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Mortality following treatment for cannabis use disorders: Predictors and causes

Mikkel Arendt, MSc, PhD [a,b,*], Povl Munk-Jørgensen, DMSc [a], Leo Sher, MD [b], Signe Olrik Wallenstein Jensen, MSc [a]

[a] Unit for Psychiatric Research, Aalborg Psychiatric Hospital, Aarhus University Hospital, Mølleparkvej 10, 9100 Aalborg, Denmark
[b] Department of Psychiatry, Division of Molecular Imaging and Neuropathology, Columbia University and New York State Psychiatric Institute, New York, NY 10032, USA

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ABSTRACT

The aim of the study was to determine excess mortality associated with cannabis use disorders. Individuals entering treatment for cannabis use disorders were followed by use of Danish registers and standardized mortality ratios (SMRs) estimated. Predictors of different causes of death were determined. A total of 6445 individuals were included and 142 deaths recorded during 26,584 person-years of follow-up. Mortality was predicted by age, comorbid use of opioids, and lifetime injection drug use. For different causes of death the SMRs were: accidents: 8.2 (95% CI 6.3–10.5), suicide: 5.3 (95% CI 3.3–7.9), homicide/violence: 3.8 (95% CI 1.5–7.9), and natural causes: 2.8 (95% CI 2.0–3.7). Following exclusion of those with secondary use of opioids, cocaine, amphetamine, or injection drug use, SMRs for all causes of death remained significantly elevated except for homicide/violence. The study underlines the need to address mortality risk associated with cannabis use disorders.

1. Introduction

Cannabis is the most frequently used illicit substance in the world with lifetime use reported by almost half of young adults (15–34 years) in the United States, Australia, and Canada, and 32% in the European Union (European Monitoring Centre for Drugs, Drug Addiction (EMCDDA) [EMCDDA], 2011; Substance Abuse and Mental Health Services Administration (SAMHSA) (SAMHSA), 2008). It is estimated that 9% of those who use cannabis become dependent (Anthony, Warner, & Kessler, 1994). Among people seeking substance abuse treatment for the first time in Europe, the proportion of those who reported cannabis as the main problem increased by 40% between 2004 and 2009 (EMCDDA, 2011). Cannabis is now the second most common illicit substance of abuse among citizens of European Union countries seeking substance abuse treatment and 23% of the total number receiving treatment in the European Union report cannabis as primary substance of abuse (EMCDDA, 2011). A similar development has taken place in the United States where treatment admissions for cannabis use disorders more than doubled between 1993 and 2005 (Budney, Roffman, Stephens, & Walker, 2007).

In spite of these facts, little is known about mortality among individuals with cannabis use disorders. Standardized mortality ratios (SMRs) associated with heavy cannabis use have been reported in two cohort studies (Arendt, Munk-Jorgensen, Sher, & Jensen, 2011; Wahren, Brandt, & Allebeck, 1997). In a previous study we found an estimate of 4.9 among cannabis users following substance abuse treatment (Arendt et al., 2011). Even higher SMRs of 7.4 and 8.0 were reported in a Swedish study concerning two cohorts of hospitalized patients (Wahren et al., 1997). However, the reasons for the high level of excess mortality are not clear. Two population-based prospective studies have investigated if baseline cannabis use is associated with subsequent increased all-cause mortality (Andreasson & Allebeck, 1990; Sidney, Beck, Tekawa, Quesenberry, & Friedman, 1997). Crude effects were observed but following adjustment for residual confounding these effects disappeared. However, both studies concern relatively infrequent cannabis users (lifetime use on more than 6 occasions in Sidney et al., 1997 and more than 50 times in Andreasson & Allebeck, 1990). No longitudinal studies have investigated predictors of all-cause mortality among individuals with heavier cannabis use or suffering from cannabis use disorders.

A number of studies are concerned with specific causes of death among cannabis users. Cannabis has been linked with increased risk of road accidents and other accidents (Calabria, Degenhardt, Hall, & Lynskey, 2010; Darke & Duflou, 2008; Eksborg & Rajs, 2008; Gerberich et al., 2003; Laumon, Gadegbeku, Martin, & Biecheler, 2005; Macdonald et al., 2003) and is often detected in homicide victims (Darke & Duflou, 2008; Macdonald et al., 2003). The substance has also been associated with affective disorders as well as suicide attempts, suicidal ideation, and completed suicide (Beautrais, Joyce, & Mulder, 1999; Chabrol, Chauchard, & Girabet, 2008; Huas, Hassler, & Choquet, 2008; Lynskey et al., 2004; Price, Hemmingsson, Lewis, Zammit, & Allebeck, 2009). While the risk of death from overdose is

* Corresponding author. Tel.: +45 72137227; fax: +45 72137235.
E-mail address: mikkaren@rm.dk (M. Arendt).

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generally considered very low (Kalant, 2004), studies have also suggested that cannabis could lead to cardiovascular fatality (Bachs & Morland, 2001) or non-cardiovascular mortality following myocardial infarction (Mukamal, Maclure, Muller, & Mittleman, 2008). Finally, some studies have looked into the risk of cancer, but results have been inconclusive (Calabria et al., 2010; Chen et al., 2008; Hall, Christie, & Currow, 2005; Hashibe et al., 2005; Mehra, Moore, Crothers, Tetrault, & Fiellin, 2006). However, the literature that exists on specific causes of death among cannabis users is predominantly cross-sectional and knowledge is particularly sparse in relation to heavy cannabis use/individuals with cannabis use disorders.

