighttime found in our study. Another possibility could be the presence during night hours of a higher substance concentration following multiple drug use episodes throughout the day. If these overdoses had occurred on the street or in private homes, the persons suffering them may have been left without assistance for a certain amount of time. However, opening during night hours would have allowed the provision of immediate assistance to these high-risk overdoses. Only opioid overdoses were registered in CAS Baluard during the study period. So, we performed a sub-analysis only for heroin use since there was a higher proportion of cocaine use during nighttime, which biased the overdose risk estimation. The higher risk found in this sub-analysis highlights the need for closer supervision of heroin use during nighttime in a DCR.

In this study, we found a larger number of women in the nighttime client group, and a higher number of nighttime visits by women. Other studies performed in a DCR in Hamburg also found a greater percentage of women attending the center during nighttime after extending the opening hours (Hedrich, 2004; Prinzleve & Martens, 2003). A possible explanation for these results could be the search for greater safety in the facility (Fairbairn, Small, Shannon, Wood & Kerr, 2008; Peacey, 2014). The fewer number of clients during nighttime, and the presence of harm reduction staff could create a more relaxed and less hostile environment in the facility than on the street.

Another point worth considering is the possible effect of the 24-hour service in the relationship with the neighborhood residents. In the 24-hour period there were nine complaints about noise during nighttime in the square where CAS Baluard is situated and on nearby streets. In the 15-hour period there were 17 complaints related to public drug use, drug dealing and hassles on other streets, but not related to CAS Baluard. Additionally, the extended operating hours of the facility led to a work overload among the professional team working in the center. Several factors contributed to this situation. First, in spite of the employment of additional personnel, there were less people working in the center during nighttime because of the limited services offered during nighttime. This led to a feeling of having less support by coworkers. The less support plus the fatigue related to working during nighttime made the professional team to demand more staff and training in order to deal with the work overload and the greater professional demands of working during nighttime. The increase in the opening hours entailed a 30% increase in the CAS Baluard budget.

An alternative to the 24-hour operation of CAS Baluard could be the opening of a night shelter for homeless PWUD, as they constitute almost half of the clients of the facility during night hours. Such a shelter

Table 6
CAS Baluard and its drug consumption room use comparison by daytime and nighttime visits in the 24h period.

	Daytime		Nighttime								
	n	%	n	%	p-value	PR		CI (95%)	aPR*		CI (95%)
Drug use episodes	9,732	27.2	4,981	42.5	<0.001	1.56	1.52	1.60	1.55	1.50	1.60
Substance used											
Injected heroin	2,347	24.1	865	17.4	<0.001	0.72	0.67	0.77	0.78	0.72	0.85
Inhaled heroin	1,601	16.5	629	12.6	<0.001	0.77	0.70	0.84	0.82	0.74	0.90
Injected heroin and cocaine	1,943	20.0	992	19.9	0.481	1.00	0.93	1.07	0.96	0.89	1.04
Injected cocaine	2,403	24.7	1,668	33.5	<0.001	1.36	1.29	1.43	1.31	1.24	1.38
Inhaled cocaine	1,110	11.4	682	13.7	<0.001	1.20	1.10	1.31	1.12	1.02	1.24
Others	328	3.4	145	2.9	0.073	0.86	0.71	1.05	0.81	0.67	1.00
Injecting site											
Upper extremities	6,228	93.0	3,332	94.3	<0.001	1.01	1.00	1.03	1.01	1.00	1.03
Lower extremities	278	4.2	115	3.3	0.028	0.78	0.63	0.97	0.82	0.63	1.06
Inguinal/jugular	194	2.9	85	2.4	0.126	0.83	0.65	1.07	0.83	0.63	1.09
Overdoses for all substance use	3	0.0	6	0.1	0.07	3.91	0.98	15.62			
Overdoses for heroin use**	3	0.0	6	0.1	0.03	4.69	1.17	18.75			

CAS Baluard: Baluard outpatient substance use care center. PR: Prevalence ratio. CI: Confidence interval. aPR: adjusted Prevalence Ratio. * Adjusted by gender, age, country of birth and residential situation. **Only takes into account cases in which the drug used was heroin.

would cover the needs of these clients, except substance use, which would help to integrate care with other social services. If most, or some of the women that visited the center during nighttime were, in fact, looking for a safer environment, a night shelter could be a pivotal service. It could provide a safe environment and it may help stabilize the residential situation of women by linking them to other social services. Furthermore, if the women are using the DCR at night for safety, it could indicate the existence of unmet needs for women who use drugs, partially fulfilled by the DCR and that may be more appropriately addressed in a night shelter. Further research with a gender approach could help clarify this issue.

Our study reveals two questions that need to be clarified in order to formulate a definitive proposal about the 24-hour opening of DCRs. First, more studies are needed to clarify the potential risk of overdose during night hours in DCRs. Second, there is a need to identify the reasons why the proportion of visits among women was higher during the night. Qualitative research on this issue could be the next step.

The 24-hour opening of CAS Baluard between July and November 2018 involved considerable effort, in both human and economic terms. In addition, most visits and nighttime overdoses occurred during the early hours of the night. Thus, a more sustainable policy could be the extension of the opening hours with a closing time between 12 p.m. and 2 a.m. Our study shows that there is a need for a closer supervision of heroin use during nighttime.

Author contributions

JMMM: Data curation, Analysis, Writing- Original draft preparation. OPB: Conceptualization, Supervision, Analysis, Writing- Reviewing and Editing. AGA, MGB, DA and AE: Writing- Reviewing and Editing. MG: Analysis supervision, Writing- Reviewing and Editing.

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Declaration of Competing Interest

None

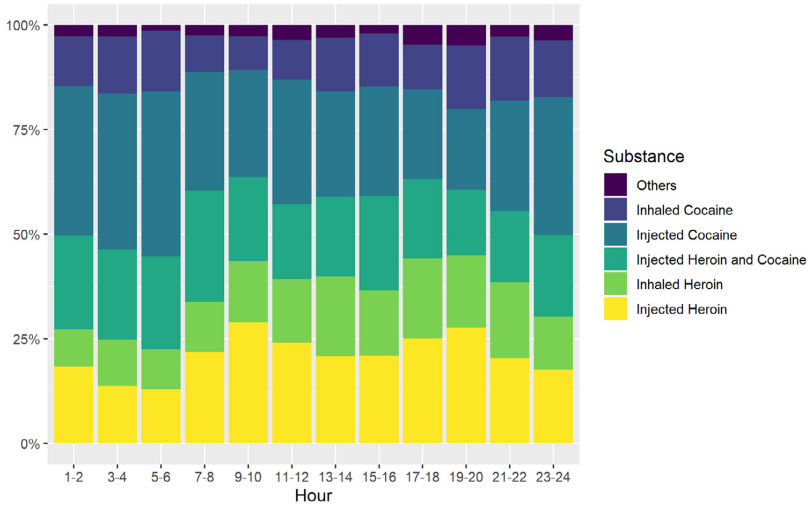

Figure 2. Substance used in the CAS Baluard supervised consumption room per hour in the 24-hour period.

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5. Discussion

In order to address the thesis' objectives to (1) describe the prevalence and associated factors of health outcomes in people who use harm reduction programs, and to (2) evaluate the extended opening of a harm reduction program, we presented three articles. First, we used data from the REDAN study, a bio-behavioral surveillance project, to analyze the prevalence and associated factors of undiagnosed HIV and Hepatitis C (Article 1) and to analyze the prevalence and associated factors of non-fatal overdose (Article 2) in people who inject drugs in Catalonia. Second, we used data from the Barcelona harm reduction information system to evaluate the impact of a 24-hour opening schedule of the CAS Baluard drug consumption room on the service use and the risk of non-fatal overdoses (Article 3). The following sections aim to provide an overall and integrated interpretation of the present thesis by discussing main findings and contributions to current knowledge, methodological considerations, implications for public health, and future research needs.

5.1 Main findings and contributions to current knowledge

Based on results from Article 1, the prevalence of HIV in people who inject drugs in Catalonia was 33% (95% CI 31%–35.5%) and the prevalence of Hepatitis C was 73% (95% CI 71.0%–74.5%). The sensitivity of self-report was around 79% for HIV and 81% for Hepatitis C. The specificity was around 97% for HIV and 81% for Hepatitis C. Therefore, the proportion of undiagnosed HIV and Hepatitis C was around 21% and 19%, respectively. The main factors associated with an undiagnosed infection in people who inject drugs

were being younger and having a lower perception of infection risk due to the lack of risk practices, such as sharing syringes (adjusted prevalence ratio (APR) 2.3, 95% CI 1.7-3.1) or having had previous sexually transmitted infections (APR 1.7, 95% CI 1.1-2.5). In contrast, enhanced access to testing through the use of health and preventive services or by having been in prison were protecting factors against being undiagnosed. The use of health and preventive services, such as access to medical care and treatment or use of drug consumption rooms, was the most significant modifiable factor preventing an undiagnosed infection.

In Article 2, we found that the prevalence of non-fatal overdose in the last 12 months among people who inject drugs in Catalonia was 17.2% (95% CI 15.7%-18.7%), while the lifetime prevalence was 54.3% (95% CI 52.3%-56.3%). The factors associated with lifetime non-fatal overdose were having a longer history of injected drug use, having received overdose training, and having been enrolled in treatment or served a prison sentence. Self-reported overdose in the last 12 months was more prevalent among PWID who shared syringes or had Hepatitis C antibodies. People who inject drugs who had used heroin in the last six months had 72% (95% CI 20%-146%) higher prevalence of non-fatal overdose compared to those who had not used heroin. In contrast, having used methadone was a protective factor of non-fatal overdose (APR 0.80, 95% CI 0.64-0.99). Participants who used a drug consumption room more frequently or received overdose training had a higher prevalence of non-fatal overdose, possibly due to increased awareness of overdose signs and symptoms and increased self-report.

In Article 3, findings indicated that opening CAS Baluard for 24 hours increased the number of clients and visits to the drug consumption room. The profile of the clients of CAS Baluard in the 24-hour period was different from the profile in the 15 hour period. In the 24-hour period, the number of visits of women and the number of cocaine injections increased while inhaled heroin use diminished in comparison to the 15 hour period. When comparing night-time versus daytime within the 24-hour period, the number of visits from women, homeless clients and frequent clients was higher during the night-time than during the daytime. During the night-time, heroin use (both injected and inhaled) was proportionally lower and cocaine use (both injected and inhaled) was proportionally higher compared to daytime. Considering only heroin use, we found a higher risk of overdose during night-time than during daytime (prevalence ratio (PR) 4.69, 95% CI 1.17-18.75).

5.2 Methodological considerations

The studies included in the present thesis were based on data from the REDAN study (Articles 1 and 2) and the Barcelona drug information system (Article 3). The methods used in the studies have limitations. Clients in harm reduction settings tend to be older, with unstable housing and a long-term history of drug use, therefore, results presented here may not be generalizable to other people who use drugs or to other settings. An analysis of the same sample used in Articles 1 and 2 showed that people attending drug consumption rooms more frequently are in worse social and medical conditions than people attending drug consumption rooms less frequently (Folch et al. 2018). Furthermore, individuals attending harm reduction services tend to be male, which prevented us from performing separate analysis by sex in any of the

articles because the proportion of women in our samples was small. Other studies in our setting have shown women who inject drugs suffer a high prevalence of physical and/or sexual assaults associated to an increased prevalence of HIV (Folch Toda et al. 2016).

In articles 1 and 2 we used a convenience sample drawn from 15 centers in the years 2008-09, 2010-11, 2012-13 and 2014-15. In Article 3 we used data from CAS Baluard, which may limit external validity since CAS Baluard may differ from other harm reduction centers. A recent study in different European cities showed a great variability in the drugs used between and within cities (European Monitoring Center for Drugs and Drug Addiction 2019a). CAS Baluard has two drug consumption rooms, one for inhaled use and one for injected use and gives service to around 65% of harm reduction clients in Barcelona.

The sample size of the three studies enabled us to analyze associated factors with statistical robustness. However, in Articles 1 and 2 we used samples that included interviews from different years and we had to exclude participants who admitted having participated in previous surveys, which resulted in fewer participants from recent surveys. When analyzing HIV prevalence (Article 1), the prevalence diminished over the years, however, we found no changes on the validity of self-report in the different survey years. Concerning non-fatal overdose (Article 2), we found no statistical differences in the prevalence of associated factors of overdose among the survey years. Thus, in both articles we were able to analyze different survey years together.

Regarding the assessment of risk behaviors, in Articles 1 and 2 we used self-reported behaviors, which may cause an underestimation of risk. However, there is previous research that shows self-reported behaviors

in people who inject drugs are valid and not influenced by social desirability bias (Darke 1998) and the results of Article 1 point to unlikely underreporting of HIV and Hepatitis C. In addition, our study population in the three articles consisted of participants who have generally experienced long histories of drug use and have survived the HIV and the overdose epidemics. This is a limitation for the three articles of this thesis, but it is a significant limitation for Article 2 since we were not able to assess the risk of fatal overdose, and thus, we may have missed associated factors of non-fatal overdose that entail a high fatality. In other words, the population of this thesis should be understood as a prevalent cohort subject to selective survivor bias, therefore, the associated factors of individuals who died sooner could not be assessed with our samples.

Regarding the study design, Articles 1 and 2 are cross-sectional studies while Article 3 is a pre-post study without comparison group. On the one hand, cross-sectional studies can fall into reverse causality bias. We hypothesized in Article 2 that results regarding a higher prevalence of non-fatal overdose in participants who reported frequent drug consumption room use and overdose training attendance was due to reverse causality bias. We were not able to refute this bias using our data, however other studies have shown service use and overdoses trainings increase the awareness of non-fatal overdose and the probability of self-reporting an overdose (Espelt et al. 2017). On the other hand, in Article 3 we were not able to have a comparison group which hinders the internal validity of the study since changes observed may not have been caused by the intervention (the 24-hour opening of CAS Baluard) but by other factors that we could not take into account

(for example, police interventions, seasonality, etc.). We were not able to assess if seasonality had any influence in the results of the study since we could not decide the timing of the implementation of the intervention. However, we did not find significant differences in the sociodemographic characteristics of clients before and after the intervention and we are not aware of any factor taking place during the intervention that could have affected the results.

5.3 Implications for public health and future research

According to the results of this thesis, access to both treatment and harm reduction was the most important factor to reduce the number of people who inject drugs who have an undiagnosed HIV or Hepatitis C infection. In order to maximize impact, harm reduction and treatment services could focus on their most at-risk clients, including people who inject drugs who are younger and have a lower perception of infection risk due to the lack of risk practices, since they may be more at risk of having an undiagnosed infection. Our results highlight the need to provide HIV and Hepatitis C tests as part of the enrolment process in outreach services. In the case of Hepatitis C, tests should be performed even when clients self-report having passed the infection, given the low specificity of self-report found in our results.

