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Mortality among individuals with cannabis, cocaine, amphetamine, MDMA, and opioid use disorders: A nationwide follow-up study of Danish substance users in treatment

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ABSTRACT

This is a register-based cohort study of 20,581 individuals in treatment for illicit substance use disorders in Denmark between 1996 and 2006. All in all, 1441 deaths were recorded during 111,445 person-years of follow-up. Standardized mortality ratios (SMRs) associated with different primary substance types were calculated and Cox-regression analyses were performed in order to establish hazard ratios (HR) associated with injection drug use and psychiatric comorbidity. SMRs for primary users of specific substances were: cannabis: 4.9 (95% confidence interval (CI): 4.2–5.8), cocaine: 6.4 (CI: 3.9–10.0), amphetamine: 6.0 (CI: 4.2–8.3), heroin: 9.1 (CI: 8.5–9.8), and other opioids 7.7 (CI: 6.6–8.9). For MDMA ('ecstasy') the crude mortality rate was 1.7/1000 person-years (CI: 0.4–7.0) and the SMR was not significantly elevated. Injection drug use was associated with significantly increased hazard ratios in users of opioids and cocaine/amphetamine. Overall, psychiatric comorbidity was not associated with increased mortality (HR: 1.1 [CI: 0.9–1.2], $p = .28$), but an association was found specifically among cocaine/amphetamine users (HR: 3.6 [CI: 2.1–6.4], $p < .001$).

1. Introduction

Several studies have shown that, in general, illicit substance use disorders are associated with excess mortality. However, the amount of scientific evidence varies considerably for different substance classes and risk factors.

Almost no publications exist concerning cannabis or methylenedioxymethamphetamine (MDMA commonly known as 'ecstasy') use disorders. For example, we located only one publication estimating excess mortality among individuals with primary cannabis use disorders (Wahren et al., 1997). This despite that cannabis is the most commonly used illegal substance in the world, and that it has been associated with a high risk of accidents (Eksborg and Rajs, 2008; Laumon et al., 2005; Macdonald et al., 2003). Rogers et al. (2009) reviewed the evidence concerning MDMA, and found that studies on mortality were mostly case series or relying on post mortem data.

Some studies on primary cocaine and amphetamine users exist (Bartu et al., 2004; Pavarin, 2008; Quan et al., 2007; Ribeiro et al., 2007; Wahren et al., 1997) but evidence is still lacking concerning estimates of overall mortality, gender differences, and risks associated with injection drug use. This despite that a number of post mortem studies have demonstrated that these substances are involved in many drug related deaths (Bernstein et al., 2007; Coffin et al., 2003; Darke et al., 2005; Hickman et al., 2007; Shah et al., 2008; Torralba et al., 1996) and that the number could be increasing in the European countries (O'Dowd, 2008; Schifano and Corkery, 2008; Steentoft et al., 2006).

There is extensive literature on opioid use disorders (e.g. reviews by Hulse et al., 1999; Wilcox et al., 2004). Studies have documented that the level of excess mortality is considerable, but with substantial differences in investigations from different countries (Bargagli et al., 2006; Colon et al., 2006; Darke and Ross, 2002; Steentoft et al., 2006), regions within countries (Bird et al., 2003), and historical time periods (Degenhardt et al., 2005a; Ghodse et al., 1998; Hickman et al., 2007; O'Dowd, 2008; Shah et al., 2008; Vlahov et al., 2008; Wahren et al., 1997).

While most individuals with opioid dependence have injected the substance, the proportion is lower among primary users of illicit stimulants (Mesquita et al., 2001; Quan et al., 2007; Ribeiro et al., 2007; Vlahov et al., 2008). Two studies have found that injecting

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drug use of opioids is associated with higher mortality (Gossop et al., 1996; Hickman et al., 2003), while two studies report no such association (Joe et al., 1982; Sanchez-Carbonell and Seus, 2000). One study on primary users of illicit stimulants (Hser et al., 2006) and one study on users of either opioids or stimulants (Johnson et al., 2005) have found no association either. However, most of the cited studies do not report on sharing of syringes which could be an important factor to explore since hepatitis B and C, as well as AIDS are the major reasons for death among users of the substances (Degenhardt et al., 2006; Fugelstad et al., 2007).