We performed a longitudinal follow-up study including all individuals in treatment for cannabis use disorders in Denmark from 1996 onwards by using nationwide registers for substance use disorders, psychiatric disorders, and causes of death. The following research questions were addressed:

1. Which factors are associated with increased hazards of mortality?
2. What are the SMRs for specific causes of death?

2. Material and methods

2.1. Study population

The sample consists of 6445 persons who received treatment for cannabis use disorders in all specialized institutions for substance use disorders in Denmark between January 1 1996 and December 31 2006.

2.2. Information from registers

The Danish Substance Abuse Treatment Register (Danish Health and Medicines Authority, 2006) was used to identify persons in treatment for cannabis use disorders. Further information on vital status, causes of death and psychiatric treatment was retrieved for all of those who had received such treatment. The linkage was based on the Civil Registration System number for each of the cannabis users. Standardized mortality ratios were established by comparing with mortality statistics from the general Danish population.

The Danish Substance Abuse Treatment Register was established in 1996 and it contains information on all individuals receiving treatment for substance use disorders in publicly funded institutions. There are only few privately operated substance abuse treatment institutions in Denmark except for alcohol use disorders. Since the present study is concerned with cannabis use disorders, this means that practically all treatment is covered. The register contains demographic as well as substance related information. The substance users are registered with one primary substance of abuse while it is possible to have numerous secondary drugs of abuse. Unfortunately, alcohol misuse is not included among the secondary drugs of abuse. It is possible to be registered with 'no main substance' in case of simultaneous use of several substances making it impossible to determine a primary substance. Regrettably, all substance use is only registered for the month before treatment entry. The variable 'injection drug use' is available for lifetime before treatment. Those who reported cannabis as primary substance of abuse were selected for the present study. Finally, the register specifies whether treatment was successfully completed or terminated for other reasons. The term 'cannabis use disorder' is used even though it could not be determined that the participants fulfilled formal diagnostic criteria. However, it is assumed that they suffered from such disorders since they received treatment in order to cease the use of cannabis.

The Danish Register of Causes of Death was used to identify deaths following substance abuse treatment. The register contains information on dates and causes of deaths for all Danish citizens (Helweg-Larsen, 2011). For each registration, it distinguishes between overall cause of death and specific causes of death. Overall cause of death is recorded in five categories: natural cause, accident, suicide, homicide/violence, and other. Accident, suicide and homicide/violence are considered unnatural causes, while the 'other' category is used in cases where it cannot be determined whether the death was natural or unnatural (Danish Health and Medicines Authority, 2008a). Aside from this there are *ICD-10* codes for further specification of the clinical cause of events leading to death. This article only contains data on the overall cause of death and not the specific *ICD-10* codes. Registrations ended on December 31, 2006 (Danish Health and Medicines Authority, 2008b). The Danish Civil Registration system was used to identify subjects who died after this date, but causes of death are not available for these individuals.

The Danish Civil Registration System (Pedersen, Gøtzsche, Møller, & Mortensen, 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. Each Danish citizen is ascribed a unique Civil Registration System number and this is used as a personal identifier in all national registers, thus enabling accurate linkage between the registers used in the study.

The Danish Psychiatric Case Register, established in 1967, (Munk-Jorgensen & Mortensen, 1997) was used to investigate the potential role of comorbid psychiatric disorders in relation to mortality. Those who had received treatment for any psychiatric disorder, excluding substance use disorders, were compared to those who had not. For further description of the register see Arendt, Rosenberg, Foldager, Perto, and Munk-Jorgensen (2007).

Mortality rates from the general 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 (SMR) were calculated by dividing observed rates of different causes of death with expected rates in age and gender stratified individuals from the background population. Data on the background population were available for 1-year age strata, for different causes of mortality, and for males and females separately.

A number of sociodemographic and substance related variables were assessed at baseline. Hazard ratios (HR) of all-cause mortality during follow-up were determined for each variable separately by use of Cox proportional hazards regression analyses. Variables significantly associated with all-cause mortality in univariate analyses were entered into a multivariate Cox proportional hazards regression model and adjusted estimates reported. Variables predicting each of the different causes of death were similarly determined by use of Cox proportional hazards analyses. All variables were entered with backward selection and adjusted hazard ratios for variables significantly associated with each outcome are reported.

In all analyses, time at risk was calculated from the first day of the first registered treatment episode and until either death, emigration, or December 31, 2006. For all SMRs and hazard ratios, 95% confidence intervals (CI) were calculated. Stata statistical software was used for all analyses (Stata Corp, 2007).

3. Results

3.1. Sample characteristics

The study population of 6445 individuals in treatment for cannabis use disorders were followed for 4.1 years on average (median = 3.4; 25 percentile = 1.7; 75 percentile = 6.1 years). At the time of first treatment contact the mean age was 26 years (median = 24; 25 percentile = 20; 75 percentile = 30 years). As

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evident from Table 1, the sample predominantly consisted of males, born in Denmark, with a low level of education, without children, and living alone. Many users reentered treatment over the follow-up period and the mean number of treatment courses after index was 1.4 (standard deviation: 2.9).