This thesis added robust evidence to previous findings regarding methadone treatment being a protective factor of non-fatal overdose. Methadone has been shown to reduce illicit opioid use (Gowing et al. 2011) and all cause and overdose mortality (Sordo et al. 2017). Our results support previous findings in the need to offer harm reduction-based methadone treatment, especially to people who use drugs with

identified associated factors of non-fatal overdose such as using heroin or sharing syringes. This thesis includes the first study reviewing the association between drug consumption room frequency of use and overdose trainings with non-fatal overdose. However, our results seem to be affected by reverse causality bias. Future research should address this issue using prospective study designs that can identify the timing of the exposure and the fatal or non-fatal overdoses.

Finally, our review of the night-time opening of a harm reduction center revealed that the use of services during the night-time was high until around 1am and the proportion of vulnerable people attending the center increased during the night hours. Extending the opening hours of harm reduction centers could improve the use of services among women, homeless people and frequent drug consumption room clients. Furthermore, we found a statistically significant higher risk of heroin overdose during the night-time, which would be a strong motive to extend opening hours. In light of this result, more studies are needed to assess if the risk of drug overdose is different during different moments of the day. Moreover, there is a need to identify the reasons why the proportion of visits among women was higher during the night.

Finally, there is a need to replicate our objectives in other locations since our results may not be applicable to other populations or settings. However, the results of this thesis point to the need to maximize access to harm reduction and treatment services. In line with the Barcelona model, this can be done through establishing outreach teams, drug consumption rooms and needle exchange programs that are well connected to treatment programs.

6. Conclusion

Overall, in keeping with the objectives, the current thesis has contributed to describe the prevalence and associated factors of health outcomes – specifically, non-fatal overdose and undiagnosed infection – in people who use harm reduction programs, and to evaluate the extended opening hours of a harm reduction program.

Access to medical care and methadone treatment was the most significant modifiable factor preventing both an undiagnosed infection and non-fatal overdose. The risk factors associated with having an undiagnosed infection were being younger and having a lower perception of infection risk due to a lack of risk practices. Risk factors associated with non-fatal overdose were having used heroin and having shared syringes.

Using a drug consumption room was associated with lower risk of an undiagnosed infection and seemed to be associated with increased awareness of overdose. Finally, the night-time opening of a drug consumption room was associated with a higher service use among the most vulnerable clients (including women and homeless people) and it may have avoided opioid related deaths since the risk of overdose during night-time was higher than during daytime. In line with the aims of the Barcelona model, the results of this thesis highlight the need to maximize access to harm reduction and treatment services.

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Annex 1: Collaboration in other articles

Apart from the three original research papers and the editorial included in this thesis, the PhD candidate co-authored the following publications related to harm reduction and drug use:

Folch C, Lorente N, Majó X, **Parés-Badell O**, Roca X, Brugal T, Roux P, Carrieri P, Colom J, Casabona J; REDAN study group. Drug consumption rooms in Catalonia: A comprehensive evaluation of social, health and harm reduction benefits. Int J Drug Policy. 2018; 62:24-29. doi: 10.1016/j.drugpo.2018.09.008.

Colell E, Domingo-Salvany A, Espelt A, **Parés-Badell O**, Brugal MT. Differences in mortality in a cohort of cocaine use disorder patients with concurrent alcohol or opiates disorder. Addiction. 2018; 113(6):1045-1055. doi: 10.1111/add.14165.

Molist G, Brugal MT, Barrio G, Mesías B, Bosque-Prous M, **Parés-Badell O**, de la Fuente L; Spanish Working Group for the Study of Mortality among Drug Users. Effect of ageing and time since first heroin and cocaine use on mortality from external and natural causes in a Spanish cohort of drug users. Int J Drug Policy. 2018; 53:8-16. doi: 10.1016/j.drugpo.2017.11.011.

Espelt A, Villalbí JR, Bosque-Prous M, **Parés-Badell O**, Mari-Dell'Olmo M, Brugal MT. The impact of harm reduction programs and police interventions on the number of syringes collected from public spaces. A time series analysis in Barcelona, 2004-2014. Int J Drug Policy. 2017; 50:11-18. doi: 10.1016/j.drugpo.2017.07.033.

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Research Paper

Drug consumption rooms in Catalonia: A comprehensive evaluation of social, health and harm reduction benefits

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ABSTRACT

Background and aims: Despite the availability of several drug consumption rooms (DCR) in different European countries few epidemiological studies have evaluated their benefits. A network of DCR for people who inject drugs (PWID) has existed in Catalonia since 2000. We aimed to study the impact of frequently attending DCR on injecting in public, infectious risk (disposal of used syringes in safe places, sharing needles and/or injecting equipment), accessing drug dependence services and non-fatal overdoses.

Methods: In 2014–2015, we performed the cross-sectional study REDAN in Catalonia's network of harm reduction centres (needle exchange programs, outreach programs, and DCR). A sample of current PWID were recruited. Self-reported data about risky and other behaviours and about access to care were collected through anonymous face-to-face structured interviews. Oral fluid samples were also collected to test for HIV and HCV antibodies. Multiple logistic regressions were used to assess the impact of frequently attending DCR on the different outcomes.

Results: Among the 730 PWID recruited, 510 reported attending DCR in the previous 6 months, of whom 21·2% were 'frequent' attenders. After multiple adjustment, frequent attenders had a 61% lower risk of injecting in public (AOR [95%CI]:0·39[0·18–0·85]) and sharing needles or other injecting equipment (0·39[0·18–0·85]) than 'medium' and 'low' attenders. They were six times more likely to place used syringes in a safe place (6·08[3·62–10·23]) and were twice as likely to access drug dependence services (2·56[1·44–4·55]). No significant effect was found for non-fatal overdoses, perhaps because of survival bias.

Conclusion: The multiple benefits found strongly advocate for the maintenance of current DCR and the promotion of new DCR, in conjunction with other harm reduction strategies, in European countries where they are not yet available.

Background

Drug consumption rooms (DCR) are supervised healthcare facilities where people who inject drugs (PWID) can consume drugs in safe conditions (European Monitoring Centre for Drugs & Drug Addiction, 2016). These facilities seek to reduce drug-related morbidity and mortality among PWID by providing a more hygienic drug use environment and by linking people to health care and social services. They also seek to reduce public drug use and neighbourhood nuisance (Potier, Laprévote, Dubois-Arber, Cottencin, & Rolland, 2014; Vecino et al., 2013).

As part of the general harm reduction policy regarding PWID in Catalonia, DCR have been a principal component of the Catalan Drug Abuse Care Centre Network (XAD) since the beginning of the 2000s.

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XAD is a public network of specialised resources providing care to people with substance use disorders. It is part of Catalonia's comprehensive harm reduction program. The first DCR was opened in Barcelona at a large open drug scene to control drug-related overdoses occurring in the city and the metropolitan area (Anoro, Ilundain, & Santisteban, 2003). Since then, 13 DCR have been created throughout Catalonia, mainly located in places where PWID who are especially marginalized buy and use drugs. In 2016, the total number of clients attending DCR in the region was 2,766, reflecting 108,231 consumptions (87·6% injected). The One-hundred and eighteen drug overdoses were managed in DCR in 2016. None was fatal.

Although DCR exist in different European countries, few epidemiological studies have explored their health and social benefits. Vancouver and Sydney are two cities where such studies have been carried out (Kerr, Mitra, Kennedy, & McNeil, 2017; Potier et al., 2014). Data on DCR effectiveness in Europe are sparse and non-published articles and reports. Moreover, there is nothing in the literature about the benefits of DCR as part of a network of services within a comprehensive Harm Reduction model. A previous study among young heroin PWID recruited by the ITINERE cohort in Madrid and Barcelona confirmed the inverse association between DCR attendance and injection with borrowed syringes, although no association was found between DCR attendance and the indirect sharing of injection equipment (Bravo et al., 2009), unlike elsewhere (Stoltz et al., 2007).

The objective of this study was to describe socio-demographic and behavioural characteristics of clients attending DCR in Catalonia and to study the impact of frequent DCR attendance on injecting in public, infectious risk (disposal of used syringes in safe places, sharing needles and/or injecting equipment), accessing drug dependence services and non-fatal overdoses.

Methods

Study design

In 2014–2015,the cross-sectional bio-behavioural study REDAN was carried out in Catalonia's network of harm reduction centres (HRC) as part of the region's Integrated HIV and Sexually Transmitted Infections (STI) Surveillance System (SIVES) (Centre d'Estudis Epidemiològics sobre les Infeccions de Transmissió Sexual i Sida de Catalunya (CEEISCAT), 2015). A total of 15 HRC participated in this first step of the study (9 of them having a DCR). They answered a set of questions about the number and characteristics of attendees in the previous year. After collecting these data, a convenience sample of PWID attending these centres was selected. Assignment to strata was proportional to the volume of visits in each centre and to the percentage of individuals attending each centre taking into account country of birth. In centres with fewer than 5% of clients born outside Spain, only Spanish-born participants were recruited. Participants were randomly selected within HRC.

Participation in REDAN was proposed to people meeting all the following eligibility criteria: 18 years old or over, reporting to have injected drugs in the previous 6 months, and attending one of the 15 participating centres. Those who agreed to participate provided written, informed consent. The study was completely anonymous. For each participant, a face-to-face interview was conducted by a trained interviewer using a structured questionnaire. Oral fluid samples were also taken to determine the prevalence of HIV and HCV infection. Anti-HIV antibodies were detected in oral fluid using Genscreen HIV-1/2 Version 2.0 assay from Bio-Rad (sensitivity = 98·5%; specificity = 100%); anti-HCV antibodies were detected using HCV 3·0 SAVe ELISA (sensitivity = 86·7%; specificity = 100%). Self-reported data and biological data were linked using a unique participant identifier. Each participant was given €12 compensation for their involvement. The Ethics Committee of Hospital Universitari Germans Trias i Pujol (Badalona, Spain) approved the study.

Study population

Included PWID who reported in the interview that a DCR was located in the area where they lived, or where they injected or purchased drugs were asked about whether they had attended the DCR or not during the previous 6 months. For this present analysis, only data from those who replied "yes" to this question were analysed (510/730).

Questionnaire and variables

Trained interviewers conducted face-to-face interviews in each centre using an anonymous structured questionnaire adapted from that used in the ITINERE project (de la Fuente et al., 2006) and the questionnaire used in the "Multi-city study on drug injecting and risk of HIV infection" project (World Health Organization, 1994). The interview lasted approximately 35 min, and the questionnaire was translated into Spanish, Romanian, Russian, English, and French. It gathered information about sociodemographic characteristics (country of origin, age, sex, education level, main source of income, place of residence, treatment for drug addiction, prison history), drug use (time since first injection, frequency of injection, substances used, sharing of syringes and/or other injecting equipment such as water containers, spoons and filters), accessing healthcare services (centres for drug dependence care and follow-up, primary health centres), place of injection, syringes disposal sites, knowledge of HIV and HCV status, and previous history of non-fatal overdose. Most questions on behaviours referred to the previous 6 months. The subcategories of these variables are listed in Tables 1 and 2.

"Frequent attendance" was defined as having attended the DCR every day when they injected drugs, "Medium attendance" as having attended more than half the days they injected drugs, and "Low attendance" as having attended half or fewer than half the days they injected drugs.

Statistical analyses

Participants were compared according to their frequency of attendance using a Chi-square or exact Fisher test for discrete variables, and Student's *t*-test for continuous variables. After measuring the effect of 'frequent attendance' on all the outcomes, using a confounding model approach we tested whether this effect was confirmed even after adjustment for possible correlates and confounders (including those not significantly associated with the outcome – such as HIV and HCV status - but known to be potential confounders). In particular, multivariate logistic regressions were used to test for an association between 'frequent attendance' and the following harm reduction and health outcomes: injecting in public, disposal of used syringes in safe places, sharing injecting material, non-fatal overdoses, and accessing drug dependence services. Each model was adjusted for age, sex, origin, injection frequency, homelessness, HIV/HCV status and years of injection. Adjusted odds ratios (AOR) and 95% confidence intervals (CIs) were calculated.

Results

Descriptive analyses of the study population

Among the 510 PWID who had attended a DCR at least once in the previous 6 months, 81·8% were male, and the mean age at recruitment was 37 years (SD = 8·1), ranging from 18 to 61 years. In terms of DCR attendance patterns, 21·2% were frequent attendees, 45·7% medium attendees and 33·1% low attendees.

Table 1 shows the main socio-demographic characteristics of the study sample according to DCR attendance patterns. The proportion of individuals under 30 years old was lower in the frequent attendee group (7·4%) than in the medium and low attendee groups (17·2% and 23·1%,

Table 1
Socio-demographic characteristics by DCR attendance.

	Frequent (n = 108) %	Medium (n = 233) %	Low (n = 169) %	Total (n = 510) %	p
Age group					0.003
18-29 years (n = 87)	7.4	17.2	23.1	17.1	
30 years or older (n = 423)	92.6	82.8	76.9	82.9	
Sex					< 0.0001
Male (n = 417)	87.0	86.3	72.2	81.8	
Female (n = 93)	13.0	13.7	27.8	18.2	
Born in Spain					< 0.0001
No (n = 250)	38.0	51.9	52.1	49.0	
Yes (n = 260)	62.0	48.1	47.9	51.0	
Currently in treatment for drug abuse					0.257
No (n = 91)	47.2	52.8	58.6	53.5	
Yes (n = 419)	52.8	47.2	41.4	46.5	
Education					0.529
Primary or lower (n = 270)	58.5	51.7	52.7	53.5	
Secondary or higher (n = 235)	41.5	48.3	47.3	46.5	
Main source of income*					0.033
Job (n = 75)	11.1	16.7	14.3	14.7	
Family/partner (n = 51)	8.3	10.3	10.7	10.7	
Pension/benefit (n = 91)	29.6	14.2	15.5	15.5	
Illegal source (n = 292)	50.9	58.8	59.5	59.5	
Living in the street (homeless)					< 0.0001
No (n = 372)	58.9	72.1	83.4	73.1	
Yes (n = 137)	41.1	27.9	16.6	26.9	
In prison (ever)					0.781
No (n = 133)	24.1	27.5	25.4	26.1	
Yes (n = 377)	75.9	72.5	74.6	73.9	

* last 6 months.

respectively, p < 0·001), as was the proportion of participants born outside Spain (38·0% *versus* 51·9% and 52·1%, respectively, p < 0·001). The proportion of homeless participants was higher for frequent attendees (41·1%) than for medium and low attendees (27·9% and 16·6%, respectively, p < 0·001).Almost half of the sample was currently taking treatment for drug abuse, mainly opioid substitution therapy (OST), with no statistically significant differences between attendance groups.

In terms of drug use patterns (Table 2), time from first injection was significantly higher for frequent attendees (mean 18·8 years) than for medium and low attendees (15·0 and 14·9 years, respectively, p = 0·002). No significant difference was seen between the three groups for frequency of injection. With regard to injecting location, most frequent and medium attendees reported that DCR was the main place of injection (90·7% and 77·7%, respectively, p < 0·001).In contrast, low attendees most frequently injected in private houses (61.6%) and outdoors settings such as cars, parks and streets (31·7%, p < 0·001). Frequent attendees were more likely to report always disposing of their used syringes in safe places than medium and low attendees (75·0% *versus* 36·1% and 30·2%, respectively; p < 0·001).