A number of longitudinal studies have investigated variables at baseline among individuals with substance use disorders associated with mortality at a later point in time (Bartu et al., 2004; Bauer et al., 2008; Colon et al., 2006; Gossop et al., 2002; Joe et al., 1982; Johnson et al., 2005; Quan et al., 2007; Ravndal and Vaglum, 1998; Ribeiro et al., 2007; Sanchez-Carbonell and Seus, 2000; Vlahov et al., 2008). However, for some reason the impact of comorbid psychiatric problems has received almost no attention. This pertains to all substance classes. The existing investigations only report sporadically on this theme and results have been mixed (Bartu et al., 2004; Bauer et al., 2008; Colon et al., 2006; Gossop et al., 2002; Hser et al., 2006; Ravndal and Vaglum, 1998). This is odd since it is known that substance use disorders are highly associated with psychiatric disorders that are presumably not substance related (e.g. Arendt and Munk-Jørgensen, 2004; Conway et al., 2006; Regier et al., 1990), that psychiatric comorbidity increases the risk of relapse following treatment for substance use disorders (Arendt et al., 2007; Landheim et al., 2006), and that these disorders are independently associated with excess mortality (e.g. Felker et al., 1996; Roshanaei-Moghaddam and Katon, 2009; Saha et al., 2007).

We performed a register-based follow-up study involving individuals in treatment for illicit substance use disorders in Denmark from 1996 onwards. The following research questions were addressed:

1. What are the standardized mortality ratios (SMRs) associated with treatment for cannabis, cocaine, amphetamine, MDMA, and opioid use disorders?
2. What are the SMRs associated with injection drug use and sharing of syringes?
3. Are comorbid psychiatric disorders associated with excess mortality?

2. Methods

2.1. Study population

The sample includes 20,581 persons who received treatment in all specialized institutions for illicit substance use disorders in Denmark between 1 January 1996 and 31 December 2006.

2.2. Information from registers

The data set consists of information linked together from different registers. The Danish Substance Abuse Treatment Register (Danish National Board of Health, 2006) was used to identify persons in treatment for different substance use disorders. The register was established in 1996 in order to supervise patterns of substance use and treatment of substance use disorders. It contains information on all individuals receiving treatment in publically funded institutions. There are very few privately funded substance use treatment institutions in Denmark, except for alcohol use disorders. As the present study is about illicit substance use disorders, this means that practically all persons in treatment are included. The substance users are registered with one primary substance used, while it is possible to be registered with numerous secondary drugs. If a primary substance cannot be determined (e.g. because of no preference for a particular substance) the person is registered with 'no main substance'. For both primary and additional substances information on frequency of use in the month prior to treatment start is registered. At the start of treatment, the substance user is asked about lifetime injection drug use and whether syringes have been shared at any point previously. There is no information on sharing of other paraphernalia such as spoons or filters. The term 'substance use disorder' is used throughout the text even though it is not clear whether the participants fulfilled formal diagnostic criteria according to the International Classification of Diseases, Tenth revision (ICD-10) (World Health Organization, 1992). However, it is assumed that they suffered from substance use disorders since they sought treatment in order to cease the use of an illicit substance.

The Danish Psychiatric Case Register (Munk-Jørgensen and Mortensen, 1997) was used to locate the clients who had received psychiatric treatment before they entered substance use treatment. It contains information on all admissions to Danish psychiatric hospitals and departments since 1970. From 1995, information on outpatient visits to psychiatric departments was also included. Diagnosis codes from the International Classification of Diseases, Eighth Revision (ICD-8) (World Health Organization, 1971) were used until 1993 when the ICD-10 was introduced. In this study, the large majority (83.7%) of registrations was based on ICD-10 criteria. During the study period there were no private psychiatric inpatient or hospital based outpatient facilities in Denmark and there was equal access to treatment. The register therefore captures all psychiatric treatment provided by hospitals and outpatient clinics in Denmark. All main, subsidiary, and additional diagnoses can be retrieved. Registrations of psychiatric treatment were used as a proxy measure of 'psychiatric comorbidity', the term used throughout the text, although only information on psychiatric problems requiring treatment is included. A person was identified as having a comorbid psychiatric disorder if any diagnosis had been given for the disorder at any point of time, as either outpatient or inpatient, before treatment for a substance use disorder. Each person was entered only once into the analyses on psychiatric comorbidity. In case of more than one registration for psychiatric treatment, the more severe diagnosis was determined based on the following hierarchy: schizophrenia spectrum disorder (ICD-10: F20, F21, or F25), affective disorder, and personality disorder. Because of a low number of registrations, bipolar disorder was not included in the analyses.