Table 2 includes information related to substance use and treatment. Cocaine or amphetamine had been used by 26%, and opioids by 6%, in the month before entering treatment. Twenty-four percent reported any lifetime injection drug use. Most received outpatient treatment (90%) for their cannabis use disorder and 15% had received treatment for a psychiatric disorder either before or after receiving substance abuse treatment.

3.2. Predictors of all-cause mortality

One hundred forty-two deaths were recorded over 26,584 person-years of observation. It was determined whether specific socio-demographic factors, as well as variables related to substance use and treatment, assessed at baseline, were associated with all-cause mortality during follow-up. Univariate analyses showed that age, comorbid use of opioids, and lifetime injection drug use were associated with higher hazards of all-cause mortality (see Tables 1 and 2). No differences were observed for gender, immigrant status, level of education, having children, partner status, age at first cannabis use, cocaine/amphetamine use, inpatient/outpatient treatment, successful completion of treatment, or history of psychiatric treatment.

Next, significant variables from the univariate analyses were included in a multivariate analysis, and adjusted hazard ratios estimated. The strongest effect on all-cause mortality was observed for opioid use in the month prior to treatment start (adjusted hazard ratio: 2.34, 95% CI 1.51–3.64, $p<.001$). Lifetime injection drug use (adjusted hazard ratio: 1.45, 95% CI 1.02–2.07, $p<.001$) and higher age (adjusted hazard ratio: 1.05, 95% CI 1.03–1.07, $p<.001$) were also significantly associated with all-cause mortality.

3.3. Causes of death

Excess mortality for different causes of death was estimated by comparing cannabis users with individuals from the general population of same age and gender. These standardized mortality ratios are included in Table 3 along with crude death rates. The most common reason for death within the sample was accidents. Compared with age and gender stratified rates from the general population this was also the specific cause of death with highest excess mortality (SMR: 8.2, 95% CI: 6.3–10.5). Suicide occurred approximately five times more frequently compared with the background population, while homicide occurred approximately four times as often. Death from natural causes, including all diseases, was three times more common.

All baseline variables (age, gender, immigrant status, education, children, living with partner, age at first cannabis use, opioid use in the month prior to treatment start, cocaine/amphetamine use in the month prior to treatment start, lifetime IV use, treated as inpatient, successfully completed treatment, and psychiatric comorbidity) were entered backwards into Cox proportional hazard models as predictors of each of the specific causes of death included in Table 3 (accidents, suicide, homicide/violence, and natural causes). These four analyses revealed that death from accidents was predicted by opioid use (adjusted hazard ratio: 4.0, 95% CI 2.2–7.5, $p<.001$), homicide/violence was predicted by opioid use (adjusted hazard ratio: 24.6, 95% CI 4.5–134.6, $p<.001$), death from natural causes was predicted by higher age (adjusted hazard ratio 1.13, 95% CI 1.10–1.17, $p<.001$), while suicide was not predicted by any of the variables. All other variables were not associated with any of the specific causes of death.

Because of the clear association between co-morbid substance use and mortality, SMRs for each specific cause of death were calculated for individuals who reported no use of opioids or stimulants in the month before entering treatment and no lifetime injection drug use (see Table 3). The SMR for homicide/violence was no longer significantly elevated and the estimate for accidents lower, while the remaining estimates were largely unaffected.

3.4. Time of death in relation to treatment

Standardized mortality ratios for specific time intervals following the beginning and end of treatment were calculated. Table 4 shows that the SMRs were particularly high in the 2 weeks following treatment start. Four deaths were recorded within this time-frame.

Table 1
Hazards for all-cause mortality in 6445 individuals treated for cannabis use disorders.

Characteristic	% of sample	No. of deaths	Person-years	Mortality rate deaths/1000 person-years [95% CI]	Unadjusted hazard ratio [95% CI]
Age					1.06 [1.04–1.08]
Gender					
Female	20	21	5269	4.0 [2.6–6.1]	1
Male	80	121	21,315	5.7 [4.8–6.8]	1.43 [0.90–2.27]
Immigrant status					
Non-immigrant	96	117	22,631	5.2 [4.3–6.2]	1
Immigrant	4	4	821	4.9 [1.8–13.0]	0.91 [0.34–2.46]
Education					
Medium/long education	3	3	571	5.3 [1.7–16.3]	1
Short education	25	32	5827	5.5 [3.9–7.8]	1.06 [0.33–3.48]
Elementary school only	73	82	17,616	4.7 [3.8–5.8]	0.89 [0.28–2.81]
Children					
Yes	13	21	3682	5.7 [3.7–8.8]	1
No	87	113	21,864	5.2 [4.3–6.2]	0.93 [0.58–1.47]
Living with partner					
Yes	20	22	5453	4.0 [2.7–6.1]	1
No	80	112	20,074	5.6 [4.6–6.7]	1.38 [0.88–2.18]

Table 2
Substance use and treatment related variables associated with mortality in 6445 individuals treated for cannabis use disorders.