As shown in Fig. 1, the prevalence of sharing of syringes and/or other injecting equipment such as water containers, spoons and filters, was significantly lower among frequent attendees (p < 0·001).

The prevalence of non-fatal overdoses in the previous year did not differ between groups (overall prevalence was 19·2%). Frequent attendees (53·7%) were more likely to report accessing primary health centres in the previous 6 months than medium and low attendees (45·9% and 34·9%, respectively, p = 0·006), and to report accessing centres for drug dependence care and follow-up in the previous 6 months (81·5% *versus* 66·1% and 55·4%, respectively, p < 0·001). No significant difference was found in HIV or HCV antibody (Ab) prevalence between the three groups (overall HIV Ab prevalence: 27·4%; HCV Ab prevalence: 67·5%) (Table 2).

Harm reduction and health outcomes associated with frequent DCR attendance

Table 3 shows that frequent DCR attendance was independently associated with several outcomes. After adjustment for age, sex, origin, injection frequency, homelessness, HIV/HCV status and years of injection, frequent attendees were less likely to inject in public (AOR = 0·27; 95%CI: 0·12–0·62), and to share needles or other injecting equipment (AOR = 0·39; 95%CI: 0·20–0·78). They were more likely to place used syringes in a safe place (AOR = 5·77; 95%CI: 3·41–9·77) and to have accessed drug dependence services in the previous six months (AOR = 2·12; 95%CI: 1·18–3·81). By contrast, no significant effect on the frequency of DCR attendance was found on non-fatal overdoses (AOR = 0·81; 95%CI: 0·45–1·47).

Discussion

The current research suggests that some benefits may have accrued as a result of frequent attendance by PWID at a DCR (within the context of an established harm-reduction services network), although additional longitudinal studies are needed to confirm this. These benefits are seen in a wide spectrum of outcomes including: HIV, HCV and other infectious disease risky behaviours, neighbourhood nuisance brought about by drug use in public spaces, and accessing care for drug dependence.

We found that one in five PWID attending HRC in Catalonia were frequent attendees of DCR. Frequent attendees are more numerous in other countries, such as Denmark and Canada (29·3% and 43·2%, respectively, reporting daily DCR attendance) (Wood et al., 2006; Kinnard, Howe, Kerr, Skjødt Hass, & Marshall, 2014). It must be noted however that in both countries, data were collected for a single DCR.

Compared to non-frequent attendees, frequent attendees were less likely to inject in public, had fewer risky behaviours in terms of injection-related HIV, HCV and bacterial infections, and were more likely to access drug dependence services. Daily injectors were the most represented group (> 50%) in the study sample, and no difference in injection frequency was seen between the three DCR attendance frequency groups (p = 0·063). This result is consistent with other previous studies reporting no evidence that the use of supervised injection facilities significantly changed self-reported injection frequency (Kinnard et al., 2014). However, other studies had showed that frequent injectors attend DCR more often than those with lower frequency of injection (Stoltz et al., 2007). This could be explained by the fact that a higher proportion of frequent attendees reported being currently on treatment for their drug abuse, mainly OST, a harm reduction strategy that has been clearly associated with reducing injection frequency.

The strong associations which we found between frequent DCR attendance and both less injection in public and less unsafe needle disposal are consistent with other studies (Stoltz et al., 2007; Wood et al., 2004; Kerr, Tyndall, Li, Montaner, & Wood, 2005). This is a major argument to convince authorities throughout Europe to open DCR. The opening of a harm reduction facility with a DCR in Barcelona in 2004, was associated with a huge reduction in the number of unsafely discarded syringes in the city (from 13,132 in 2004 to 3,190 in 2012) (Vecino et al., 2013).

Another result which is consistent with previous international studies (Kerr et al., 2005; Kinnard et al., 2014), is that frequent DCR

Table 2
Drug use patterns, access to services, overdose history and HIV/HCV prevalence by DCR attendance.

	Frequent (n = 108) %	Medium (n = 233) %	Low (n = 169) %	Total (n = 510) %	p
Years of injection					0.002
Mean (SD)	18.8 (10.2)	15.0 (9.5)	14.9 (9.5)	15.8 (9.8)	
Injection frequency*					0.063
Daily (n = 275)	44.4	55.2	58.6	54.0	
Weekly (n = 170)	34.3	32.8	33.7	33.4	
Monthly or less (n = 64)	21.3	12.1	7.7	12.6	
Place of injection (more frequent)					< 0.0001
Houses (n = 128)	0.9	11.4	61.6	25.5	
Street, cars, parks, …(n = 86)	8.3	10.9	31.7	17.2	
Drug Consumption Rooms (n = 287)	90.7	77.7	6.7	57.3	
Disposal of used syringes in safe places					< 0.0001
Not always (n = 294)	25.0	63.9	69.8	57.6	
Yes, always ** (n = 216)	75.0	36.1	30.2	42.4	
Access to Primary Health Centre					0.006
No (n = 286)	46.3	54.1	65.1	56.1	
Yes (n = 224)	53.7	45.9	34.9	43.9	
Access to Drug Dependence Services					< 0.0001
No (n = 174)	18.5	33.9	44.6	34.2	
Yes (n = 335)	81.5	66.1	55.4	65.8	
Self-reported non-fatal overdose (last 12 months)					0.660
No (n = 409)	82.4	80.7	78.1	80.2	
Yes (n = 101)	17.6	19.3	21.9	19.8	
HIV infection (biological sample)					0.062
No (n = 361)	63.5	75.0	75.2	72.6	
Yes (n = 136)	36.5	25,0	24.8	27.4	
HCV infection (biological sample)					0.128
No (n = 161)	31.7	28.5	38.2	32.4	
Yes (n = 336)	68.3	71.5	61.8	67.5	

* last 6 months.
** Needle exchange, DCR.

attendance was associated with fewer direct and indirect risky injecting behaviours. This is very important in terms of reducing the risk of blood-borne disease transmission, given that 'frequent' DCR attendees in our study were more likely to be HIV-infected than 'medium' and 'low' attendees. It also suggests that peers and health staff supervising DCR may have a real effect on reducing risk, thanks to their providing adequate education about drug-related risks (R. A. Wood et al., 2008). It is important to note that while previous data in Spain from the ITINERE Cohort suggested that DCR use was associated with lower needle sharing rates, no association was found between the use of these facilities and the sharing of other injection equipment (Bravo et al., 2009).

In our study, frequent DCR attendance was positively associated with higher levels of accessing care for drug dependence. This may be a result of PWID perceiving DCR to be safe and welcoming environments (Small, Moore, Shoveller, Wood, & Kerr, 2012). Regular attendance therefore would be an indirect proxy of the trust between staff and the client. This trustful relationship makes DCR an important gateway to better engagement of PWID in general and specialised health care. Our result showing that frequent DCR attendees were more likely to access drug dependence centres, especially for opioid dependence, is consistent with the results from an evaluation of the Canadian DCR 'Insite' (Wood, Tyndall, Zhang, Montaner, & Kerr, 2007). This may be particularly important for our target population as care for opioid dependence is associated with less injection, less drug-related offences and incarcerations, as well as better quality of life and greater social insertion (Amato et al., 2008; Gowing, Farrell, Bornemann, Sullivan, & Ali, 2008).

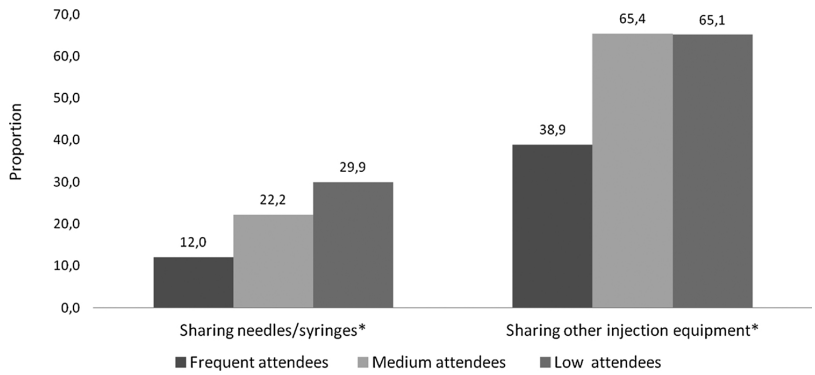

Fig. 1. Prevalence of injecting risk behaviours by DCR attendance.
*p < 0.01

Table 3
Association between frequent attendance and several harm reduction and health outcomes.

	Injection in public AOR (95%CI)	Disposal used syringes in safe places AOR (95%CI)	Sharing needles and/or injecting equipment AOR (95%CI)	Accessing drug dependence services AOR (95%CI)	Non-fatal overdoses experience AOR (95%CI)
Frequent attendance (ref: medium, low attendance)	0.27* (0.12-0.62)	5.77* (3.41-9.77)	0.39* (0.20-0.78)	2.12* (1.18-3.81)	0.81 (0.45-1.47)
30 or more (ref: less than 30)	0.73 (0.35-1.51)	2.42* (1.27-4.62)	0.47* (0.24-0.91)	0.92 (0.52-1.64)	0.74 (0.37-1.48)
Female (ref: male)	1.41 (0.73-2.70)	0.98 (0.57-1.69)	2.51* (1.42-4.41)	0.79 (0.45-1.36)	1.03 (0.57-1.88)
Born in Spain (ref: born outside Spain)	1.05 (0.61-1.80)	1.42 (0.93-2.15)	1.69* (1.02-2.80)	3.13* (2.02-4.85)	1.82* (1.11-3.00)
Injected weekly or less (ref: daily)	0.52* (0.30-0.90)	1.02 (0.68-1.52)	0.32* (0.19-0.54)	0.79 (0.52-1.19)	0.85 (0.53-1.35)
HIV positive (biological data) (ref: HIV negative)	0.93 (0.51-1.72)	0.70 (0.44-1.13)	1.08 (0.63-1.87)	1.30 (0.78-2.16)	1.34 (0.80-2.25)
HCV positive (biological data) (ref: HCV negative)	1.34 (0.74-2.45)	0.86 (0.55-1.35)	0.90 (0.54-1.52)	1.12 (0.71-1.75)	1.23 (0.73-2.08)
Homelessness (ref: no)	3.80* (2.23-6.46)	1.23 (0.78-1.94)	2.31* (1.39-3.83)	2.44* (1.47-4.05)	0.92 (0.54-1.58)
Years of injection (ref: 0-5 years)	0.70 (0.34-1.46)	0.62 (0.35-0.12)	0.43* (0.21-0.86)	0.62 (0.36-1.06)	1.00 (0.52-1.93)

* Significant differences ($p < 0.05$); AOR: adjusted odds ratio; CI: confidence interval.

Unexpectedly, we did not find differences between the three DCR attendance frequency groups on the non-fatal overdose in the previous year. However, this result needs to be considered with caution, as our data were as based on self-reports and not on officially recorded overdose events. Previous studies in Vancouver confirmed that overdose events were not uncommon in DCR facilities but fatal overdoses were less frequent than in non-DCR locations (Marshall, Milloy, Wood, Montaner, & Kerr, 2011). In Catalonia, no fatal overdose event occurred in any DCR.

The lack of an association between frequent DCR attendance and non-fatal overdose is perhaps due to the fact that frequent attendees are at higher risk of overdose than less frequent attendees as they inject more frequently. Therefore the lack of any significant association between overdose reports and frequency of attendance could be due to the fact that frequent attendees have an overdose risk comparable with that of non-frequent attendees. Future studies in Catalonia should explore the impact of DCR not only in the incidence of overdoses in the area, if not in their severity –fatal or nonfatal overdoses or overdose mortality. To explore the relationship between DCR and fatal and non-fatal overdose risk, future studies in Catalonia should set up a surveillance system on fatal and non-fatal overdoses and correlate attendance rates with these figures.

The proportion of homeless participants among 'frequent' DCR attendees in our study was higher than among 'medium' and 'low' frequency attendees. Homelessness, which is a common factor in PWID in public, has been associated with frequent DCR use (Stoltz et al., 2007; Wood et al., 2006; Scherbaum, Specka, Schifano, Bombeck, & Marrziniak, 2010). Considering that a homeless person would not necessarily have the option of a safe place to inject, it is not be surprising that this particular group of injectors might be more willing to use DCR on a regular basis. In fact, previous studies exploring the major reasons for not attending DCR included injecting at home, already having a safe place to inject, and desire to inject in private (Reddon et al., 2011).

There are several limitations in the study that need to be highlighted. First, the results are only representative of individuals attending HRC (approximately 6000 PWID attend these centres annually in Catalonia). The profile of frequent DCR attendees in our study is quite similar to that generally found across Europe, *i.e.*, older, long-term, homeless users. However, younger people and females may perhaps be underrepresented in this sample. Another limitation is that the prevalence of certain risk behaviours may have been underestimated through underreporting, despite the data collectors' attempts to create a confidential environment for the interviews and their attention to using simple and understandable language. Furthermore, comparison with "DCR non-attendees" (n = 29) was not possible because the initial study population was recruited in 15 HRC, the majority of which (9/15) having a DCR. In fact, almost all those included had already attended a DCR in the previous 6 months so DCR non-attendees were very few. Moreover, only those who reported that a DCR was located in the area where they lived, or where they injected or purchased drugs, were asked about DCR attendance frequency, so we do not know if other individuals attended DCR outside of these locations. Finally, the cross-sectional behavioural design of the survey prevented us from making inferences about temporal associations and causal pathways between measured factors. Furthermore, the study design also inhibited us from being able to distinguish the effect of a single intervention in isolation from other interventions occurring concomitantly (such as NEPs and/or OST).

To conclude, the benefits of frequent DCR attendance presented here highlight the necessity to maintain current DCR and to promote the opening of others in European countries where they are not yet available. DCR complement other harm-reduction strategies strategies (*e.g.*, NEP and OST) already successfully implemented in Catalonia. Further research is needed in Catalonia to evaluate the long-term benefits of DCR. Creating a trustful relationship with DCR attendees can encourage them to attend more frequently, something which has major consequences for individual, public health, and social benefits.

Conflict of interest

Non declare.

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

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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 and Participants** A cohort of 10 539 cocaine use disorder individuals entering drug treatment in public out-patient 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), standardized 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-years (PY); 95% confidence interval (CI) = 5.1–7.0 for CUD, CMR = 5.8/1000 PY (95% CI = 4.9–6.7) for CAUD and CMR = 20.7/1000 PY (95% CI = 18.8–22.8) for COUD, with no significant differences among sexes. Compared with 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 10 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** Mortality risk and excess mortality are significantly greater among those with cocaine and opiates use disorder than among people with only cocaine use disorder or cocaine and alcohol use disorder.

Keywords Alcohol use disorder, cause of death, cocaine use disorder, excess mortality, longitudinal study, mortality rate, opioid use disorder, Spain.