The Danish Civil Registration System (Pedersen et al., 2006), established in 1968, includes all persons alive and residing in Denmark. Among other variables, it contains information on Civil Registration System number and continuously updated information on vital status. The Civil Registration System number is used as a personal identifier in all national registers enabling accurate linkage between the registers used in the study.

Expected mortality rates from the Danish population were retrieved from a public register run by Statistics Denmark (Statistics Denmark, 2009).

The study was approved by the Danish Data Protection Agency.

2.3. Data analysis

Standardized mortality ratios (SMRs) were calculated by dividing the observed number of deaths following the first day of the first registered treatment episode for substance use disorders with the expected number of deaths based on data from the background population. Data on mortality in the general population were available for one-year age strata. Standardized mortality ratios were stratified for gender since mortality rates differ substantially between young men and young women in the general Danish population and because there was a substantially higher number of males compared with females in the sample. The total SMRs, as well as SMRs concerning injection drug use and psychiatric comorbidity, were adjusted for gender differences. Cox-regression analyses were performed in order to establish hazard ratios associated with injection drug use and psychiatric comorbidity. These analyses were adjusted for age and gender, and time at risk was calculated from the first day of the first registered treatment episode and until either death or emigration (annual rates between 0.7 and 0.8% in the period 1996–2006 (Statistics Denmark, 2009)), or 31 December 2006. Injection drug use was treated as a time dependent variable and information from the substance abuse treatment register was used to determine whether injection drug use developed during follow-up. The assumption of proportional hazards was met for all these analyses. For all SMRs and hazard ratios, 95% confidence intervals (CIs) were calculated. Stata statistical software was used for all analyses (Stata Corp, 2007).

3. Results

At the time of first treatment contact for illicit substance use disorders, the mean age among the 20,581 individuals was 29 years (median: 28 years, 25 percentile: 22 years; 75 percentile: 35 years), 76% were males, 73% were single, 78% had no children, 8% did not have a permanent address, and 71% had no education beyond elementary school. Only 14% were currently employed whereas the remainder lived on subsidies from the state.

The number of persons listed with different primary substances used is evident from Table 1. Use of illicit substances, aside from the main substance used, in the month before treatment start was reported by 33% of cannabis users, 52% of cocaine/amphetamine users, 66% of heroin users, and 59% of other opioid users.

Table 1
Deaths per 1000 person-years and standardized mortality ratios (SMRs) among 20,581 persons with substance use disorders.

Primary substance	N	Deaths	Deaths per 1000 person-years [95% CI]			SMR[a] [95% CI]		
			Males	Females	Total	Males	Females	Total
Cannabis	6445	142	5.7 [4.8–6.8]	4.0 [2.6–6.1]	5.3 [4.5–6.3]	4.8 [4.0–5.7]	5.9 [3.9–9.1]	4.9 [4.2–5.8]
Cocaine	838	18	6.6 [3.8–11.4]	8.2 [3.4–19.8]	7.0 [4.4–11.1]	5.2 [3.0–9.0]	16.3 [6.8–39.2]	6.4 [3.9–10.0]
Amphetamine	1553	33	6.6 [4.6–9.6]	2.7 [1.1–6.4]	5.4 [3.8–7.6]	6.0 [4.2–8.7]	5.8 [2.4–13.9]	6.0 [4.2–8.3]
Ecstasy	295	2	1.4 [0.2–10.3]	2.2 [0.3–15.7]	1.7 [0.4–7.0]	1.7 [0.2–12.3]	6.7 [0.9–47.2]	2.7 [0.5–9.1]
Heroin	6666	778	18.0 [16.7–19.5]	13.2 [11.2–15.6]	16.9 [15.8–18.2]	8.7 [8.0–9.4]	12.2 [10.3–14.4]	9.1 [8.5–9.8]
Other opioids[b]	1330	164	23.1 [19.2–27.9]	19.7 [15.0–25.8]	21.9 [18.8–25.5]	7.3 [6.1–8.8]	8.7 [6.6–11.3]	7.7 [6.6–8.9]
No main substance	3454	304	15.9 [14.0–18.0]	9.5 [7.4–12.3]	14.1 [12.6–15.7]	7.7 [6.8–8.8]	7.0 [5.4–9.1]	7.6 [6.8–8.5]
Total	20,581	1441	13.8 [13.0–14.6]	10.3 [9.2–11.5]	12.9 [12.3–13.6]	7.5 [7.1–8.0]	9.2 [8.2–10.3]	7.8 [7.4–8.2]