Characteristic	%	No. of deaths	Person-years	Mortality rate deaths/1000 person-years [95% CI]	Unadjusted hazard ratio [95% CI]
Age at first use of cannabis					
16 or more	35	41	8088	5.1 [3.7–6.9]	1
13–15 years	52	52	11,162	4.7 [3.6–6.1]	0.92 [0.61–1.38]
<13 years	13	19	3051	6.2 [4.0–9.8]	1.23 [0.71–2.12]
Opioid use[a]					
No	94	117	24,674	4.7 [4.0–5.7]	1
Yes	6	25	1910	13.1 [8.9–19.4]	2.76 [1.79–4.26]
Cocaine/amphetamine use[a]					
No	74	103	19,790	5.2 [4.3–6.3]	1
Yes	26	39	6794	5.7 [4.2–7.9]	1.10 [0.76–1.59]
Ever injected drugs					
No	76	59	14,005	4.2 [3.3–5.4]	1
Yes	24	48	6238	7.7 [5.8–10.2]	1.67 [1.18–2.37]
Treated as inpatient					
No	90	82	15,651	5.2 [4.2–6.5]	1
Yes	10	16	2305	6.1 [3.6–10.3]	1.19 [0.67–2.13]
Successfully completed treatment					
Yes	35	19	4833	3.9 [2.5–6.2]	1
No	65	44	8916	4.9 [3.7–6.6]	1.27 [0.74–2.17]
Psychiatric comorbidity[b]					
No	85	86	18,877	4.6 [3.7–5.6]	1
Yes–prior to treatment	11	10	2410	4.1 [2.2–7.7]	0.66 [0.34–1.29]
Yes–following treatment	4	7	1649	4.2 [2.0–8.9]	0.96 [0.44–2.08]

[a] In the month before treatment entry.
[b] Excluding treatment for substance use disorders in a psychiatric setting.

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Table 3
Standardized mortality ratios[a] (SMR) for different causes of death following start of treatment for cannabis use disorders.

	Accident	Suicide	Homicide/violence	Natural causes[b]	Other/unknown	Total
Number of deaths	60	21	6	41	14	142
Crude rates deaths per 1000 person-years [95% CI]	2.3 [1.7–2.9]	0.8 [0.5–1.2]	0.2 [0.1–0.5]	1.5 [1.1–2.1]	0.5 [0.5–1.2]	5.3 [4.5–6.3]
SMR [95% CI]	8.2 [6.3–10.5]	5.3 [3.3–7.9]	3.8 [1.5–7.9]	2.8 [2.0–3.7]	12.0 [6.5–20.4]	4.9 [4.2–5.8]
SMR excluding users of opioids, cocaine, amphetamine, or injection drug use [95% CI][c]	5.2 [3.2–8.0]	4.8 [2.4–8.9]	1.4 [0.1–7.1]	3.0 [1.8–4.7]	4.4 [0.7–14.5]	3.9 [2.9–5.1]

[a] Standardized with respect to age and gender.
[b] Covers all diseases.
[c] Opioid, cocaine, and amphetamine use is reported for the month before treatment entry. Injection drug use is reported for lifetime before treatment entry.

Two of the diseased reported lifetime injection drug use and the other two secondary use of amphetamine or cocaine. Following treatment entry, the SMRs were lowest in the time intervals from 2 weeks until the end of the first year. SMRs were not clearly lower in the time period immediately after the end of treatment neither for the entire population nor for the group of users who were terminated following successful treatment.

4. Discussion

This is the first longitudinal study to follow a large nationwide cohort of persons treated for cannabis use disorders in order to establish causes of subsequent death. In this section we will summarize the main findings and discuss them in relation to the existing literature.

4.1. Predictors of all-cause mortality

High age, opioid use, and lifetime IV use were predictors of all-cause mortality during follow-up. The fact that opioid use in the month prior to treatment predicted the hazard of mortality is consistent with the significantly higher mortality rates observed among primary users of opioids (Hulse, English, Milne, & Holman, 1999). However, secondary use of opioids was reported by only 6% in our sample, and even after exclusion of these individuals there was a high level of excess mortality. Whether opioid use developed during follow-up was not assessed, but we have previously reported that 10.4% in treatment for cannabis use disorders received treatment for opioid use disorders at a later point in time (Arendt et al., 2007). All in all, it thus seems reasonable to conclude that comorbid opioid use explained some, but not all, of the excess mortality.

Two cohort studies have reported on the association between cannabis use and all-cause mortality. Both found that cannabis use as well as a number of other baseline variables were highly associated with subsequent death. Andreasson and Allebeck (1990) performed a study on Swedish conscripts and found that lifetime cannabis use over 50 times was associated with a relative risk of 2.8. However, following adjustment for social background variables the association disappeared. Sidney et al. (1997) studied a large cohort enrolled in a medical care program. Lifetime marijuana use on more than six occasions as well as current use were associated with increased AIDS mortality in men, but not with other causes of death. Based on these findings, it is surprising that other variables were not associated with all-cause mortality.

4.2. Overall mortality

Those in treatment for cannabis use disorders were five times more likely to die during follow-up compared with individuals from the general population of same age and gender. Wahren et al. (1997) have previously reported SMRs of 8.0 and 7.4, in two cohorts followed from 1971 to 1972 and from 1981 to 1982, among cannabis users who had been hospitalized for either somatic or psychiatric problems. They did not report on predictors of death or causes of death specifically for cannabis users. The lower estimate in the current study could be explained by the fact that many received outpatient treatment.