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INTRODUCTION

Cocaine is the most commonly used illicit stimulant drug in Europe. More than 2 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 specialized 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 approximately 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% confidence interval (CI) = 1.54–4.13] among those aged 15–54 years [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 (PY), 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 socio-economic 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 marginalized users who use cocaine in conjunction with opiates [12–14], recording a higher mortality risk among users of both cocaine and heroin and among those injecting drugs.

Concurrent alcohol use disorder is also common among those seeking treatment for cocaine dependence [15,16], with codependent 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 out-patient treatment centres in the city of Barcelona. These fully accessible public treatment centres with no waiting list are distributed evenly in the territory, covering different socio-economic areas, and represent 73.8% of all cocaine treatment starts in the city. Treatment is provided universally free of charge, including opiate substitution treatment if needed. To estimate differences in mortality, participants were divided into 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 use disorder in addition to cocaine (CAUD) and those with cocaine and heroin or other opioids use 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 or not they had a criminal record. 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 ever use of injected drugs, 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 December 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 socio-demographic, health and drug use pattern variables. CMR were expressed in PY of follow-up. Each subject contributed to PY from baseline (date of treatment entry) until the date of death or 31 December 2011 (end of study). Standardized 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 1997–98 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 divided into subcategories. Codes included in each category are shown as Supporting information (Table S1). CMR and RR were also calculated per cause of death for each group. Finally, a multivariable Cox regression model was fitted in order to obtain 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 PY of follow-up.

Baseline characteristics

Table 1 shows participants' descriptive characteristics at treatment entry by group of drug use disorder. CUD represented 34% of the total, CAUD 43% and COUD 23%. The proportions of women were 23, 16 and 20%, respectively. Mean age at entry was 31.6 years [standard deviation (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 completed only primary education, while among COUD the figure was 72%. Furthermore, only 20% of COUD were working at baseline, compared to approximately 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, approximately 60% of CUD and CAUD perceived their health as good, whereas among COUD the corresponding figure was 40%. Conversely, more than 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% with 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 fewer than 5 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. 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). Higher CMR were found in all groups among those categorized 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 CMR and RR per age group and SMR 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 higher among CAUD (SMR = 3.4) and more than 10 times higher among COUD (SMR = 11.6). SMR 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. Also, results by age group indicate that the largest contribution to excess mortality corresponded to the youngest group. Mortality RR 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 socio-demographic, health and use pattern 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 also leading this category 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,

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)*[a]		*n*	*(%)*	*deaths*	*person-years*	*CMR/1000 PY (95% CI)*[a]		*n*	*(%)*	*deaths*	*person-years*	*CMR/1000 PY (95% CI)*[a]	
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)
Socio-demographic																		
Mean age (SD)	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)

(*Continues*)

Table 1. (Continued)

	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)*[a]		*n*	(%)	*deaths*	*person-years*	*CMR/1000 PY (95% CI)*[a]		*n*	(%)	*deaths*	*person-years*	*CMR/1000 PY (95% CI)*[a]	
6–10 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)

[a]Crude mortality rates (CMR) per 1000 person-years (PY) and 95% confidence interval (CI).

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 SMR were higher among women compared to men in the three groups.

As mentioned previously, 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 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. The proportion of HIV infection, probably linked to injection use, was larger among the latter group.

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.

		Total			*Males*			*Females*		
	Age groups	*CMR/1000 PY (95% CI)*[a]	*RR (95% CI)*[b]	*SMR (95% CI)*[c]	*CMR/1000 PY (95% CI)*[a]	*RR (95% CI)*[b]	*SMR (95% CI)*[c]	*CMR/1000 PY (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 (CMR) per 1000 person-years (PY) and 95% confidence interval (CI); [b]rate ratio (RR) and 95% CI calculated using Barcelona 2011 population as the reference; [c]standardized mortality ratio (SMR) and 95% CI using Barcelona 2011 population as the reference. CUD = cocaine use disorder only; CAUD = cocaine and alcohol use disorder; COUD = cocaine and opioids use disorder.

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 external injuries	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 disease	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 disease	30	4.2	9	6.1	10	6.3	11	2.7
Other forms of heart disease	35	4.9	12	8.2	9	5.7	14	3.4
Other circulatory disease	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 oedema and respiratory insufficiency	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

CUD = cocaine use disorder only; CAUD = cocaine and alcohol use disorder; COUD = cocaine and opioids use disorder.

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 socio-demographic, health and use pattern 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. 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 should 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 leads frequently to depression which would, in turn, increase the probability of suicide during the first year. A higher risk for suicide has already been described among cocaine users linked to comorbid depression [19–21]. 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 oedema and respiratory

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 use disorder only (CUD)*			*Cocaine and alcohol use disorder (CAUD)*			*Cocaine and opiates use disorder (COUD)*		
	CMR/1000[a]	*Deaths*	*CMR/1000 PY (95% CI)*[b]	*RR (95% CI)*[c]	*Deaths*	*CMR/1000 PY (95% CI)*[b]	*RR (95% CI)*[c]	*Deaths*	*CMR/1000 PY (95% CI)*[b]	*RR (95% CI)*[c]	*Deaths*	*CMR/1000 PY (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 84.9–9.6)
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 (CMR) per 1000 people; [b]CMR per 1000 person-years and 95% confidence interval (CI); [c]rate ratio (RR) and 95% CI calculated using Barcelona 2011 population as the reference.

insufficiency, the leading cause within respiratory diseases in the three groups of our cohort, could add further to the final overdose figure. A study aimed at validating the underlying cause of death of the Mortality Register in Spain [24] found that more than 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 due in fact to external injuries, mainly 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 mainly 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]. As other studies have already pointed out [28], knowledge of 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, the only exception being women with cocaine and alcohol use disorder, due probably 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 extremely 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 is concentrated among those aged more than 45 years, the age group showing the lowest excess mortality in our cohort. We also need 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. Conversely, 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 SMR of women compared to men can be explained by the lower mortality rates of women in all age groups in the general population, as shown by Guitart *et al.* [31].

It should also be considered that our study covers deaths occurring during 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], due probably to the decrease of fatal overdoses and HIV-related mortality following the implementation of opioid substitution therapy programmes 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, although 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 proved to be a helpful way to shed some light on mortality associated with cocaine use. However, some other limitations should 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 might 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 upon 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 under-representation of patients from a more advantaged socio-economic 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 overestimated 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.

Declaration of interests

None.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article.

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 1997–11.

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Research paper

Effect of ageing and time since first heroin and cocaine use on mortality from external and natural causes in a Spanish cohort of drug users

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ABSTRACT

Background: We aimed to assess the effect of ageing and time since first heroin/cocaine use on cause-specific mortality risk and age disparities in excess mortality among heroin (HUs) and cocaine users (CUs) in Spain.
Methods: A cohort of 15,305 HUs and 11,905 CUs aged 15–49 starting drug treatment during 1997–2007 in Madrid and Barcelona was followed until December 2008. Effects of ageing and time since first heroin/cocaine use were estimated using a competing risk Cox model and the relative and absolute excess mortality compared to the general population through directly age-sex standardized rate ratios (SRRs) and differences (SRDs), respectively.
Results: Mortality risk from natural causes increased with time since first heroin use, whereas that from overdose declined after having peaked in the first quinquennium. Significant effects of time since first cocaine use were not identified, although fatal overdose risk seemed higher in CUs after five years. Mortality risk from natural causes (HUs and CUs), injuries (HUs), and overdoses (CUs) increased with age, the latter without reaching statistical significance. Crude mortality rates from overdoses and injuries remained very high at age 40–59 among both HUs (595 and 217 deaths/100,000 person-years, respectively) and CUs (191 and 88 deaths/100,000 person-years). SRDs from all and natural causes were much higher at age 40–59 than 15–29 in both HUs (2134 vs. 834 deaths/100,000 person-years) and CUs (927 vs. 221 deaths/100,000 person-years), while the opposite occurred with SRRs.
Conclusion: The high mortality risk among HUs and CUs at all ages from both external and natural causes, and increased SRDs with ageing, suggest that high-level healthcare and harm reduction services should be established early and maintained throughout the lifetime of these populations.

1 Introduction

Heroin and cocaine use disorders are chronic and relapsing diseases, which can seriously affect drug users' health for many years. In a recent *meta*-analysis the pooled mortality risk compared to the general population (GP) was 15 and 4–8 times higher among heroin users and cocaine users, respectively (Degenhardt, Bucello et al., 2011; Degenhardt, Singleton et al., 2011). However, the mortality risk also depends greatly on other cohort characteristics, especially drug-injecting prevalence or time in opioid substitution treatment (OST). Thus, among heroin users one meta-analysis

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found that mortality risk in cohorts with drug-injecting prevalence >85% was double that of those with lower prevalence (Degenhardt, Bucello et al., 2011), while another found it was triple during the period outside OST than when they were in OST (Sordo et al., 2017). Among heroin users such excess mortality is largely due to overdoses, although injuries (unintentional injuries, suicide and homicide) also contribute substantially (Degenhardt, Bucello et al., 2011; Degenhardt, Larney, Randall, Burns, & Hall, 2014; Pierce, Bird, Hickman, & Millar, 2015). In cocaine users, overdose, injuries and circulatory diseases may make an important contribution to excess mortality, although the evidence is scarce (Degenhardt, Singleton et al., 2011). Finally, in some cohorts with high drug-injecting prevalence, infectious diseases (mainly HIV) are a major cause of death (Degenhardt, Bucello et al., 2011; Degenhardt, Singleton et al., 2011).

In developed countries, problem heroin and cocaine users are getting older, and long-term users (Arndt, Clayton, & Schultz, 2011; Armstrong, 2007; Barrio et al., 2013; Degenhardt et al., 2014; EMCDDA, 2015; Wu & Blazer, 2011) are accumulating many comorbidities and increased social isolation (Darke et al., 2009; Giraudon, Vicente, Matias, Mounteney, & Griffiths, 2012; Rosen, Smith, & ReynoldsIII, 2008; Larney et al., 2015; Rosen, Hunsaker, Albert, Cornelius, & ReynoldsIII, 2011; Wu and Blazer, 2011). This could partly explain why, despite improved care (i.e., OST), their mortality risk has not declined greatly, except for HIV-related causes (EMCDDA, 2015; Giraudon et al., 2012; Hedegaard, Chen, & Warner, 2015). Quantifying changes in cause-specific mortality by age and time since first heroin/cocaine use is important to target intervention programs more accurately. However, few studies among such drug users have focused on these aspects (Degenhardt, Bucello et al., 2011; Degenhardt et al., 2014; Nambiar et al., 2015; Pierce et al., 2015), and they sometimes show inconsistent results. There is evidence that among heroin users and drug injectors, the main causes of death change with age, with external causes (overdose and injuries) predominating among younger users, and natural causes (i.e., liver disease) among older ones (Clausen, Waal, Thoresen, & Gossop, 2009; Degenhardt et al., 2014; Maxwell et al., 2005; Maxwell, Pullum, & Tannert, 2005). Moreover, it is generally accepted that fatal and non-fatal overdose occur not only among the youngest and most inexperienced opioid users, but also in older users with many years of drug use (Darke & Hall, 2003; UNODC, 2015; Warner-Smith, Darke, Lynskey, & Hall, 2001). Many studies have found that fatal overdose risk does not decrease with age (Bartu, Freeman, Gawthorne, Codde, & Holman, 2004; Bird, Hutchinson, & Goldberg, 2003; Buster, van Brussel, & van den Brink, 2002; Clausen et al., 2009; Merrall, Bird, & Hutchinson, 2012; Odegard, Amundsen, & Kielland, 2007; Pierce et al., 2015) or time since first opioid use (Odegard et al., 2007). Mortality risk from natural causes usually increases with age, especially after age 50 (Brugal et al., 2005; Clausen et al., 2009; EMCDDA, 2015; Larney et al., 2015; Pierce et al., 2015), the same as in the GP, whereas fatal-injury risk shows inconsistent results between studies, with increases (Clausen et al., 2009), stability (Larney et al., 2015; Pierce et al., 2015), and decreases (Copeland, Budd, Robertson, & Elton, 2004; Degenhardt et al., 2014) with age. Among cocaine users, the aforementioned effects have rarely been studied, although considering the morbidity studies (Bernstein et al., 2007; Chen, Scheier, & Kandel, 1996; Kaye & Darke, 2004; Santos et al., 2012) and the increased all-cause mortality with age (Hser et al., 2006; Hser et al., 2012; Pavarin, 2008; de la Fuente et al., 2014), an increase of mortality risk from cocaine overdose (acute intoxication) and natural causes with age and time since first cocaine use can be reasonably expected. The effects of age and time since first drug use on mortality can influence each other given their high correlation (Odegard et al., 2007), thus the age effect in users under 45–50 may sometimes be reduced or disappear after adjusting by time since first drug use (Ortí et al., 1996). Disentangling the two effects is important to prioritize and target interventions more effectively, and to assess changes by age in excess mortality of drug users compared with the GP. However, excess mortality has generally been measured using standardized mortality ratios (SMRs), which presents methodological problems (Brugal et al., 2016). For example, the higher all-cause SMR in younger than older drug users (Degenhardt, Bucello et al., 2011) is largely due to very low mortality among young people in the GP (EMCDDA, 2015). To assess healthcare needs, it is also relevant to use absolute measures of excess mortality, which, however, may often yield results opposite to the SMR. The objective of this study was to assess the effect of ageing and time since first heroin/cocaine use on mortality risk from overdose, injuries and natural causes, as well as to quantify age changes in excess mortality from such causes among heroin and cocaine users admitted to drug treatment in Spain during 1997–2008 compared to the GP.

2 Methods

2.1 Cohort participants

A retrospective cohort was recruited. The main characteristics can be found elsewhere (Brugal et al., 2016; de la Fuente et al., 2014). It included all heroin (HUs) and cocaine users (CUs) aged 15–49 admitted to outpatient drug dependence treatment in publicly funded facilities during 1997–2007 in Madrid and Barcelona, regardless of any previous admission. Double counting was avoided using a personal identifier. All HUs were using heroin when starting treatment, regardless of whether they were also using cocaine, while CUs were using cocaine but not heroin. The criterion for heroin (or cocaine) use was having requested treatment to control the use of such drug or having used it within 30 days prior to admission.

2.2 Baseline assessment

When treatment began, information was collected on recruitment date, personal identifiers (first name, surname, birthdate and sex), socio-demographic variables (age, education attainment, and current employment), and drug use (lifetime drug injection, current frequency of heroin/cocaine use, and calendar-year of first heroin/cocaine use). Frequency of heroin/cocaine use referred to the last 30 days prior to treatment admission. Missing values were less than 4% for all variables. Data were stored in two databases on separate computers, one containing identifiers, and another the study variables, and later linked with a meaningless code.