[a] Standardized with respect to age distribution in the Danish population for males and females separately (e.g. SMRs for male users reflect mortality compared with males of comparable age in the background population).
[b] Other opioids includes illegally acquired opioids such as morphine, methadone, and buprenorphine.

3.1. Overall mortality

The mean follow-up time was 5.4 years (median: 5.0, 25 percentile: 2.5, 75 percentile: 8.4) and the total number of person-years equaled 111,445. During follow-up 1441 deaths were registered. Table 1 displays the number of deaths per 1000 person-years at risk as well as the overall and gender stratified SMRs. Mortality rates were significantly elevated for all substances, except MDMA, for both genders compared with the background population. Gender comparisons revealed that the number of deaths per 1000 person-years at risk was highest for males and specifically for male heroin users, while gender stratified SMRs were highest for females and specifically for female heroin users.

3.2. Injection drug use

The consequences of lifetime injection drug use were further evaluated. Separate analyses were made for opioids (heroin or 'other opioids'), and cocaine/amphetamine collapsed into one group. In total, 25.7% of cocaine/amphetamine users and 68.3% of opioid users reported lifetime injection drug use. Among injectors, opioid users were more likely to have shared syringes at some point compared with cocaine/amphetamine users (49.8% vs. 23.2%, $\chi^2 = 124.5$, $p < .001$). For opioid users the SMR associated with no injection drug use was 6.3 (95% CI: 5.2–7.6), those who had injected without sharing syringes 9.5 (95% CI: 8.3–10.9), and for those who had shared syringes 10.3 (95% CI: 9.1–11.6). For cocaine/amphetamine the corresponding SMRs were: never injection drug use: 2.5 (95% CI: 1.2–4.6), injected but never shared syringes: 6.1 (95% CI 3.2–10.6), and shared syringes: 15.6 (95% CI: 8.9–25.5). Hazard ratios, adjusted for age and gender, were calculated with no injection drug use as reference. For opioid users with lifetime injection drug use who had not shared syringes the hazard ratio was 1.3 (95% CI: 1.0–1.7, $p = .02$), while the hazard ratio among those who had shared syringes was 1.5 (95% CI: 1.2–1.8, $p = .002$). For cocaine/amphetamine the corresponding hazard ratios were 2.5 (95% CI: 1.0–6.1, $p = .04$) and 6.8 (95% CI: 2.8–16.4, $p < .001$).

3.3. Psychiatric comorbidity

Table 2 includes SMRs for different types of psychiatric comorbidity in various substance use disorders standardized with respect to age and gender. Bipolar disorder is not included in the table because of few deaths among subjects with this comorbidity. Overall, the table shows that psychiatric comorbidity was not associated with elevated SMRs. However, in primary cocaine/amphetamine users any comorbid psychiatric disorder resulted in an adjusted hazard ratio of 3.6 (95% CI: 2.1–6.4, $p < .001$) compared with no comorbid psychiatric disorder. No significant associations were observed in primary cannabis, heroin and other opioid users, or in those with no main substance used.

4. Discussion

In this section we will summarize and discuss the main results with an emphasis on the findings with the least amount of evidence from previously published investigations.