4.3. Accidents

We found that accidental death was the most common specific cause of death in absolute numbers and the sample was over eight times more likely to die from this cause compared with age and gender matched individuals from the general population. No other cohort study has explored the significance of cannabis use disorders at baseline for later mortality due to accidents. However, an association between cannabis use and injuries, and especially traffic accidents, has previously been reported (Kalant, 2004; Macdonald et al., 2003; Ramaekers, Berghaus, Van, & Drummer, 2004; Sewell, Poling, & Sofuoglu, 2009). The majority of the existing studies concern drivers involved in crashes who were subsequently tested for the presence of cannabis (Biecheler, Peytavin, Facy, & Martineau, 2008; Brodie, Lyndal, & Elias, 2009; Drummer et al., 2003; Eksborg & Rajs, 2008; Laumon et al., 2005; Mura et al., 2006).

Two retrospective cohort studies have examined associations between baseline cannabis use and subsequent involvement in accidents. Fergusson and Horwood (2001) and Fergusson, Horwood, and Boden (2008) reported data from two separate time points in a follow-up study from New Zealand. In both studies there were links between cannabis use and the risk of being involved in an accident. However, following adjustment for confounders, including use of

Table 4
Standardized mortality ratios (SMR)[a] associated with treatment start and ending.

	≤2 weeks SMR [95%CI]	>2 weeks ≤1 month SMR [95%CI]	>1 month ≤3 months SMR [95%CI]	>3 months ≤1 year SMR [95%CI]	>1 year	Full follow-up SMR [95%CI]
Deaths following treatment start	17.3 [5.5–42.0]	0	3.3 [1.2–7.4]	2.5 [1.5–4.0]	4.9 [4.1–5.9]	4.9 [4.2–5.8]
Deaths following end of treatment	0	3.5 [0.2–17.0]	4.7 [1.5–11.2]	2.9 [1.5–5.2]	4.3 [3.2–5.7]	5.8 [4.4–7.4]
Death following successful end of treatment[b]	0	11.4 [0.6–56.1]	0	3.8 [0.2–18.5]	3.8 [2.1.–6.5]	4.4 [2.5–7.3]

[a] Standardized with respect to age and gender.
[b] Estimates for the 35% of the population who successfully completing treatment.

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alcohol and risk taking behavior, the associations were no longer significant in either study. Gerberich et al. (2003) found that men who were current users of cannabis at baseline were more likely to experience any injury requiring hospitalization, and specifically motor vehicle accidents, assaults, and self-inflicted injury during follow-up. Women who were current users a baseline had higher rates of all-cause injury and self-inflicted injury. However, the studies are all concerned relatively infrequent cannabis users rather than individuals with cannabis disorders as in the current study.

4.4. Suicide

Suicide occurred five times as frequently during follow-up in our sample compared with individuals from the general population. A longitudinal study by Price et al. (2009) also found an association between baseline cannabis use and completed suicide at a later point in time, but the association disappeared following adjustment for residual confounding. At least three cohort studies have investigated cannabis use as a predictor of suicidal ideation or suicide attempts (Fergusson, Horwood, & Swain-Campbell, 2002; Pedersen, 2008; Wilcox & Anthony, 2004). All studies have found that cannabis use predict the outcomes, but only for specific age or gender-related subgroups. A number of cross-sectional or retrospective studies have found an association between cannabis use and suicidal ideation, suicide attempts, or completed suicide (Beautrais et al., 1999; Chabrol et al., 2008; Huas et al., 2008; Kung, Pearson, & Liu, 2003; Lynskey et al., 2004). This association could be dose-related, with higher risks among heavier users (Fergusson et al., 2002; Huas et al., 2008; Pedersen, 2008). However, associations have often been markedly lower, or even non-significant, following adjustment for residual confounding. The fact that results from other studies are often based on infrequent cannabis users, cross-sectional designs or short follow up intervals complicates a comparison with the results of the current study.

4.5. Homicide/violence

The SMR for homicide or violent death was approximately four. We located no cohort studies describing this outcome among individuals with cannabis use disorders. However, post mortem studies show that cannabis is frequently detected in murder victims (Darke & Duflou, 2008; Eksborg & Rajs, 2008; Galea, Ahern, Tardiff, Leon, & Vlahov, 2002; Macdonald et al., 2003). Comorbid opioid use was found to be a strong predictor of homicide/violence and no excess mortality for this cause was observed among cannabis users without secondary opioid or stimulant use. This indicates that the excess of homicides could result from the lifestyle associated with use of opioids.