2.3 Follow-up

The follow-up ended on 31-12-2008. Vital status, date and underlying cause of death were obtained through record linkage with the general mortality register using the personal identifier. Individuals not identified as dead were considered alive at the end of follow-up. It was estimated that during follow-up 0.2% of the GP aged 15–59 emigrated abroad (INE, 2017). The cause of death initially assigned was the underlying cause coded following the International Classification of Diseases –ICD- (ICD-9 for 1997–1998 and ICD-10 for 1999–2008). However, since in Spain coding of external causes in the general register has limitations, especially for overdose (Santos et al., 2010), in Barcelona the forensic-toxicological register was consulted, assigning the cause from this source to discrepant cases. In this consultation, it was observed that 81% of the deaths included in the general register under nonspecific codes such as cardiac arrest (427.5, I46), pulmonary oedema (514, 518.4, J81), respiratory failure (799.1, J96), ill-defined conditions (780–799, R00-R74, R76-R99) and toxic effects of alcohol (980.0) were actually overdoses. Since forensic and toxicological consultation to correct the underlying

cause of death could not be done in Madrid, the above-mentioned codes were classified as overdose in HU and CU cohorts.

2.4 Statistical analysis

Outcomes were deaths from all-causes, overdose, injuries (external causes other than overdose) and natural causes (Randall, Roxburgh, Gibson, & Degenhardt, 2009). ICD overdose codes were selected following recommendations of European institutions (EMCDDA, 2010), validation studies (Santos et al., 2010) and consultation with the Barcelona forensic-toxicological register (Table S1). All analyses were performed separately for CUs and HUs. The time since first heroin (or cocaine) use was calculated as the difference between the calendar-year of death risk assessment (changing during follow-up from baseline to 2008) and the calendar-year of first heroin/cocaine use (fixed for each participant). This means that time since first heroin/cocaine use, as well as age, were analysed as time-varying variables, using the dynamic method of allocation of deaths and persons-year at risk (py) to each of their categories. Crude mortality rates (CRs) for HUs, CUs and the GP living in Madrid and Barcelona during 1997–2008 were calculated and expressed per 100,000 py. Directly *age-sex standardized mortality rates* (SRs) were also calculated using weights from the 2013 European Standard Population stratified into 5-year age groups.

Independent effects of age and time since first heroin/cocaine use were assessed with the adjusted hazard ratio (aHR), which was estimated using proportional cause-specific hazard models (Competing-risk Cox regression). Time from treatment admission (from treatment admission to death or 31-12-2008) was used as the time-scale for the outcome. Results were adjusted by gender, calendar-year of death, city of recruitment, lifetime drug injection, education level, employment, and frequency of cocaine and heroin use, the last four referring to 30 days before treatment admission. A competing risk model was built separately for each cause of death, with deaths from other causes (competing causes) treated as censored observations at the death date and removed from the set of people at risk. The HR expresses how many times higher the instantaneous risk is in a given category compared to the reference among survivors of all competing events to this time point (Putter, Fiocco, & Geskus, 2007). The proportional hazards assumption was checked by smoothed Schoenfeld residuals. All variables fulfilled the assumption, except those entered as time-varying. CRs by 5-year age group were modelled with Joinpoint regression and plotted on an additive and multiplicative scale to observe age changes in absolute and relative excess mortality, respectively, in drug users compared with the GP. Excess mortality was more formally estimated by using age-sex directly standardized rate differences (SRDs) and ratios (SRRs). 95% confidence intervals (95%CIs) of SRR and SRD were estimated by adding the two variances of SRs intervening in SRD and the variance formula for natural logarithm of SRR, respectively (Rothman, Greenland, & Lash, 2008). The proportional contribution of each specific cause of death to all-cause absolute excess mortality was calculated as follows: (specific-cause SRD/all-cause SRD)*100. Analyses were performed with Stata 14.0 (Stata Corporation, College Station, Texas).

3 Results

3.1 Baseline characteristics at recruitment

The study population included 15,305 heroin users (HUs) and 11,905 cocaine users (CUs). About half of participants were aged ≥40. Most of them were men and had at least secondary education. Many were unemployed. HUs were older than CUs, recruited in an earlier calendar-year, had lower education, higher unemployment, and higher prevalence of lifetime drug injection (48% vs. 7%). 57.7% of HUs had used cocaine in the last 30 days. HUs who used cocaine showed higher frequency and time since first cocaine use than CUs (Table S2). Mean age and time since first cocaine use at baseline were significantly higher among HUs than CUs 33.1 vs. 30.0, and 12.4 vs. 8.9 years, respectively. The mean time since first heroin use at baseline was 12.1 years.

3.2 Cause-specific mortality by age

Participants generated 118,902 (HUs) and 65,346 (CUs) py with an average of 6.8 years of follow-up. We recorded 2354 deaths in HUs and 349 in CUs. The most common cause of death at age 15–29 was drug overdose, among both HUs (53.0%) and CUs (49.3%), whereas at age 40–59 it was natural causes (68.1% and 70.1%, respectively). The SRs were higher at age 40–59 than at 15–29 for all causes and natural causes (HUs and CUs), overdose (CUs) and injuries (HUs). However the opposite occurred for overdose (HUs) and injuries (CUs) (Table 1). CRs and proportional mortality by age,

Table 1
Mortality among heroin and cocaine users by cause and age group. Madrid and Barcelona, 1997–2008.

Cause of death and age[a]	Heroin users					Cocaine users				
	N° of deaths	CR	95%CI	SR	95%CI	N° of deaths	CR	95%CI	SR	95%CI
All-causes										
15–29	232	1284	1119–1449	846	622–1070	75	325	252–399	252	140–365
30–39	1100	1814	1707–1921	1689	1567–1812	147	512	429–595	548	425–671
40–59	1022	2544	2388–2699	2428	1989–2867	127	935	772–1098	1221	819–1624
Overdose										
15–29	123	681	560–801	535	323–747	37	160	109–212	93	42–143
30–39	383	631	568–695	563	495–632	54	188	138–238	189	118–261
40–59	239	595	519–670	388	311–465	26	191	118–265	203	51–355
Injuries										
15–29	45	249	176–322	115	71–159	26	113	69–156	123	26–221
30–39	141	232	194–271	192	154–230	46	160	114–207	197	119–276
40–59	87	217	171–262	409	38–779	12	88	38–138	56	7–105
Natural causes										
15–29	64	354	267–441	196	137–255	12	52	23–81	36	10–63
30–39	576	950	872–1027	934	839–1028	47	164	117–211	161	98–225
40–59	696	1732	1603–1861	1632	1408–1856	89	655	519–791	962	592–1333

CR: Crude Mortality Rate per 100,000 person-years. **95%CI:** Confidence interval at 95%. **SR:** Age-sex directly standardized mortality rate per 100,000 person-years.
[a] Age was entered as a time-varying variable.

gender and more specific causes of death are shown in Tables S3-S16. Infectious/parasitic diseases represented more than 30% of deaths among HUs aged 30–59.

3.3 Effect of age and time since first drug use on mortality risk from selected causes

The aHRs from Cox regression by age and time since first heroin and cocaine use are shown in Table 2. The mortality risk from natural causes increased with age among both HUs and CUs, and the same happened with injuries among HUs. However, the fatal overdose risk remained stable with age among HUs and appeared to increase among CUs, albeit without reaching statistical significance.

Mortality risk from natural causes increased with time since first heroin use, while that from overdose decreased. Thus, fatal overdose risk in HUs with less than 10 years of heroin use was significantly higher than in former HUs (aHR $_{<5}$ = 1.6 and aHR$_{5-9}$ = 1.2). Statistically significant effects of time since first cocaine use on cause-specific mortality risk among CUs or HUs were not identified, although fatal overdose risk seemed lower in CUs with <5 years of use (Table 2).

3.4 Excess mortality in drug users compared to the general population by age

An increase in absolute excess mortality from all causes with age can be observed by focusing on the difference in CRs between drug users (HUs or CUs) and the GP in the graph with the additive scale, while a decrease in relative excess mortality with age can be observed by focusing on the same difference in the graph with the multiplicative (logarithmic) scale (Fig. 1). Absolute and relative excess mortality of HUs and CUs compared to the GP by age group and cause of death using SRs is shown in Table 3. In HUs the all-cause SRR was much higher at age 15–29 than 40–59 (26.6 vs. 8.3), while the opposite occurred with SRD (814 vs. 2134 deaths/100,000 person-years). In CUs the pattern was similar, although the age-group disparity appeared less pronounced when using SRR (7.9 at age 15–29 vs. 4.2 at age 40–59) than when using SRD (221 vs. 927 deaths/100,000 person-years). Considering the cause of death, the SRD tends to increase with age, except for overdose (HUs) and injuries (CUs). However, the SRR from overdose and natural causes seems to decrease with age among HUs and to increase among CUs, whereas the opposite occurs with SRR from injuries. Among HUs, the main contributing causes to absolute excess mortality from all-causes were overdose at age 15–29 (66%), and natural causes at ages 30–39 (54%) and 40–59 (63%), while among CUs they were injuries at age 15–29 (51%), overdose and injuries at age 30–39 (40% and 40%), and natural causes at age 40–59 (74%) (Table 3).

4 Discussion

4.1 Main findings

Among HUs, mortality risk from natural causes and injuries increased with age, and the risk from natural causes also increased with time since first of heroin use. Fatal overdose risk decreased with time since first heroin use, with the highest risk found in people using heroin for <5 years. Among CUs, natural mortality increased with age, while fatal overdose increased with age and time since first cocaine use. Fatal overdose and injuries remained very high at age 40–59 among both HUs and CUs. Absolute excess mortality from all and natural causes increased with age in both HUs and CUs, whereas the opposite occurred with relative excess mortality.

4.2 The effect of age and time since first heroin use on mortality in heroin users

Our findings suggest that among HUs mortality risk from natural causes increases with time since first heroin use and especially with age. The age effect has consistently been identified elsewhere (Brugal et al., 2005; Clausen et al., 2009; EMCDDA, 2015; Larney et al., 2015; Pierce et al., 2015), while the length effect has been identified in some studies (Ortí et al., 1996; Brugal et al., 2005), but not others (Langendam, van Brussel, Coutinho, & van Ameijden, 2001; Evans et al., 2012), probably due to low statistical power. Such effects are compatible with increased prevalence of somatic comorbidities (i.e., infections, hepatic and circulatory diseases) and poorer physical health with increasing age or time since first use due to long exposure to multiple risk factors (Hser, Hoffman, Grella, & Anglin, 2001; Hser et al., 2012; Larney et al., 2015; Rosen et al., 2008, 2011). This is also reflected in an increase in all-cause mortality with increasing age or time since first use (Oppenheimer, Tobutt, Taylor, & Andrew, 1994; Ortí et al., 1996; Bartu et al., 2004; Brugal et al., 2005; Clausen et al., 2009; Langendam et al., 2001; Odegard et al., 2007; Quan et al., 2007; van Haastrecht et al., 1996; Beynon, McVeigh, Hurst, & Marr, 2010; Cousins et al., 2016; Degenhardt et al., 2014; Larney et al., 2015; Lee et al., 2013; Merrall et al., 2012; Pierce et al., 2015). Findings also suggest that fatal overdose risk changes little with age and continues to be very high at relatively old ages (i.e., 595 deaths/100,000 py at age 40–59). Fatal overdose risk measured by the SR decreased with age, but not after adjusting for time since first heroin use, because this variable has an opposite effect. Thus, the aHR for <5 compared to ≥10 years of use was 1.6. Most studies have not found a decreasing fatal overdose risk with age (Bartu et al., 2004; Bird et al., 2003; Buster et al., 2002; Clausen et al., 2009; Merrall et al., 2012; Odegard et al., 2007; Pierce et al., 2015), but some do (Copeland et al., 2004; Cousins et al., 2011; Larney et al., 2015; Lee et al., 2013). Moreover, most non-fatal overdose studies have found a greater risk in younger than older opioid users (Bergenstrom et al., 2008; Coffin et al., 2007; Horyniak et al., 2013; Kerr et al., 2007; Kinner et al., 2012; Seal et al., 2001; Bretteville-Jensen, Lillehagen, Gjersing, & Andreas, 2015). Regarding time since first heroin use, a fatal overdose study found a higher risk in long-term users (Odegard et al., 2007), while non-fatal overdose studies have generally found higher risk in short-term users (Powis et al., 1999; Stewart, Gossop, & Marsden, 2002; Bazazi et al., 2015; Brugal et al., 2002), although some do not (Darke et al., 2009; Uuskula et al., 2015). Admitting that non-fatal overdose risk declines with age, the persistence of a high fatal overdose risk among older heroin users and its low decline with age could be explained primarily by an increased overdose lethality at older ages due mainly to increased disease burden (i.e., hepatic disease) (Stoove et al., 2009; Warner-Smith et al., 2001; Merrall et al., 2012). The higher fatal overdose risk in short-term heroin users could be explained by less skills and experience to avoid overdose, lower opioid tolerance, lower exposure to harm reduction interventions (i.e., OST), higher frequency of heroin use or overdose risk factors (i.e., concurrent use of opioids and other depressants, use of injecting route) compared to long-term users (Coffin et al., 2007; Galea et al., 2006; Larney et al., 2015). The mortality risk from injuries (unintentional injuries, suicide or homicide) increased with ageing and remained very high at age 40–59 among HUs (217 deaths/100,000 py). The reasons are unclear, although psychiatric comorbidities, prolonged opioid-addicted life-style and small protective effect of OST may predispose to traumatic deaths (Clausen et al., 2009; Darke et al., 2009). An increase or lack of decline in such risk with age has been also found elsewhere (Clausen et al., 2009; Larney et al., 2015; Lee et al., 2013; Merrall et al., 2012; Pierce et al., 2015), but not in all studies (Copeland

Table 2
Effect of age and time since first heroin and cocaine use on cause-specific mortality risk among people admitted to drug treatment. Madrid and Barcelona. 1997–2008.