4.1. Mortality for different substances

A primary cannabis use disorder was associated with a five-fold increase in mortality. Although this is a slightly smaller SMR

Table 2
Deaths per 1000 person-years, standardized mortality ratios (SMRs) and hazard ratios (HR) according to psychiatric comorbidity.

	Deaths per 1000 person-years/SMR[a] [95% confidence interval (CI)]					HR[b] [95% CI]
	No comorbid psychiatric disorder	Comorbid schizophrenia-spectrum disorder	Comorbid affective disorder[c]	Comorbid personality disorder	Any comorbid psychiatric disorder[d]	'No' vs. 'Any' comorbid psychiatric disorder
Cannabis	5.5/4.7 [4.0–5.7]	2.4/1.8 [0.5–7.2]	3.4/2.4 [1.0–5.8]	5.8/4.3 [2.5–7.2]	4.5/3.2 [2.1–5.0]	0.7 [0.4–1.1], $p = .15$
Cocaine/amphetamine	4.0/3.6 [2.5–5.2]	11.0/9.5 [3.1–29.6]	13.1/10.2 [4.3–24.5]	18.9/16.3 [9.6–27.5]	15.8/13.1 [8.6–20.0]	3.6 [2.1–6.4], $p < .001$
Heroin	16.3/8.1 [7.5–8.8]	20.5/11.3 [7.5–17.0]	12.4/6.0 [3.7–9.6]	24.4/10.1 [8.1–12.6]	21.0/9.3 [7.8–11.1]	1.2 [1.0–1.5], $p = .06$
Other opioids	21.0/6.5 [5.5–7.7]	31.4/10.6 [4.0–28.3]	13.5/3.4 [1.1–10.7]	29.2/7.7 [5.2–11.3]	26.6/7.1 [5.0–9.9]	1.2 [0.8–1.7], $p = .44$
No main subst.	14.2/7.0 [6.2–7.9]	12.1/6.6 [3.1–13.8]	14.7/5.7 [3.0–11.0]	13.1/4.8 [3.3–7.0]	13.2/5.2 [3.8–7.0]	0.9 [0.6–1.2], $p = .47$
Total	12.8/7.0 [6.6–7.4]	13.3/7.9 [5.7–10.8]	9.6/4.9 [3.6–6.7]	17.2/7.6 [6.5–8.8]	14.6/7.0 [6.1–7.9]	1.1 [0.9–1.2], $p = .28$

[a] Standardized with respect to age and gender.
[b] Adjusted for age and gender.
[c] Excluding bipolar disorder.
[d] Excluding all substance use disorders (ICD-10: F10.x–F19.x).

than what was found for cocaine/amphetamine or opioids it is noteworthy. Only one previous study has reported SMRs for primary cannabis users. Wahren et al. (1997) found estimates of 8.0 and 7.4 in two Swedish cohorts from 1971 to 1972 and 1981 to 1982. However, the Swedish study involved just 16 deaths among cannabis users and it concerned only users who had been hospitalized for psychiatric disorders or somatic illnesses. Other studies have reported on deaths associated with cannabis use rather than cannabis use disorders. Sidney et al. (1997) found that cannabis use was associated with increased risk of AIDS-related mortality in men, but failed to demonstrate other effects, and the study was about rather infrequent users ('high use' defined as lifetime use on more than six occasions). Andreasson and Allebeck (1990) found a relative risk of death among high consumers of cannabis (use on more than 50 occasions) of 2.8, but the association disappeared following adjustment for social background variables.

Although some case evidence about cannabis and cardiovascular fatalities has been published (Bachs and Morland, 2001; Mukamal et al., 2008) deaths resulting from overdose due to cannabis alone are very unlikely. Instead the increased mortality found in the present study could be the result of a higher propensity to road accidents (Eksborg and Rajs, 2008; Macdonald et al., 2003), intentional/violent injuries or homicides (Darke and Duflou, 2008; Macdonald et al., 2003), and various other types of accidents or injuries associated with cannabis use.

