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Research paper

A literature review and meta-analyses of cannabis use and suicidality

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ABSTRACT

Background: We lack a review of the epidemiological literature on cannabis use (acute use and chronic-usual quantity/frequency and heavy use) and suicidality (suicide death, suicide ideation, suicide attempt).
Methods: The English language literature on Medline, PsychInfo, Google Scholar, and public-use databases was searched for original articles, critical review reports, and public use data on cannabis use and suicide for the period ranging from 1990–2015 (February). Odds ratios (OR) from random effects in meta-analyses for any cannabis use and heavy cannabis use were calculated.
Results: The acute cannabis-suicidality literature mostly includes descriptive toxicology reports. In terms of death by suicide, the average positive cannabis rate was 9.50% for studies sampling from all suicides, with higher cannabis detection rates amongst suicide decedents by non-overdose methods. We found only 4 studies providing estimates for any chronic cannabis use and death by suicide (OR=2.56 (1.25–5.27)). After deleting duplicates we found 6 studies on any cannabis use and suicide ideation (OR=1.43 (1.13–1.83)), 5 studies on heavy cannabis use and suicide ideation (OR=2.53 (1.00–6.39)), 6 studies on any cannabis use and suicide attempt (OR=2.23 (1.24–4.00)) and 6 studies on heavy cannabis use and suicide attempt (OR=3.20 (1.72–5.94)).
Conclusions: We currently lack evidence that **acute** cannabis use increases imminent risk for suicidality. The evidence tends to support that **chronic** cannabis use can predict suicidality, but the lack of homogeneity in the measurement of cannabis exposure and, in some instances, the lack of systematic control for known risk factors tempered this finding.

1. Introduction

The last report from the Institute for Health Metrics and Evaluation (IHME), Global Burden of Disease (GBD) group on the burden of mental and substance use disorders on deaths by suicide (Ferrari et al., 2014), did not include cannabis dependence as a risk factor for suicide. Another update from the GDB study group (Hall and Degenhardt, 2014), that included 2 new studies and another review paper (Moore et al., 2007), considered this association somehow contradictory and possibly biased. These reviews tend to include suicidal behavior (i.e., death by suicide and non-fatal suicide attempts) as part of mental health consequences of cannabis use and plainly disregard the cannabis-suicidal behavior association. A current international report on suicide (World Health Organization, 2014), only briefly mentions an association between cannabis dependence and suicide. We believe that a separation of outcomes (suicidal ideation, attempt and death; hereby referred to as "suicidality") is needed if we want to understand this phenomenon at a fine-grained level (i.e., to determine specifically where there is indeed a lack of evidence and/or a need for additional studies/analyses in order to determine evidence of an association). Also, while prior reviews acknowledge the limitations of what is considered cannabis/marijuana exposure (any use, frequency of regular use, disorders) they all discuss the long-term effects of cannabis exposure. To the best of our knowledge, no review has included an evaluation of a potential short-term, acute triggering effect of cannabis use on suicidal behavior, a matter of potential relevance similar to the acute use of alcohol (Cherpitel et al., 2004; Bagge and Sher, 2008; Bagge and Schumacher, 2010). The possibility of an association between acute and chronic cannabis use and suicidality is relevant because cannabis use and cannabis use disorders are amongst the most common form of illicit substance use and illicit substance use disorders worldwide (Degenhardt et al., 2008; Degenhardt and Hall, 2012), and its role on suicidality could potentially have implications for the calculations of the burden of disease.

A new review suggested possible mechanisms for cannabis use

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to have an effect on suicidality, including causal effects, reverse causation, correlated liabilities and by triggering effects (Agrawal and Lynskey, 2014). Cross-sectional analyses based on community-based twin samples have found modest associations between cannabis use with suicide ideation and unplanned suicide attempts (Delforterie et al., 2015) adjusting for psychiatric disorders and substance involvement. We currently lack an overall evaluation of the potential cannabis-suicidality association using a fine-grained approach and, most importantly, recommendations are needed to (1) best determine whether this relation exists and to (2) responsibly respond to the public debate on the topic. Given the above limitations of prior reviews, we will provide an updated (1990–[1995 for acute use] up to February 2015) revision of the epidemiological literature on acute and chronic effects of cannabis on suicidality, with discussions on suicidal ideation, attempts and deaths.