Cause of death and age	Heroin Users				Cocaine Users			
	No. deaths	CR	aHR (95% CI)		No. deaths	CR	aHR (95% CI)	
All-causes								
Age[a]								
15–29	232	1283.7	1		75	325.3	1	
30–39	1100	1813.7	1.4	(1.0–1.9)	147	512.0	1.8	(1.1–3.1)
40–59	1022	2543.5	2.2	(1.6–3.1)	127	935.1	3.3	(1.9–5.7)
Years since first heroin use[a]								
<5	94	1513.0	0.9	(0.7–1.2)				
5–9	243	1408.0	0.8	(0.7–0.9)				
≥10	1992	2115.1	1					
Years since first cocaine use[a]								
<5	39	1338.5	0.7	(0.5–1.0)	26	327.9	0.8	(0.5–1.3)
5–9	144	1657.0	1.0	(0.8–1.2)	86	441.9	1.0	(0.8–1.3)
≥10	1149	2090.0	1		233	620.4	1	
Overdose								
Age[a]								
15–29	123	680.6	1		37	160.5	1	
30–39	383	631.5	1.0	(0.7–1.5)	54	188.1	2.0	(0.9–4.6)
40–59	239	594.8	1.1	(0.7–1.6)	26	191.4	2.0	(0.8–5.1)
Years since first heroin use[a]								
<5	55	885.3	1.6	(1.1–2.1)				
5–9	124	718.5	1.2	(1.0–1.5)				
≥10	552	586.1	1					
Years since first cocaine use[a]								
<5	16	549.1	0.6	(0.4–1.1)	6	75.7	0.5	(0.2–1.3)
5–9	68	782.5	1.1	(0.8–1.4)	37	190.1	1.2	(0.7–1.8)
≥10	332	603.9	1		73	194.4	1	
Injuries								
Age[a]								
15–29	45	249.0	1		26	112.8	1	
30–39	141	232.5	3.5	(1.1–11.8)	46	160.2	1.4	(0.6–3.2)
40–59	87	216.5	3.1	(0.9–10.4)	12	88.4	1.3	(0.5–3.0)
Years since first heroin use[a]								
<5	15	241.4	1.2	(0.7–2.1)				
5–9	29	168.0	0.7	(0.5–1.1)				
≥10	226	240.0	1					
Years since first cocaine use[a]								
<5	4	137.3	0.5	(0.2–1.5)	12	151.3	1.1	(0.5–2.5)
5–9	18	207.1	0.9	(0.6–1.5)	23	118.2	0.9	(0.5–1.6)
≥10	138	251.0	1		49	130.5	1	
Natural causes								
Age[a]								
15–29	64	354.1	1		12	52.0	1	
30–39	576	949.7	2.6	(1.2–5.6)	47	163.7	3.2	(0.7–14.4)
40–59	696	1732.2	6.3	(2.9–13.6)	89	655.3	17.8	(4.1–76.8)
Years since first heroin use[a]								
<5	24	386.3	0.5	(0.3–0.8)				
5–9	90	521.5	0.6	(0.5–0.8)				
≥10	1214	1289.0	1					
Years since first cocaine use[a]								
<5	19	652.1	1.0	(0.6–1.5)	8	100.9	0.9	(0.4–1.9)
5–9	58	667.4	0.9	(0.7–1.2)	26	133.6	1.0	(0.6–1.5)
≥10	679	1235.1	1		111	295.5	1	

CR: Crude mortality rate per 100,000 person-years. **aHR (95%CI): H**azard ratio adjusted by covariates in the table plus gender, calendar-year of death, city of recruitment, lifetime drug injection, education attainment, employment, frequency of cocaine and heroin. **95%CI:** 95% confidence interval of aHR.
[a] Entered in the model as a time-varying variable.

et al., 2004; Degenhardt et al., 2014). Moreover, the population risk of drug-related injuries decreased after age 44 in a cross-sectional study (Webb et al., 2003). The variable age at first use could have been entered into the multivariate model instead of time since first use (since the two variables are highly correlated they cannot be assessed together). When time since first use was replaced by age

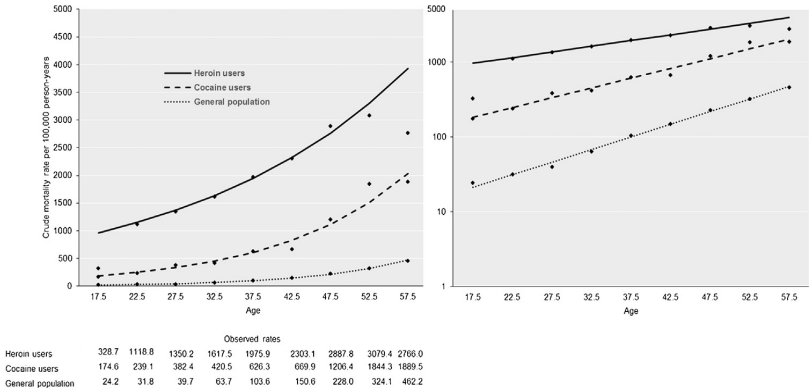

Fig. 1. All-cause crude mortality rate by age among heroin users, cocaine users and the general population aged 15–59. Madrid and Barcelona. 1997–2008.
1A. Additive scale.
1B. Logarithmic or multiplicative scale.
On the abscissa axis the midpoint of each five-year age group is represented. Lines represent mortality rates modelled with joinpoint regression, and markers correspond to observed rates. The absolute excess mortality of heroin and cocaine users can be observed by looking at the differences between their mortality rates and those of the general population in Fig. 1A (left), while relative excess mortality can be observed by looking at the same differences in Fig. 1 B (right).

at first use, the results were quite consistent (i.e., the mortality risk from natural causes increases with increasing time since first heroin use, while such risk increases with decreasing age at first heroin use) However, it should be emphasized that an increased risk of fatal overdose in those starting heroin use earlier (<18 years or <22 years) was not found (data not shown).

4.3 The effect of age and time since first cocaine use on mortality in cocaine users

Mortality risk from natural causes significantly increased with age, especially at age 40–59. Findings also suggest that fatal overdose risk could increase with age and time since first cocaine use. Although the effects of such variables on cause-specific mortality have rarely been studied among CUs, some studies have found increases in all-cause mortality risk with age (Hser et al., 2006; Hser et al., 2012; Pavarin, 2008; de la Fuente et al., 2014) and increases in risk of non-fatal overdose or cocaine-related physical problems with age or time since first cocaine use (Chen et al., 1996; Kaye & Drake, 2004; Bernstein et al., 2007; Santos et al., 2012). However, it should be noted that diagnosing acute cocaine intoxications (overdoses) is not easy (Stephens, Jentzen, Karch, Wetli, & Mash, 2004; Graham & Hanzlick, 2008), so they may be poorly classified in mortality statistics. The increases in mortality

Table 3
Excess mortality of heroin and cocaine users compared to the general population by age group and cause of death. Madrid and Barcelona. 1997–2008.

Cause of death and age[a]	Heroin Users					Cocaine Users				
	SRD	95%CI of SRD	Proportional excess mortality (%)	SRR	95%CI of SRR	SRD	95%CI of SRD	Proportional excess mortality (%)	SRR	95%CI of SRR
All-causes										
15–29	814	590–1038	100	26.6	20.4–34.8	221	182–259	100	7.9	5.1–12.4
30–39	1605	1483–1728	100	20.2	18.7–21.8	464	436–492	100	6.5	5.2–8.2
40–59	2134	1695–2573	100	8.3	6.9–9.9	927	750–1104	100	4.2	3.0–5.8
Overdose										
15–29	533	461–605	65.5	328.1	215.7–499.2	91	40–141	41.2	56.8	32.3–99.7
30–39	559	544–575	34.8	135.7	115.9–159.0	185	114–257	39.9	45.6	30.9–67.4
40–59	386	352–419	18.1	185.4	147.4–233.3	201	49–353	21.6	97.0	45.5–206.9
Injuries										
15–29	104	89–119	12.8	10.3	7.0–15.2	112	15–209	50.8	11.1	5.0–24.4
30–39	179	170–187	11.1	14.2	11.5–17.5	184	106–262	39.6	14.6	9.8–21.8
40–59	395	232–557	18.5	29.6	12.0–73.4	42	-7–91	4.5	4.1	1.7–9.7
Natural causes										
15–29	177	138–236	21.7	10.3	7.6–14.0	18	9–26	7.9	1.9	0.9–4.0
30–39	868	773–962	54.0	14.1	12.7–15.7	95	81–110	20.5	2.4	1.6–3.6
40–59	1354	1130–1578	63.4	5.9	5.1–6.7	684	522–847	73.8	3.5	2.4–5.1

SRD Directly Standardized Rate Difference between drug users and the general population. It is expressed in deaths per 100 000 person-years. 95%CI: 95% confidence interval. **Proportional excess mortality (%):** (cause-specific SRD/all-cause SRD)*100. It expresses the contribution of each specific cause of death to the absolute excess mortality from all causes within each age group. **SRR:** Directly Standardized Rate Ratio between drug users and the general population (people aged 15–59 living in Madrid and Barcelona in 1997–2008).
[a] Among heroin and cocaine users age was entered as a time-varying variable.

risk from overdose or natural causes could be due to pre-existing health problems (i.e., atherosclerosis, heart disease), whose prevalence increases with age and may be exacerbated by cocaine use (Beynon, 2009; Galea et al., 2006). Cocaine may have time-lagged cumulative effects, especially on the circulatory system, triggering acute problems when a threshold is reached (Bernstein et al., 2007; Chen et al., 1996). Also, age-related changes in drug pharmacokinetics may lead to higher blood cocaine concentration or higher sensitivity to cocaine (Lynskey, Day, & Hall, 2003). Mortality risk from injuries was high, especially before age 40. The association of cocaine use with non-fatal and fatal unintentional or intentional injuries among young adults has been reported in multiple studies (Chermack & Blow, 2002; Doherty,Robertson, Green, Fothergill, & Ensminger, 2012; Macdonald et al., 2003; Marzuk et al., 1995; Merrall et al., 2012; Murray et al., 2008; Pavarin et al., 2011; Pennay et al., 2016; Silverman, Raj, Mucci, & Hathaway, 2001; Stoduto, Mann, Ialomiteanu, Wickens, & Brands, 2012; Walton et al., 2009).

4.4 Age differences in excess mortality of heroin and cocaine users

Most previous studies on age disparity in excess mortality in HUs or drug injectors have used only relative indicators of excess mortality like standardized mortality ratios (SMRs) (Degenhardt, Bucello et al., 2011; Nambiar et al., 2015; Oppenheimer et al., 1994; Pierce et al., 2015), and have usually found higher all-cause SMRs in younger participants (Degenhardt, Bucello et al., 2011; EMCDDA, 2015; Nambiar et al., 2015; Oppenheimer et al., 1994). There are few studies of this subject among CUs. In our study disparity indicators on an absolute (SRD) or relative (SRR) scale were used to assess age-group disparities in excess mortality among HUs and CUs compared to the GP. It is known that one might arrive at opposite conclusions, depending on which disparity measure (absolute or relative) was chosen (King, Harper, & Young, 2012; Brugal et al., 2016). Thus, in our study SRD from all and natural causes increased with age in both HUs and CUs, whereas the opposite occurred with SRR. The contradiction is only apparent because this means a stronger association between being HU or CU and mortality at younger ages and yet a greater impact of such conditions on population mortality at older ages. SRR is higher in young drug users because they would engage in harmful behaviours with the same or higher frequency than older users, and dying young is a rare event in the GP in wealthy countries. With ageing, the mortality risk increases in both drug users and the GP due to organic deterioration, resulting in a decreased SRR (relative excess mortality) but an increased SRD (absolute excess mortality). This latter is mainly due to increased SRD from natural causes (i.e., infectious/parasitic diseases, liver diseases, cancer) among older users, although the persistently high SRDs from overdose (HUs and CUs) and injuries (HUs) also contributed. The important contribution of natural causes, especially infectious/parasitic and liver diseases, to excess mortality in older HUs or drug injectors has been reported in numerous studies (Alejos et al., 2016; Beynon et al., 2010; EMCDDA, 2015; Larney et al., 2015; Pierce et al., 2015). A substantial increase in excess mortality (SRD and SRR) from injuries with age was observed in our HU cohort, which is relevant to public health practice because these are clearly preventable causes. Such a finding has rarely been reported, although one study also found an increase in homicide SMR with age (Degenhardt et al., 2014). The huge increase in all-cause SRD with ageing among CUs was mainly due to natural causes, although until age 39 external causes also contributed. Changes by age in excess mortality from overdose are difficult to interpret and are probably attributable to differences in the allocation of cause of death between the cohort and GP.

4.5 Strengths and limitations

This is perhaps the first study to calculate age disparity in excess mortality of HUs and CUs compared to the GP using both absolute and relative disparity measures. It is also one of the first to assess mortality risk by age or time since first cocaine use among cocaine users, after excluding subjects who also used heroin. An appropriate methodology has been used to analyse cause-specific mortality and to disentangle the effects of age and time since first drug use (competing risk Cox regression). Our study also has limitations. First, there was no assessment of drug use or injecting status during follow-up. This could bias the results if behavioural changes (i.e., cessation of opioid use) were differential by age. Valid data on drug use patterns which could explain age disparities in mortality (i.e., recent drug injection, benzodiazepines or alcohol use, exposure to harm reduction, etc.) were not available. There may be some misclassification of cause of death, especially for overdose. Overdoses in Spain are almost always initially certified as non-specific deaths (e.g., pulmonary oedema). These causes often remain as definitive in the general mortality register because they are not changed based on forensic and toxicological data (Santos et al., 2012). To improve the classification, in Barcelona the forensic registry was consulted, and codes in the general register for HUs and CUs were corrected in accordance with the new data. As mentioned above, the vast majority of deaths classified under nonspecific codes in the general register were actually overdoses, so in the Madrid cohort, for which forensic consultation could not be performed, deaths under these codes were classified as overdoses. Finally, 55.7% of deaths classified as overdoses in the drug users' cohort corresponded to nonspecific ICD codes such as ill-defined conditions (41.0%), pulmonary oedema (8.6%), cardiac arrest (3.2%), and respiratory failure (2.9%). Some misclassification of drug use patterns at baseline may occur due to recall biases, socially desirable responses or limitations of treatment registers. Finally, the statistical power remains low for less common mortality causes (i.e., injuries).

4.6 Implications for policy and practice

In 1997–2008 in Spain (and probably in other developed countries), a substantial part of the absolute excess mortality in HUs and CUs compared to the GP appears at a fairly advanced age. Thus, in our study HUs and CUs aged 40 or more accounted for 46.9% and 56.6%, respectively, of all the absolute excess mortality of HUs and CUs of 15–59 years. Although excess mortality is largely due to chronic diseases caused by harmful behaviours initiated long before, these drug users remain at high risk of mortality from acute short-term preventable problems such as overdose or injuries after age 40. Consequently, a high level of harm reduction and healthcare services (i.e., OST, take-home naloxone, HIV and hepatitis C diagnosis and treatment, etc.) in older drug users should be maintained (Degenhardt et al., 2014; Larney et al., 2015). Social support services are also needed because these people usually have limited family support. Also, healthcare professionals should be prepared to deal with heroin and cocaine problems in users at relatively advanced ages.

Contributors

Gregorio Barrio (GB) and Luis de la Fuente (LF) conceived the article and coordinated the design of the study and writing of the article; Oleguer Parés (OP) and Marina Bosque-Prous (MBP) carried out the search for information, Gemma Molist (GM) and MBP carried out the analysis and reviewed the consistency of data included in the paper; GM and OP wrote the first draft of the

manuscript; Beatriz Mesías, M.Teresa Brugal, GB and LF contributed to the interpretation of the results and wrote the final version given their experience in analyzing information systems; all authors critically reviewed and approved the final version. All authors believe in the overall validity of the paper and take public responsibility for its contents.

Conflict of interest

None.

Ethics approval

This study was conducted with the approval of the Clinical Research Ethics Committee of the Municipal Institute of Health Care (CEIC-IMAS), Barcelona

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.drugpo.2017.11.011.