4.6. Natural cause

Natural cause, including all diseases, was the second most common cause of death. Compared with persons of same age and gender those with cannabis use disorders were three times as likely to die during follow-up from diseases. A potential association between cannabis use and cancer has been investigated in a number of studies (Hall et al., 2005; Hashibe et al., 2005; Mehra et al., 2006). The existing reviews all conclude that the evidence is conflicting, but that there is reason to suspect that cannabis can cause some cancer forms. Caution is warranted, however, since most studies suffer from severe limitations, such as small sample sizes, retrospective designs, and particularly the problem of ruling out the consequences of tobacco smoking (Chen et al., 2008). There are some studies on cardiovascular fatality related to cannabis use (Bachs & Morland, 2001; Sidney, 2002; Westover, McBride, & Haley, 2007). Results indicate that cannabis could cause death from this cause among individuals with existing vulnerability (Mukamal et al., 2008) but more evidence is needed before firm conclusions can be drawn. Unfortunately, in the current study it was not possible to provide estimates of SMRs for specific diseases. Also, it was not feasible to adjust for the effects of use of other substances such as tobacco or alcohol, or factors associated with an unhealthy lifestyle (e.g. malnutrition, lack of exercise). Therefore, it is likely that some of the excess mortality can be explained by causes aside from cannabis use.

4.7. Protective effects of treatment

Four deaths were recorded during the first 2 weeks of treatment, but in all cases this could be explained by use of stimulants or injection drug use. The lowest SMRs were found between 2 weeks and the first year after treatment start indicating that being in treatment could be protective. In contrast, a protective effect following the end of treatment could not be demonstrated. There are no publications on mortality among people in treatment for cannabis use disorders with which results can be compared.

4.8. Strengths and limitations

The study has several strengths compared to the existing scientific literature on cannabis and mortality. First, the number of individuals with cannabis use disorders was large. Second, the sample was followed over time and number of person-years substantial. Third, a number of specific reasons for death were assessed, including some for which no previous cohort studies have been published. Fourth, mortality rates were compared with individuals from the general population of same age and gender. Finally, only individuals with cannabis use disorders were included. The few other existing cohort studies concern relatively infrequent users of cannabis for whom potential damaging effects are therefore less likely to be detected.

Limitations include the following. The sample consisted of individuals in treatment for cannabis use disorders. Rates could therefore be inflated due to the presence of clinical problems. Conversely, successful treatment could deflate estimates. This means that results cannot be uncritically generalized outside substance abuse treatment settings. However, this is a common problem in research on mortality associated with all types of substance use disorders. The vast majority of studies are thus concerned with treatment seekers (e.g. Degenhardt, Hall, & Warner-Smith, 2006; Wilcox, Conner, & Caine, 2004).

Another limitation is the lack of control for some potentially important confounders in the evaluations of causes of death. A related issue is that proportional hazards analyses were all performed within a group of individuals with cannabis use disorders. As a whole, this group differs in several important ways from the general population. For example, the demographic data show that the level of education was low and that many lived of subsidies from the state. To establish whether cannabis cause the high level of mortality it is preferable to compare with non-users, for example by studying a cohort including both individuals with and without cannabis use disorders. On the other hand, aside from age, none of the socio-demographic variables were associated with increased mortality among individuals in the current study. Bearing this limitation in mind, it can be firmly concluded that individuals in treatment for cannabis use disorders have a high level of excess mortality, overall as well as for accidents, suicides, and natural causes, but also that the reasons for these associations should be further explored in future studies.

The use of registers is associated with several limitations. Unfortunately the substance abuse treatment register only contains information on comorbid substance use during the month prior to

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treatment entry. Opioid or stimulant use at an earlier point could thus be present. On the other hand, there is information on lifetime injection drug use and many of those who use opioids or stimulants administer the substances in this way. Use of register data means that it was not feasible to determine whether diagnostic criteria for cannabis use disorders or secondary substance use problems were met. Also, the type of treatment is not registered. Although information on the outcome of treatment was available, the data could not be used to establish whether relapse or development of new substance use disorders, not leading to treatment, took place during follow-up. Cohort studies have shown that cannabis use is a strong predictor of development of other substance use disorders (Fergusson et al., 2002; Wittchen et al., 2007), and it is possible that this explains some of the excess mortality. For further information about changes in primary substances of abuse following treatment for cannabis disorders please see Arendt et al. (2007).

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References

Andreasson, S., & Allebeck, P. (1990). Cannabis and mortality among young men: A longitudinal study of Swedish conscripts. *Scandinavian Journal of Social Medicine*, *18*, 9–15.

Anthony, J. C., Warner, L. A., & Kessler, R. C. (1994). Comparative epidemiology of dependence on tobacco, alcohol, controlled substances and inhalants: Basic findings from the National Comorbidity Survey. *Experimental and Clinical Psychopharmacology*, *2*, 244–268.

Arendt, M., Munk-Jorgensen, P., Sher, L., & Jensen, S. O. (2011). Mortality among individuals with cannabis, cocaine, amphetamine, MDMA, and opioid use disorders: A nationwide follow-up study of Danish substance users in treatment. *Drug and Alcohol Dependence*, *114*, 134–139.

Arendt, M., Rosenberg, R., Foldager, L., Perto, G., & Munk-Jorgensen, P. (2007). Psychopathology among cannabis-dependent treatment seekers and association with later substance abuse treatment. *Journal of Substance Abuse Treatment*, *32*, 113–119.

Bachs, L., & Morland, H. (2001). Acute cardiovascular fatalities following cannabis use. *Forensic Science International*, *124*, 200–203.

Beautrais, A. L., Joyce, P. R., & Mulder, R. T. (1999). Cannabis abuse and serious suicide attempts. *Addiction*, *94*, 1155–1164.