Another possibility is that secondary use of other substances explains some of the excess mortality. Thirty-three percent of the primary cannabis users had a history of comorbid use of either illicit stimulants or opioids in the month before entering treatment. Similarly, while cannabis is unlikely to be the sole substance used in cases of fatal overdose, the substance is often found along with other drugs in such cases (Darke and Duflou, 2008; Gueye et al., 2002; Shields et al., 2007). For example, a post mortem study from the Nordic countries reported that cannabis was detected in between one-fourth and one-third of the cases (Steentoft et al., 2006).

It was found that primary users of both cocaine and amphetamine have approximately six times higher death rates compared with individuals from the general population of same age. There is comparably less knowledge about the excess mortality among persons in treatment for illicit stimulant use disorders. Most publications involve few individuals or report on poly-drug users without specific estimates for illicit stimulants. Pavarin (2008) found a SMR of 4.8 among Italian male cocaine users, while no fatalities were observed among females. This estimate is similar to the finding of the current study. Wahren et al. (1997) reported SMRs of 9.6 and 10.0 among primary stimulant users, and Ribeiro et al. (2007) found an SMR of 7.6 in a sample of Brazilian users of crack cocaine. However, both studies deal with subjects who had been hospitalized and the results might therefore not generalize to outpatient substance use treatment, which is the most common for these disorders (Knapp et al., 2007). A study from Thailand reported a SMR of 4.4 among non-injecting drug users of whom 56.4% used amphetamines, and a crude mortality rate of 24.1 pr. 1000 person-years among non-injecting amphetamine users (Quan et al., 2007). Previous studies have documented that the excess mortality among illicit stimulant users is likely to result from several contributing factors such as overdose, cardiovascular disorders, HIV/AIDS and other physical conditions, injuries, homicide/violent deaths, and suicide (Degenhardt et al., 2005a; Joe et al., 1982; Macdonald et al., 2003; Mesquita et al., 2001; Pavarin, 2008; Ribeiro et al., 2007; Westover et al., 2007).

Primary use of MDMA was relatively rare, which is in accordance with other studies (Degenhardt et al., 2005b; Rogers et al., 2009; Schifano, 2004). Primary MDMA use was associated with a crude all-cause mortality ratio of 1.7/1000 person-years. The SMRs were not significantly elevated compared with the background population, possibly due to lack of statistical power resulting from few deaths in this group. While a number of post mortem studies exist, we located no previous studies reporting comparable mortality rates in primary MDMA users.

The overall estimates of excess mortality in primary opioid users are comparable to most previously published investigations (Bargagli et al., 2006; Colon et al., 2006; Davoli et al., 2007; Hickman et al., 2003; Oppenheimer et al., 1994; Perucci et al., 1991; Quaglio et al., 2001; Quan et al., 2007; Sanchez-Carbonell and Seus, 2000; Vlahov et al., 2004). A meta-analysis by Hulse et al. (1999) reported a pooled SMR estimate of 13.2 (95% CI: 12.3–14.1) which is significantly higher but close to our findings.

4.2. Injection drug use

Mortality was significantly increased among lifetime injection drug users. Some studies have reported similar results (Gossop et al., 1996; Quan et al., 2007; Ribeiro et al., 2007), but the findings are in contrast to other research papers on both opioid and cocaine/amphetamine users where no association between injection drug use and mortality has been demonstrated (Colon et al., 2006; Gossop et al., 2002; Hickman et al., 2003; Hser et al., 2006; Joe et al., 1982; Johnson et al., 2005; Sanchez-Carbonell and Seus, 2000). One study has inquired about sharing of syringes but found no association with increased mortality (Gossop et al., 2002). Other studies suggest that injection drug use could be associated with increased mortality, for example by showing a high risk of overdose related to this mode of administration (Swift et al., 1999; Sherman et al., 2007) and a very high rate of injection drug use prior to substance-related fatalities (Darke et al., 2000, 2005). In general, however, there is limited direct evidence from prospective studies of risks associated with injection drug use in relation to mortality, especially among primary cocaine/amphetamine users. This emphasizes the importance of the association with excess mortality observed in the present study. The results show that this is an important issue to address in treatment and prevention as well as in studies on predictors of mortality in substance use populations.