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Research paper

The impact of harm reduction programs and police interventions on the number of syringes collected from public spaces. A time series analysis in Barcelona, 2004–2014

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ABSTRACT

Background: To estimate the effect of opening two services for people who use drugs and three police interventions on the number of discarded syringes collected from public spaces in Barcelona between 2004 and 2014.
Methods: We conducted an interrupted time-series analysis of the monthly number of syringes collected from public spaces during this period. The dependent variable was the number of syringes collected per month. The main independent variables were month and five dummy variables (the opening of two facilities with safe consumption rooms, and three police interventions). To examine which interventions affected the number of syringes collected, we performed an interrupted time-series analysis using a quasi-Poisson regression model, obtaining relative risks (RR) and 95% confidence intervals (CIs).
Results: The number of syringes collected per month in Barcelona decreased from 13,800 in 2004 to 1655 in 2014 after several interventions. For example, following the closure of an open drug scene in District A of the city, we observed a decreasing trend in the number of syringes collected [RR = 0.88 (95% CI: 0.82–0.95)], but an increasing trend in the remaining districts [RR = 1.11 (95% CI: 1.05–1.17) and 1.08 (95% CI: 0.99–1.18) for districts B and C, respectively]. Following the opening of a harm reduction facility in District C, we observed an initial increase in the number collected in this district [RR = 2.72 (95% CI: 1.57–4.71)] and stabilization of the trend thereafter [RR = 0.97 (95% CI: 0.91–1.03)].
Conclusion: The overall number of discarded syringes collected from public spaces has decreased consistently in parallel with a combination of police interventions and the opening of harm reduction facilities.

Introduction

Many people who inject drugs (PWID) do so in public spaces near where they obtained the substance (65% report having done so during the previous year) (de la Fuente et al., 2006), and some abandon injection material nearby. Discarded syringes reflect recent drug use and are often found in streets, squares or parks in the vicinity of drug markets. The presence of syringes can cause public alarm and fear of infection. The main objectives of harm reduction services, including supervised drug consumption facilities, are to prevent blood-borne infections and overdose mortality, as well as other social and health problems. Moreover, by reducing injection in public spaces, they may also reduce the number of discarded syringes in public settings. While harm reduction programs are known to be effective in reducing health risks among people who use drugs (PWUD), the impact of supervised drug consumption facilities on the number of discarded syringes has not been evaluated (Emmanuelli & Desenclos, 2005; Rhodes & Hedrich, 2010; Strang et al., 2012). This is an important issue, as harm reduction services and facilities are often criticized because people living nearby perceive that they attract drug dealing and drug use, which threatens the centres' sustainability. Discarded syringes in public spaces also pose a risk of infection transmission

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(Canadian Paediatric Society, 2008; Escobar et al., 2013; García-Algar & Vall, 1997; Zamora et al., 1998), and are a very intuitive indicator of the nuisance caused by drug dealing and drug use to citizens who do not use drugs (Babor et al., 2009).

Like other cities in southern Europe, Barcelona is a compact city with a high population density. During the 1990s, a sizable proportion of opiate and cocaine dealing was concentrated in Can Tunis, an open scene separated from the urban grid by the port. The expansion of the port led to its demolition in 2004, displacing its last residents (about 100 persons in 20 family units) to other parts of the metropolitan area. Consequently, drug trafficking returned to several areas of the city, especially to the Old City district, accompanied by a rise in the amount of visible discarded injecting material in public spaces (Illundain, 2006). The collection of syringes from the public space had always been performed by the municipal litter collection services, and reinforced for many years in some areas of the Old City by a syringe collection project involving community workers (Bechich et al., 2001). This project was then expanded to incorporate systematic counting of collected syringes by all parties involved, evolving into a comprehensive program to deal with discarded syringes. Police operations to reduce the supply of drugs were also undertaken (unlike in other countries, drug use or the possession of small amounts for personal use has not been a crime in Spain since the 1970s). At the same time, a strategy was developed by the public health service to expand their outreach and treatment activities for PWUD, including harm reduction programs (Rhodes & Hedrich, 2010). The opening of a supervised drug consumption facility in the Old City was a major component of this strategy. However it had to deal with resistance from local residents, which was fuelled by some media and other organisations (Sepúlveda, Báez, & Montenegro, 2008). Following a decline in incidence (Sanchez-Niubo et al., 2007; Sanchez-Niubo, Domingo-Salvany, Melis, Brugal, & Scalia-Tomba, 2007), the size of the city's heroin-using population has been relatively stable over the last decade (Brugal, Guitart, & Espelt, 2013), although there is still a high proportion of injection and frequent consumption in public spaces (de la Fuente et al., 2005).

The objective of this study was to estimate the effect of opening two facilities providing services to PWUD and of three police interventions on the number of syringes collected from public spaces in Barcelona between 2004 and 2014, and trends therein. Our specific aims were to describe the number of syringes collected in the city and in six specific areas over a 10 year period, and to study the impact of five specific events on these numbers: the opening of two facilities providing services to PWUD (one focusing on harm reduction), and three major police interventions.

Methods

Design

We analysed data using an interrupted time-series design (López, Marí-Dell'Olmo, Pérez-Giménez, & Nebot, 2011). We analysed the number of syringes that were collected from public spaces, as reported by community health workers from the Barcelona Public Health Agency (ASPB), the municipal institute for parks and gardens, and the city cleaning services. All these organizations report this information every month to the ASPB's integrated information system. This system has compiled information on syringes collected from public spaces (streets, parks or public gardens) in several districts of Barcelona since 2004, although the syringe collection system existed before this time. For this study, we included a special analysis for five of Barcelona's 10 administrative districts (labelled Districts A to E for the purposes of this study), where the quantity of discarded syringes in public spaces is considered problematic. The remaining five districts were excluded from the analysis as they accounted for <1% of the total number of syringes collected in the city during 2014, a similar percentage to that between 2004 and 2014. In these five districts, less than two syringes per month were collected, which makes this issue much less relevant for public health and makes any thorough statistical analysis difficult. The districts included are mapped in Fig. 1 and include 824,637 citizens (52% of the entire city).

Variables

The dependent variable in this study was the number of syringes collected from public spaces, as reported to the ASPB (Vecino et al., 2013). This information had been collected for districts A, B and E since 2004 and for districts C and D since 2007. The main independent variables were the events or interventions that may have influenced drug traffic and use in the city, as discussed in the Board of the Action Plan on Drugs (Brugal et al., 2013), as follows:

- *Urban change, Intervention 1*: The Can Tunis social housing project in district A was demolished in summer 2004 and its residents were relocated to other parts of the metropolitan area, either within the city or in neighbouring towns. For many years, a very high proportion of all drug dealing in Barcelona was concentrated in this enclave.
- *Services for PWUD, Intervention 2*: A safe consumption facility was opened in district B in December 2004, and other treatment and harm reduction services already operating in the district for PWUD were expanded.
- *Police operation, Intervention 3*: A major police operation took place in district E between November 2005 and February 2006.
- *Police operation, Intervention 4*: A major police operation took place in district A in the summer of 2008, beginning in June.
- *Services for PWUD, Intervention 5*: A new addiction treatment facility opened in district C in December 2010.
- *Police operation, Intervention 6*: A police intervention in December 2011 resulted in the arrest of one of the main drug dealing networks in district D.

The three police operations considered in this study were major interventions, involving months of investigation. Police, with judicial permission, broke into several private residences that were suspected of being the base for drug trafficking and were targeted in order to disrupt the core of local traffic networks and to remove or greatly reduce the extent of drug dealing in the area. The two interventions labelled as harm reduction and treatment had a health focus. The major harm reduction facility in the Old City provides low-threshold substitution therapy, and is a gateway to enter formal treatment. The treatment facility (similar to most of the other ASPB centres) provides opioid substitution therapy, syringe exchange services, and a space for safe consumption (which began after some months of operation).

Some other independent variables were taken into account to ensure that the association between the intervention and the number of syringes collected did not depend on trends in these indicators. These variables were: (a) the monthly number of overdose deaths in Barcelona between 2004 and 2014, obtained from the register of the Legal Medicine Institute; (b) the monthly number of outpatients enrolled in treatment for opioid use disorder between 2004 and 2014; and (c) the monthly percentage (2004–2014) of distributed syringes that were not returned to the exchange programs. Regarding outpatients enrolled in treatment, we included all treatment admissions for opioid use disorder (American Psychiatric Association, 2013, p. 5) at public outpatient

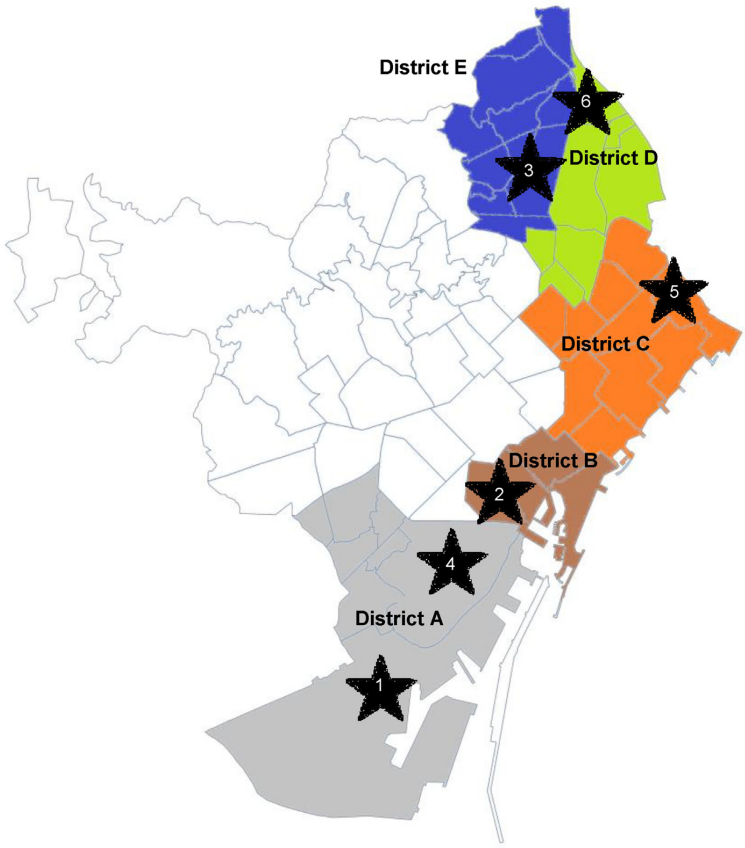

Fig. 1. Districts with higher concentration of drug selling, highlighting major police and harm reduction intervention. Barcelona, 2004–14.
Intervention 1: Urban Change Intervention in District A;
Intervention 2: New facility serving PWUD in District B;
Intervention 3: Police Operation in District E;
Intervention 4: Police Operation in District A;
Intervention 5: New facility serving PWUD in District C;
Intervention 6: Police Operation in District D.

Addiction Treatment Centres in Barcelona. In 2014 there were 14 different centres offering professional specialised treatment, most of which are independent outpatient facilities, while some are hospital-based outpatient clinics. All districts have one or more reference centres. Regarding distributed syringes, there are several syringe exchange points in Barcelona, all of which are monitored. All variables for the various districts of Barcelona were extracted from the ASPB's drug information system.

Statistical analysis

We first performed a descriptive analysis of the number of syringes collected each month, the number of outpatients who began treatment for opioid use disorder, and the number of overdose deaths in the city. We also analysed the number of syringes collected each month in each district. To evaluate changes in the number of syringes collected from public spaces after the events mentioned above, we performed an interrupted time-series analysis with quasi-poisson regression models for overdispersed count data (Ver Hoef & Boveng, 2007). We compared the number of syringes collected per month throughout the time series, controlling for time trend and seasonal patterns using linear trend and including Fourier series terms in the model (Bhaskaran, Gasparrini, Hajat, Smeeth, & Armstrong, 2013; Novoa et al., 2010). Finally, to evaluate which interventions had an effect on the trend and changes in the number of syringes collected from public spaces, we introduced a term for the interaction between the trend and some dummy variables. This represented the various interventions, and computed relative risks (RR) and their 95% confidence intervals (CIs). The model for the number of syringes collected was as follows:

$$\ln[E(Y_t)] = \beta_0 + \beta_1 T_t + \beta_2 X_t + \sum_k \left[\beta_{3k}\sin\left(\frac{2K\pi}{T}\right) + \beta_{4k}\cos\left(\frac{2K\pi}{T}\right)\right] + \beta_5 X_t T_t + \sum_j \left(\beta_{6j} Z_{jt}\right)$$

Where Y_t is the number of syringes collected in the time t ($t = 1, \ldots, T$). T_t is the time period ($T_1 = 1$ for the first month of the series, $T_2 = 2$ for the second, etc.); X_t identifies the pre-intervention ($X_t = 0$) and post-intervention ($X_t = 1$) periods for each

intervention; K takes values between 1 and 6 (K = 1 for annual seasonality; K = 2 for 6 monthly seasonality, etc.); T is the number of periods described by each sinusoidal function (e.g. T=12 months); Z_{jt} are other covariables introduced; and *j* is the number of covariables introduced. All analyses were performed separately for each district. All statistical analyses were performed using STATA 13.0.

Results

Fig. 2 shows the number of syringes collected per month from public spaces in five districts of Barcelona between July 2004 and December 2014; harm reduction and policy interventions conducted during this period are also shown. The number of syringes collected per month decreased from 13,800 in July 2004 to 1655 in December 2014. The strongest decline occurred in the first years following the closure of Can Tunis and the opening of a harm reduction facility in District B. Patterns of change in the number of syringes collected varied between districts: In 2004, districts A, B and E had a major problem with the number of discarded syringes, and in these districts there was a gradual decrease in the number of syringes collected. In contrast, the number of syringes collected in districts C and D increased and had become a public concern by 2011. The greatest decline in the number of syringes collected was observed in District A. Fig. 3 shows that the number of syringes collected in District A began to decrease in 2004, whereas thisnumber began to increase in districts with a higher absolute number of discarded syringes (districts B and E). Following the opening of a harm reduction centre in District B (*Services for PWUD, Intervention 2*), which had a serious problem with visible discarded syringes, we observed a drop in the number of syringes collected in this district. After a police operation in District E (police operation, intervention 3), we observed a decrease in the number of syringes collected in districts B and E, but a slight

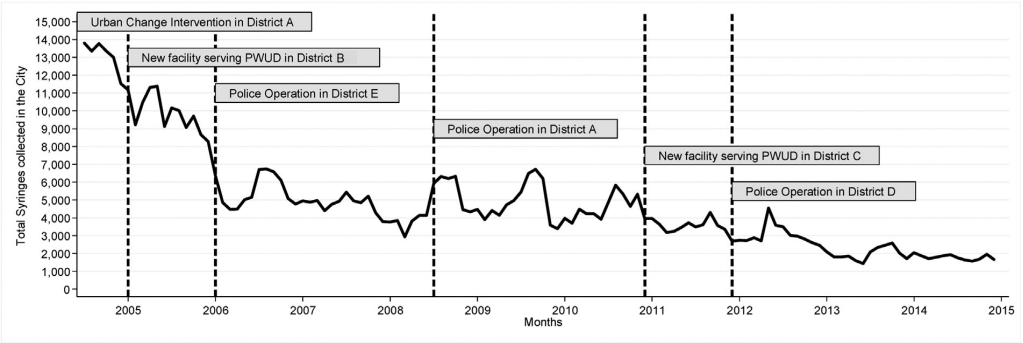

Fig. 2. Number of syringes collected in public spaces per month, Barcelona, 2004-14. Major policing and harm reduction interventions are indicated.