Biecheler, M. B., Peytavin, J. F., Facy, F., & Martineau, H. (2008). SAM survey on "drugs and fatal accidents": Search of substances consumed and comparison between drivers involved under the influence of alcohol or cannabis. *Traffic Injury Prevention*, *9*, 11–21.

Brodie, L., Lyndal, B., & Elias, I. J. (2009). Heavy vehicle driver fatalities: Learning's from fatal road crash investigations in Victoria. *Accident Analysis and Prevention*, *41*, 557–564.

Budney, A. J., Roffman, R., Stephens, R. S., & Walker, D. (2007). Marijuana dependence and its treatment. *Addiction Science & Clinical Practice*, *4*, 4–16.

Calabria, B., Degenhardt, L., Hall, W., & Lynskey, M. (2010). Does cannabis use increase the risk of death? Systematic review of epidemiological evidence on adverse effects of cannabis use. *Drug and Alcohol Review*, *29*, 318–330.

Chabrol, H., Chauchard, E., & Girabet, J. (2008). Cannabis use and suicidal behaviours in high-school students. *Addictive Behaviors*, *33*, 152–155.

Chen, A. L., Chen, T. J., Braverman, E. R., Acuri, V., Kemer, M., Varshavskiy, M., et al. (2008). Hypothesizing that marijuana smokers are at a significantly lower risk of carcinogenicity relative to tobacco-non-marijuana smokers: Evidenced based on statistical reevaluation of current literature. *Journal of Psychoactive Drugs*, *40*, 263–272.

Danish Health and Medicines Authority (2006). Variables in the Danish Substance Abuse Treatment Register. Copenhagen: Danish Health and Medicines Authority.

Danish Health and Medicines Authority (2008a). Principles and guidance for registration of causes of death and other clinical data in the death certificate. [Principper og vejledning i registrering af dødsårsager og andre kliniske oplysninger i dødsattesten]. Copenhagen: Danish Health and Medicines Authority.

Danish Health and Medicines Authority. (2008b). Report No.: Nye tal fra Sundhedsstyrelse 10 [new data from the National Board of Health, Denmark 10]. Copenhagen: Danish Health and Medicines Authority.

Darke, S., & Duflou, J. (2008). Toxicology and circumstances of death of homicide victims in New South Wales, Australia 1996–2005. *Journal of Forensic Science*, *53*, 447–451.

Degenhardt, L., Hall, W., & Warner-Smith, M. (2006). Using cohort studies to estimate mortality among injecting drug users that is not attributable to AIDS. *Sexually Transmitted Infections*, *82*, iii56–iii63.

Drummer, O. H., Gerostamoulos, J., Batziris, H., Chu, M., Caplehorn, J. R., Robertson, M. D., et al. (2003). The incidence of drugs in drivers killed in Australian road traffic crashes. *Forensic Science International*, *134*, 154–162.

Eksborg, S., & Rajs, J. (2008). Causes and manners of death among users of heroin, methadone, amphetamine, and cannabis in relation to postmortem chemical tests for illegal drugs. *Substance Use & Misuse*, *43*, 1326–1339.

European Monitoring Centre for Drugs, Drug Addiction (EMCDDA) (2011). *The state of the drugs problem in Europe—Annual report.* .

Fergusson, D. M., & Horwood, L. J. (2001). Cannabis use and traffic accidents in a birth cohort of young adults. *Accident Analysis and Prevention*, *33*, 703–711.

Fergusson, D. M., Horwood, L. J., & Boden, J. M. (2008). Is driving under the influence of cannabis becoming a greater risk to driver safety than drink driving? Findings from a longitudinal study. *Accident Analysis and Prevention*, *40*, 1345–1350.

Fergusson, D. M., Horwood, L. J., & Swain-Campbell, N. (2002). Cannabis use and psychosocial adjustment in adolescence and young adulthood. *Addiction*, *97*, 1123–1135.

Galea, S., Ahern, J., Tardiff, K., Leon, A., & Vlahov, D. (2002). Drugs and firearm deaths in New York City 1990–1998. *Journal of Urban Health: Bulletin of the New York Academy of Medicine*, *79*, 70–86.

Gerberich, S. G., Sidney, S., Braun, B. L., Tekawa, I. S., Tolan, K. K., & Quesenberry, C. P. (2003). Marijuana use and injury events resulting in hospitalization. *Annals of Epidemiology*, *13*, 230–237.

Hall, W., Christie, M., & Currow, D. (2005). Cannabinoids and cancer: Causation, remediation, and palliation. *Lancet Oncology*, *6*, 35–42.

Hashibe, M., Straif, K., Tashkin, D. P., Morgenstern, H., Greenland, S., & Zhang, Z. F. (2005). Epidemiologic review of marijuana use and cancer risk. *Alcohol*, *35*, 265–275.

Helweg-Larsen (2011). The Danish Register of Causes of Death. *Scandinavian Journal of Public Health*, *39*(Suppl 7), 26–29.

Huas, C., Hassler, C., & Choquet, M. (2008). Has occasional cannabis use among adolescents also to be considered as a risk marker? *European Journal of Public Health*, *18*, 626–629.

Hulse, G. K., English, D. R., Milne, E., & Holman, C. D. (1999). The quantification of mortality resulting from the regular use of illicit opiates. *Addiction*, *94*, 221–229.