2. Methods

Our approach to understanding the cannabis-suicidality relation closely models a set of reviews (Hufford, 2001; Cherpitel et al., 2004; Borges and Loera, 2010), and a conceptual framework (Bagge and Sher, 2008), distinguishing between acute and chronic use of alcohol in their relations with suicidality.

For this review, the English language literature on Medline, PsychInfo, Google Scholar, and public-use databases (e.g., Substance Abuse and Mental Health Services Administration) was searched for original articles, critical review reports, and public use data on cannabis use and suicidity. All references in English language with 'cannabis' or 'marijuana' or 'marihuana' and 'suicide' or 'suicide attempt' or 'suicide ideation' or 'suicidal' or 'suicidality' were included and reviewed. Prior reviews were inspected for missing references. The final selection of papers emphasized longitudinal, case-control, and case-crossover study designs. Other designs such as case-series, coroner-toxicological descriptive reports, and cross-sectional studies are covered to a lesser extent. Epidemiological studies of well-defined populations are highlighted, and samples of selected patients and case-reports from areas with few reports are discussed. Notably, this review does not cover synthetic cannabinoid use, given that this substance has different pharmacological properties compared to those of the cannabis sativa plant.

Common Odds ratios (OR) and 95% Confidence Intervals from random effects in meta-analyses for any cannabis use and heavy cannabis use were calculated using STATA software. We pooled the effect size for suicidality after cannabis use across studies using the DerSimonian and Laird random- effects method implemented in the "metan" command (Harris et al., 2008; Stata Statistical Sofware, 2013). When ORs were presented separately for different populations (e.g. by gender) in the original article, we reported them separately for each population provided. Publication bias was assessed by visual inspection of funnel plots depicting the standard normal deviate of the estimates (the odds ratio divided by its standard error) against their precision (inverse of the S.E.) and by Egger's regression-based test, where asymmetry was assessed with $p < 0.10$, due to the small number of studies included (Egger et al., 1997). Between-study heterogeneity was quantified by I^2 and Cochran's Q (Higgins et al., 2003). I^2 can be interpreted as the percentage of the total variance due to between-study heterogeneity.

We considered acute cannabis use as cannabis consumed on a specific occasion and its acute consequences, sometimes given by self-report of consumption in a given time-frame (i.e., last 6 h), by attribution of treating personnel in emergency departments and sometimes as given by biological specimen collected post-mortem. Chronic cannabis use refers to cannabis use patterns, symptoms of cannabis use disorder and heavy cannabis use. For chronic cannabis use, we first grouped studies that reported only some measure of any cannabis use, either as a lifetime measure or any use on a more limited time frame; next, studies that reported some measure of heavy cannabis involvement, including DSM diagnostics (American Psychiatric Association, 2013), high number of times consumed or high frequency of consumption per some cut points were considered separately.

3. Results

3.1. Acute effect of cannabis on suicidality

3.1.1. Suicidal ideation and attempt

To our knowledge, only one study exists which hints at the possibility that acute cannabis use can induce suicidal ideation. A case study (Raja and Azzoni, 2009), describes a patient who presented to the emergency department (ED) with suicidal ideation (and urge to attempt suicide by fall), anxiety, and agitation after smoking cannabis use a few hours prior.

The Drug Abuse Warning Network DAWN (Subtance Abuse And Mental Health Services Administration, 2011), provides 2011 national US estimates of cannabis use among drug-related emergency department visits for suicide attempts (which includes any use of prescription or over-the-counter medication, illicit drugs, or substances inhaled for their specific effects). Presence of cannabis use is rated as positive if hospital personnel deemed cannabis to cause or contribute to the ED visit for suicide attempts. Results indicate that 15,615/228366 (6.8%) of drug-related suicide attempts were cannabis-related. Of those where cannabis was deemed as influencing the attempt, 45.7% also used alcohol. Approximately, 23% of drug-related suicide attempt visits had a toxicology report. Out of those who had a toxicology report (n=51,910) 8707 had a positive detection of cannabis (16.8%). However, performance of toxicology tests within DAWN are not routine and, when conducted, could result in a positive test when last use was weeks prior to the suicide attempt.