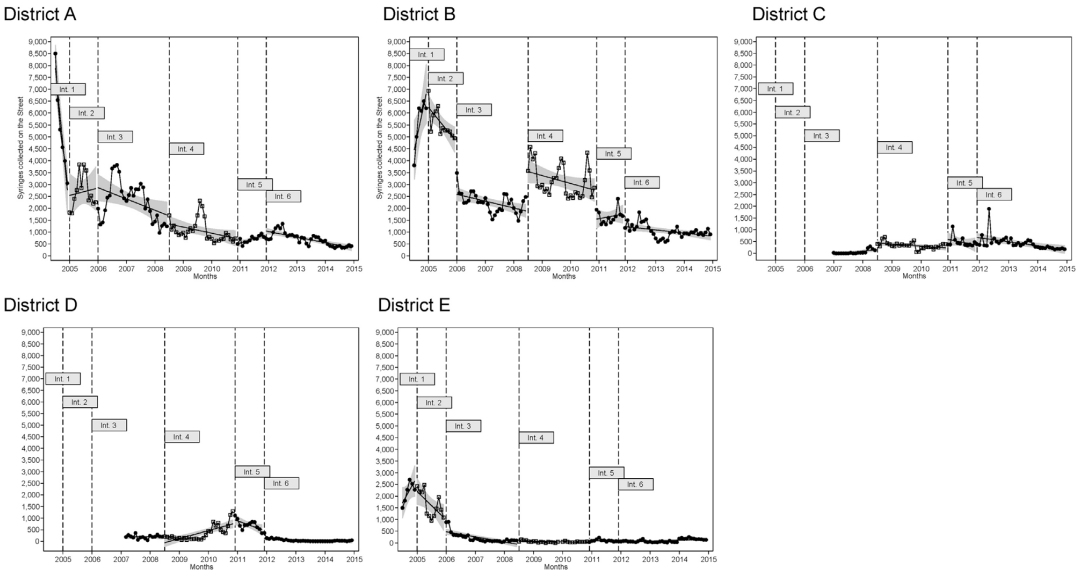

Fig. 3. Number of syringes collected in public spaces per month in each district, Barcelona, 2004-14. Major policing and harm reduction interventions are indicated. **Intervention 1:** Urban Change Intervention in District A; **Intervention 2:** New facility serving PWUD in District B; **Intervention 3:** Police Operation in District E; **Intervention 4:** Police Operation in District A; **Intervention 5:** New facility serving PWUD in Intervention District C; **Intervention 6:** Police Operation in District D.

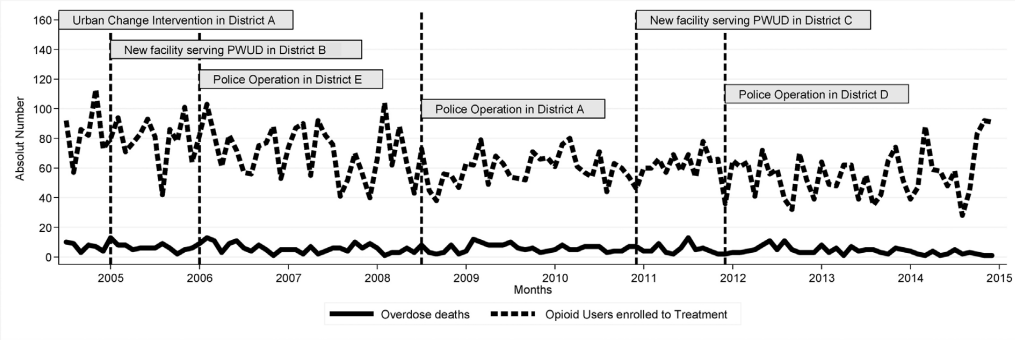

Fig. 4. Number of patients who initiated outpatient treatment for opioid use disorder, and number of overdose deaths per month. Barcelona, 2004–14.

increase in District A. After a major police intervention in District A in 2008 (police operation, intervention 4), we observed no change in the number of discarded syringes collected in District A, but rather a sudden increase in District B, and statistically non-significant increases in districts C and D. The opening of a treatment centre in District C in 2011 (services to PWUD, intervention 5) appeared to have been followed by a decrease in the number of discarded syringes in districts C and D.

Fig. 4 shows that the number of overdose-related deaths per month and the number of outpatients who began treatment for opioid use disorder in public treatment centres in Barcelona remained relatively constant between July 2004 and December 2014 (with a decrease in the former between 2013 and 2015). Fig. 5 shows that, over time, the number of syringes distributed by exchange program tended to be equal to the number returned. The Spearman correlation coefficients between the number of discarded syringes and the percentage of syringes returned and not returned per month were −0.67 (p-value <0.001) and 0.81 (p-value <0.001), respectively. This indicates that the number of syringes collected from public spaces was lower during months in which a higher number of syringes was returned to the exchange program.

Table 1 shows the RR for the trend in the number of syringes collected, and the RR for specific changes in the number of syringes collected after the various interventions. After *Intervention 1* [urban change in District A], we observed a decreasing trend in the number of syringes collected in this district [RR = 0.88 (95% CI: 0.82–0.95)], but an increasing trend in the other districts [RR = 1.11 (95% CI: 1.05–1.17) and 1.08 (95% CI: 0.99–1.18) in districts B and E, respectively]. The trend remained stable following *Intervention 2* (opening of a harm reduction centre in District B), and between interventions 1 and 2 there was no statistically significant change in the number of syringes collected in any district. After *Intervention 5* (opening of a harm reduction facility in District C), we observed an increase in the number of syringes collected in this district [RR = 2.72 (95% CI: 1.57–4.71)], and stabilization of the trend [RR = 0.97 (95% CI: 0.91–1.03)]. Finally, after *Intervention 6* (police operation in District D), we observed a decrease in the number of syringes collected in this district, and a non-significant increase in District C; the tendency in both districts began to decline following this last intervention (Table 1).

Discussion

The main result of our study is the observation of a decrease in the number of discarded syringes collected from public spaces between 2004 and 2014. This decrease was enhanced following the opening of harm reduction facilities and police interventions. We observed that police interventions were followed by some displacement in the volume of syringes from one district to another. In contrast, the opening of harm reduction facilities was followed by a general decrease in the number of discarded syringes, both locally and throughout the city. However, in some cases and only over the short-term, we have observed an increase in the number of syringes collected near the harm reduction facility. In summary, we found that the number of syringes collected from public spaces varies after these interventions, and their joint effects may explain the decline observed since 2004.

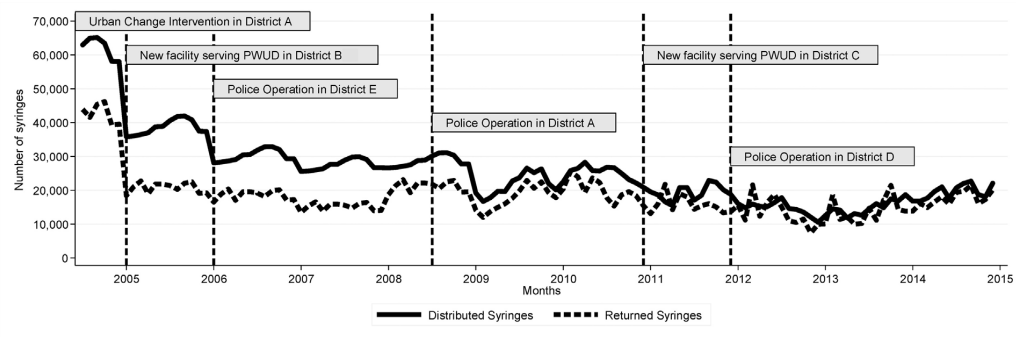

Fig. 5. Number of syringes distributed by and returned to exchange programs per month. Barcelona, 2004–14.

Table 1
Relative risks for trend and changes in the monthly number of syringes collected from public spaces for each district after the various interventions. Barcelona, 2004–14.

		District A		District B		District C		District D		District E	
		Sign[a]	RR (95% CI)[b]	Sign[a]	RR (95% CI)[b]	Sign[a]	RR (95% CI)[b]	Sign[a]	RR (95% CI)[b]	Sign[a]	RR (95% CI)[b]
Urban change intervention 1 in **District A**	Trend	–	0.88 (0.82–0.95)	+	1.11 (1.05–1.17)					=	1.08 (0.99–1.18)
New facility serving PWUD intervention 2 in **District B**	Change. number[d]		1.25 (0.99–1.58)		1.06 (0.88–1.29)						1.15 (0.82–1.64)
	Trend	=	0.98 (0.94–1.02)	–	0.96 (0.94–0.98)					=	0.99 (0.95–1.03)
Police operation intervention 3 in **District E**	Change. number[d]		1.28 (1.01–1.64)		0.62 (0.53–0.73)						0.46 (0.33–0.65)
	Trend	=	0.98 (0.95–1.02)	–	0.99 (0.98–0.99)	+	1.39 (1.15–1.68)	=	0.99 (0.93–1.04)	–	0.91 (0.90–0.93)
Police operation intervention 4 in **District A**	Change. number[d]		0.78 (0.61–1.01)		1.80 (1.56–2.10)		1.68 (0.76–3.75)		0.38 (0.19–0.75)		3.09 (1.21–7.85)
	Trend	–	0.98 (0.97–0.99)	–	0.99 (0.98–0.99)	–	0.98 (0.96–0.99)	+	1.10 (1.08–1.12)	–	0.96 (0.93–0.99)
New facility serving PWUD intervention 5 in **District C**	Change. number[d]		0.87 (0.55–1.39)		0.65 (0.52–0.80)		2.72 (1.57–4.71)		0.94 (0.62–1.43)		3.08 (1.23–7.70)
	Trend	=	1.01 (0.95–1.07)	=	0.99 (0.96–1.02)	=	0.97 (0.91–1.03)	–	0.95 (0.90–0.99)	=	1.03 (0.94–1.13)
Police operation intervention 6 in **District D**	Change. number[d]		1.47 (0.81–2.69)		0.86 (0.62–1.18)		1.79 (0.81–3.96)		0.24 (0.12–0.48)		0.47 (0.15–1.49)
	Trend	–	0.97 (0.96–0.98)	–	0.99 (0.98–0.99)	–	0.97 (0.95–0.98)	–	0.89 (0.85–0.94)	+	1.04 (1.02–1.06)

[a] **Sign:** + Positive slope trend; – Negative slope trend; = no slope trend.
[b] Adjusted by monthly number of overdose deaths, outpatients enrolled in treatment for opioid use disorder, and percentage of syringes not returned per month.

Our study supports the notion that harm reduction centres, which are already known to decrease health risks among drug users (Bravo et al., 2009; Cox, Lawless, Cassin, & Geoghegan, 2000; Laufer, 2001), have tremendous potential to decrease public nuisance in their surroundings by reducing the presence of discarded syringes in public spaces, most likely by decreasing drug use in the street. This effect has also been documented in both Vancouver and Montreal, Canada (de Montigny, Vernez Moudon, Leigh, Kim, & Young, 2010; Vecino et al., 2013; Wood et al., 2006). Harm reduction programs and services were initially criticised by some media and political groups (Europa Press, 2013), and have often been attacked on ideological grounds due to the perception that they attract PWUD and drug traffic to the local neighbourhood and cause public nuisance for residents (Parkin, 2016). Our study suggests that after an initial phase, harm reduction facilities have a positive effect on indicators of drug-related public nuisance in the local area, and in the city as a whole (beyond their value for the health of PWUD). It also shows that these indicators are influenced by changes related to drug trafficking or the effects derived from police operations (Cooper, Moore, Gruskin, & Krieger, 2005; Parkin, 2016; Vecino et al., 2013; Evan Wood et al., 2004). Setting up such harm reduction facilities, which improve PWUD's prospects, requires sensitive management (Parkin & Coomber, 2011), and the fact that they may also help to resolve drug-related problems for residents is relevant for advocates and decision makers. However, there continued to be a substantial number of discarded syringes collected from public areas during 2015. Qualitative studies are needed to understand PWUDs' perceptions about harm reduction programs.

We have found that the opening of harm reduction centres may be followed by a short-term increase in the number of discarded syringes in their vicinities. This is likely because these centres offer safer injection options that attract PWUD from other areas of the city, and even from neighbouring cities in the metropolitan area; many of these PWUDs are also clients of methadone maintenance programs (Anoro, Ilundain, & Santisteban, 2003). Proponents of harm reduction must incorporate these concerns when planning actions. Consistent with previous studies, after police interventions we observed an increase in the number of syringes collected from other city districts. This suggests that efforts to control illicit drug use may not alter the price of drugs or the frequency of use, nor encourage enrolment in methadone treatment programs, but instead cause a displacement of injecting drug use from the crackdown area to adjacent zones in the city (Evan Wood et al., 2004).

One of the strongest facets of our study is that the syringes were collected in a systematic manner by organized programs; the resulting data are then a robust and intuitive indicator of problematic drug consumption and drug traffic areas. Elected politicians in the city use these data in public hearings and other meetings, in the same way that data on overdose-related deaths were incorporated in the late 1980s. As an indicator of drug use, this measure provides somewhat stable data on time and place of use, although it may be biased by some factors, such as occasionally finding and cleaning previously unknown injecting spots. This may create a sudden peak in the number of syringes collected in the area. The time required to collect and process these data is faster than for other data included in the drug information systems. Although an indirect indicator, this measure provides cheaper and less biased information for monitoring the visible use of injected drugs in public spaces than other measures, such as counting PWUDs, which is more limited in time and space. Apart from in the Canadian cities mentioned above, we are not aware that this measure has been used systematically, but we think it is a

promising indicator (de Montigny et al., 2010; Wood et al., 2004). In Spain syringe sales in pharmacies are not subject to limitations, and we have not identified general changes in access to syringes by people who inject drugs (PWID), although there may be minor local variations.

One of the important limitations of this study is that we were only able to control for the number of PWUD who requested treatment for opioid use disorder, and we could not account for the total number of PWID in Barcelona. However, although there are no specific estimates covering the entire period, the incidence of heroin consumption, and patterns therein, in the city of Barcelona appear to have been stable during the first decade of this new century (Nordt et al., 2010). Another important limitation is that we have no information about areas beyond Barcelona's city limits, and there may have been an increase in the problem of discarded syringes outside the city due to displacement of PWUD resulting from police pressure. Finally, given the nature of our analysis, we cannot infer a causal association between these interventions and numbers of syringes collected, although the temporal association is suggestive.

Conclusions

We observed a decline in the total number of syringes discarded in public settings in the city of Barcelona. This followed interventions to disrupt an enclave that had turned into an open drug scene. However, this general decline coincided with temporary increases in the number of discarded syringes in some areas. Following various interventions (new services for PWUD and police operations), we observed a reduction and redistribution of the number of discarded syringes. The combination of these interventions may explain the decrease in the number of discarded syringes collected in public spaces, from 13,800 in July 2004 to 1655 in December 2014.

Conflict of interest

The authors declare no conflict of interest.

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