Kalant, H. (2004). Adverse effects of cannabis on health: An update of the literature since 1996. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *28*, 849–863.

Kung, H., Pearson, J. L., & Liu, X. (2003). Risk for male and female suicide decedents ages 15–64 in the United States. Results from the 1993 National Mortality Followback Survey. *Social Psychiatry and Psychiatric Epidemiology*, *38*, 419–426.

Laumon, B., Gadegbeku, B., Martin, J. L., & Biecheler, M. B. (2005). Cannabis intoxication and fatal road crashes in France: Population based case-control study. *British Medical Journal*, *331*, 1371.

Lynskey, M. T., Glowinski, A. L., Todorov, A. A., Bucholz, K. K., Madden, P. A., Nelson, E. C., et al. (2004). Major depressive disorder, suicidal ideation, and suicide attempt in twins discordant for cannabis dependence and early-onset cannabis use. *Archives of General Psychiatry*, *61*, 1026–1032.

Macdonald, S., Anglin-Bodrug, K., Mann, R. E., Erickson, P., Hathaway, A., Chipman, M., et al. (2003). Injury risk associated with cannabis and cocaine use. *Drug and Alcohol Dependence*, *72*, 99–115.

Mehra, R., Moore, B. A., Crothers, K., Tetrault, J., & Fiellin, D. A. (2006). The association between marijuana smoking and lung cancer: A systematic review. *Archives of Internal Medicine*, *166*, 1359–1367.

Mukamal, K. J., Maclure, M., Muller, J. E., & Mittleman, M. A. (2008). An exploratory prospective study of marijuana use and mortality following acute myocardial infarction. *American Heart Journal*, *155*, 465–470.

Munk-Jorgensen, P., & Mortensen, P. B. (1997). The Danish Psychiatric Central Register. *Danish Medical Bulletin*, *44*, 82–84.

Mura, P., Chatelain, C., Dumestre, V., Gaulier, J. M., Ghysel, M. H., Lacroix, C., et al. (2006). Use of drugs of abuse in less than 30-year-old drivers killed in a road crash in France: A spectacular increase for cannabis, cocaine and amphetamines. *Forensic Science International*, *160*, 168–172.

Pedersen, W. (2008). Does cannabis use lead to depression and suicidal behaviours? A population-based longitudinal study. *Acta Psychiatrica Scandinavica*, *118*, 395–403.

Pedersen, C. B., Gøtzsche, H., Møller, J., & Mortensen, P. (2006). The Danish Civil Registration System. *Danish Medical Bulletin*, *53*, 441–449.

Price, C., Hemmingsson, T., Lewis, G., Zammit, S., & Allebeck, P. (2009). Cannabis and suicide: Longitudinal study. *The British Journal of Psychiatry*, *195*, 492–497.

Ramaekers, J. G., Berghaus, G., Van, L. M., & Drummer, O. H. (2004). Dose related risk of motor vehicle crashes after cannabis use. *Drug and Alcohol Dependence*, *73*, 109–119.

Sewell, R. A., Poling, J., & Sofuoglu, M. (2009). The effect of cannabis compared with alcohol on driving. *American Journal on Addictions*, *18*, 185–193.

Sidney, S. (2002). Cardiovascular consequences of marijuana use. *The Journal of Clinical Pharmacology*, *42*, 64S–70S.

Sidney, S., Beck, J. E., Tekawa, I. S., Quesenberry, C. P., & Friedman, G. D. (1997). Marijuana use and mortality. *American Journal of Public Health*, *87*, 585–590.

Stata Corp (2007). *Stata Statistical Software, Release 10.* College Station, TX: Stata Corp LP.

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Statistics Denmark (2009). www.statistikbanken.dk/statbank5a (accessed on 07.01.2009)

Substance Abuse and Mental Health Services Administration (SAMHSA) (2008). *Results from the 2007 National Survey on Drug Use and Health: National Findings.* : Office of Applied Studies (NSDUH Series H-34, DHHS Publication No. SMA 08–4343.

Wahren, C. A., Brandt, L., & Allebeck, P. (1997). Has mortality in drug addicts increased? A comparison between two hospitalized cohorts in Stockholm. *International Journal of Epidemiology*, *26*, 1219–1226.

Westover, A., McBride, S., & Haley, R. (2007). Stroke in young adults who abuse amphetamines and cocaine. *Archives of General Psychiatry*, *64*, 495–502.

Wilcox, H. C., & Anthony, J. C. (2004). The development of suicide ideation and attempts: An epidemiologic study of first graders followed into young adulthood. *Drug and Alcohol Dependence*, *76*, S53–S67.

Wilcox, H. C., Conner, K. R., & Caine, E. D. (2004). Association of alcohol and drug use disorders and completed suicide: An empirical review of cohort studies. *Drug and Alcohol Dependence*, *76*, S11–S19.

Wittchen, H. U., Frolich, C., Behrendt, S., Gunther, A., Rehm, J., Zimmermann, P., et al. (2007). Cannabis use and cannabis use disorders and their relationship to mental disorders: A 10-year prospective-longitudinal community study in adolescents. *Drug and Alcohol Dependence*, *88*, 60–70.

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