The most detailed study to date (Bagge and Borges, 2015; Borges and Bagge, 2015), on the acute effects of cannabis use on suicide attempts, investigated this phenomenon among 363 patients who presented to a level 1 trauma hospital within 24 h of a suicide attempt. Self-reported use of cannabis in the 24 h prior to the suicide attempt (case period) and the matched 24 h the day before (control period) was assessed with the Timeline-Followback Interview for Suicide Attempts (Bagge et al., 2013a, 2013b, 2013c). This interview gathers information on the timing of alcohol and drug use within 48 h prior to the suicide attempt, after basic information is gathered (e.g., periods of sleep, other activities, and location) to serve as anchors for recall. These results demonstrated that 10.2% of recent suicide attempters used cannabis within 24 h of the attempt and 13.2% used cannabis the day before the attempt. Within-subject analyses revealed that one is at decreased odds of attempting suicide soon after use of cannabis compared to no cannabis use (Odds Ratio-OR=0.39 [95% CI, 0.16 to 0.93), $p < .05$). Specifically, for a small fraction of those that were pure users of cannabis (about 11/363 of all patients; 3.03%) in the twenty-four hours before the attempt, such acute use of these drugs may have decreased the risk of an attempt.

3.1.2. Suicide death

We reviewed 10 studies on death by suicide that included data on the presence/detection of cannabis use. Data largely consisted of positive toxicology results from coroner/medical examiner reports using a retrospective or prospective case-series study design. Countries represented in this portion of the review include the

following: United States (n=6); Australia (n=2); Switzerland (n=1); and Sweden (n=1). The majority of studies (n=7) included sample rates for the general population of suicides, while a minority focused on special populations, including adolescent/young adults (n=2) and illicit drug users (n=1). Studies which focused on a single non-overdose method of suicide, or who excluded/included participants based on a specific use of a substance, were not included in this review.

Table 1 displays prevalence rates of the presence of cannabis use within broad categories (inclusion of decedents using all suicide methods, overdose methods, and non-overdose methods). For studies that sampled from the general population of suicide decedents across suicide methods, the average percent testing positive for cannabis use was 9.50% (Dhossche et al., 2001;Department of Health and Human Services Centers for Disease Control and Prevention, 2006; Piper et al., 2006; Shields et al., 2006; Sheehan et al., 2013). Interestingly, the comparable rate testing positive for cannabis use for adolescent/young adult samples (i.e., ages 0–18 or 12–24; (Perret et al., 2006; Naso et al., 2008), was much higher (27.30%). This is perhaps driven by the fact that cannabis was the illicit drug class most frequently detected and occurred exclusively in the 13–18 year age group within one study (Naso et al., 2008), and that the other study's age range (12–24) also spans a time period with the highest rates of cannabis use (i.e., ages 12–25 compared to older individuals (Subtance Abuse And Mental Health Services Administration, 2011). Within a large sample of suicide decedents (Eksborg and Rajs, 2008), selected based on evidence of any illicit drug use at the time of death, the average percent testing positive for cannabis across suicide methods (27.0%), was similar in magnitude to the adolescent/young adult average prevalence rate.

Studies examining cannabis detection rates by the broad categories of overdose and/or non-overdose methods of suicide, find rates that are higher among decedents who used non-overdose methods (rate: 11.6%; (Shields et al., 2006; Department of Health and Human Services Centers for Disease Control and Prevention, 2006; Darke et al., 2009a), than overdose suicide methods (rate 9.2%; (Department of Health and Human Services Centers for Disease Control and Prevention, 2006; Shields et al., 2006), within general population studies. The same pattern is found amongst decedents who were illicit drug users (non-overdose: 46.2%; overdose: 13.5%; (Eksborg and Rajs, 2008)).

Table 2 displays controlled comparisons of interest for this line of research. First, comparisons within suicide decedent samples (comparisons between broad suicide method categories and comparisons between biological sex) are displayed. Only two studies have examined within-study comparisons between cannabis use detection rates among individuals using non-overdose and overdose suicide methods. One US state-wide study (Shields et al., 2006), failed to find any association (OR=1.22, ns), while another US nationally representative study (Department of Health and Human Services Centers for Disease Control and Prevention, 2006), showed an elevated detection rate among those who used non-overdose methods (OR=1.74, 95% CI=1.13, 2.68). A single study (Eksborg and Rajs, 2008), sampling illicit drug user suicide decedents also found that those who used non-overdose methods had higher rates of cannabis detected than those who used overdose methods (OR=5.49, 95% CI=2.32, 12.98). Data from two studies (Shields et al., 2006; Darke et al., 2009b), suggest that the presence of cannabis is higher among males than females for individuals who used non-overdose methods (ORs range from 1.72 to 1.87). No evidence of acute biological sex differences in cannabis detection rates were found for overdose methods of suicides (Shields et al., 2006). Considering all methods of suicide within samples, one study (Shields et al., 2006), found that males had higher cannabis detection rates than females, while another (Sheehan et al., 2013), failed to find a statistically significant difference in rates.