4.3. Psychiatric comorbidity

The presence of comorbid psychiatric disorder was not associated with increased SMRs except for primary users of cocaine/amphetamine. These findings are noteworthy, since there are almost no publications on the significance of psychiatric comorbidity in relation to excess mortality among illicit substance users.

The overall lack of significance of psychiatric comorbidity is consistent with findings from two other studies (Bauer et al., 2008; Colon et al., 2006). Some associations have been published but the strength is generally limited and the existing studies typically assess only one specific type of symptoms (Bartu et al., 2004; Gossop et al., 2002; Johnson et al., 2005; Ravndal and Vaglum, 1998). Also, no data exist for many substances. While there is limited literature from substance use treatment studies, there are several studies on comorbid substance use among individuals with primary psychiatric disorders. Generally, excess mortality has been reported in these investigations (e.g. Rosen et al., 2008; Zivin et al., 2007).

The finding that cocaine/amphetamine users with psychiatric comorbidity have a hazard ratio of 3.6, compared to those without, is interesting. This result indicates that either use of these substances is especially harmful for individuals with psychiatric disorders, or that use of stimulants could lead to psychiatric disorders resulting in excess mortality. It could also be a chance finding due to the relatively large number of statistical tests. The exact

nature of the association should be further investigated in future studies.

4.4. Limitations

The study is about treatment seekers, and this could result in higher estimates of excess mortality than would be found among individuals with substance use disorders in the general population. Conversely, the estimates could be attenuated due to protective effects of treatment. Caution is therefore warranted in extrapolating results outside treatment contexts. On the other hand, it is very important to know the SMRs for individuals in treatment, because specific risk factors can be addressed directly in such settings, e.g. injection drug use, the sharing of syringes, and psychiatric comorbidity.

As noted above the SMRs concerning opioids and stimulants are consistent with studies from other countries. This indicates that findings on mortality associated with cannabis use, stimulant use, injection drug use and psychiatric comorbidity could generalize to other cultural settings. Conversely, demographic variation as well as differences in public support systems should be taken into account.

Another limitation is the lack of control for other potential variables associated with both substance dependence and excess mortality (e.g. unhealthy lifestyle, risk seeking behavior, low socioeconomic status). It is probable that some of the increased death risk results from these factors rather than substance use per se.

The extent of secondary substance use was high and the results on mortality associated with primary substances should be interpreted with caution. Also, development of new, and potentially more harmful, substance use over the follow-up period is likely. For example, using the same registers as in the present study we have previously reported that 10.4% in treatment for cannabis use disorders received treatment for primary opioid use disorders at a later point of time (Arendt et al., 2007). Thus, the excess mortality among primary cannabis users could result from opioid dependence developing over the follow-up period. On the other hand, it could be argued that use of more than one illicit substance reflects the reality of substance use disorders. Consistent with this, post mortem studies have detected more than one substance in the majority of individuals who die from substance use disorders (Coffin et al., 2003; Gueye et al., 2002; Hickman et al., 2007; Shah et al., 2008; Shields et al., 2007).

It is likely that the lack of specific effects from psychiatric comorbidity can be attributed to a small number of deaths for specific substances and sufferers of specific disorders, as evidenced by the wide confidence intervals in some of the cells in Table 2. This potential lack of statistical power is a limitation of these results. Also, the analyses are based on individuals who had received psychiatric treatment and caution is warranted in generalizing to the general population.

A relatively high number of statistical tests were performed resulting in risk of type-I error. We chose not to adjust for this, and this should be taken into account in the interpretation of the results.

4.5. Implications

The high level of excess mortality among cannabis and stimulant users is important. The reasons behind the findings should be the focus of future investigations. In light of the widespread use of cannabis and stimulants, it is important to determine whether use of the substances in itself is the cause or whether it is explained by other factors (e.g. increased risk of other drug use, socioeconomic variables). Similarly, the causes of death should be further explored. Specifically, the consequences of injection drug use and sharing of syringes in stimulant users should be investigated. Most of the findings concerning psychiatric comorbidity in relation to mortality were negative. There is a paucity of studies on comorbid psychiatric disorders in illicit substance users and these surprising findings need further attention.

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