Results also indicate that cannabis detection rates are significantly higher among homicide deaths than suicide deaths across all methods (ORs range from 2.56 to 4.61; n=2) and non-overdose methods (OR=2.39; n=1) for studies sampling from the general population (Darke et al., 2009a; Sheehan et al., 2013), and illicit drug users (Eksborg and Rajs, 2008). For adolescents/young adults (Naso et al., 2008), presence of cannabis use was lower amongst accidental than suicide deaths across methods (OR=.08, 95% CI=.02 to.25), and no differences were found between homicides and suicides.

Table 1
Rates of acute cannabis use by broad categories of suicide methods.

	General population (6 Total studies) Mean (%)	Adolescents/young adults (2 Total studies) Mean (%)	Illicit drug user (1 Study)
All methods	9.50%	27.30%	27.00%
Overdose	9.20%		13.50%
Non-overdose	11.60%		46.20%

Table 2
Comparisons within suicide samples and between Non-Suicide control samples.

	General population (4 Total studies)		Adolescents/young adults (1 Study)		Illicit drug user (1 Study)	
	OR	95% ci	OR	95% ci	OR	95% ci
Non-overdose vs. Overdose	1.22	0.81 To 1.85			**5.49**	2.32 To 12.98
	1.74	1.13 To 2.68				
Male vs. female						
All methods	1.60	0.91 To 2.84				
	1.76	1.19 To 2.59				
Overdose	1.84	1.19 To 2.59				
Non-Overdose	**1.87**	1.10 To 3.15				
	1.72	1.08 To 2.73				
Homicide vs. suicide						
All methods	**4.61**	3.65 To 5.82	1.15	0.48 To 2.79	**2.56**	1.20 To 5.46
Non-Overdose	**2.39**	1.80 To 3.17				
Accident vs. suicide						
All methods			**0.08**	0.02 To 0.25	0.84	0.54 To 1.28

3.2. Chronic effect of cannabis on suicidality

3.2.1. Suicide ideation and attempt

A total of 12 studies reported on chronic cannabis use and suicidal ideation and 15 reported on suicide attempt, which includes two studies using a composite measure of ideation and/or attempt (Petronis et al., 1990; Newcomb et al., 1993; Fergusson et al., 1996; Fergusson and Horwood, 1997;J uon and Ensminger, 1997; Beautrais et al., 1999; Newcomb et al., 1999; Wichstrøm, 2000; Bovasso, 2001; Borowsky et al., 2001; Fergusson et al., 2002; Wilcox and Anthony, 2004; McGee et al., 2005; Tekin and Markowitz, 2008; Pedersen, 2008; Roberts and Roberts, 2010; Van Ours et al., 2013; Rasic et al., 2013; Silins et al., 2014; Zhang and Wu, 2014; Clarke et al., 2014). Of note, some studies included multiple estimates (i.e., for ideation and then attempts), some are based on the same cohort measured and reported on more than one occasion, and some studies did not present OR/RR estimates that could be used for figures and pooled meta-analyses. Table 3 displays all studies that provided OR/RR estimates for the relation between chronic cannabis use and suicide ideation or attempt.

Fig. 1 presents estimates from 6 studies that reported some form of epidemiological measure of the association between any chronic/distal cannabis use and suicide ideation, while Fig. 2 presents 5 studies that reported estimates for heavy cannabis use and suicide ideation. For each study included, we provide in the figures the ORs or RRs, the information on exposure to cannabis, the population studied, gender and whether the ORs or RR was adjusted or not. Only two studies reported crude ORs, but many more reported adjusted estimates. We found no case–control study on suicide ideation and all estimates were derived from longitudinal studies. As per the pooled meta-analyses in Fig. 1, any cannabis use was associated with increasing suicide ideation (OR=1.43, 95%CI=1.13–1.83) and heavy cannabis use was associated with a higher OR of 2.53 (95% CI=1.00–6.39). Among all reports for cannabis use and suicide ideation, there was only one OR below 1 (non-significant). In both meta-analyses, there is evidence of heterogeneity in the OR/RR. Egger's test indicated asymmetry for the cannabis use studies (bias=2.26 (90% CI=0.56–3.96), p=0.042) but not for those on heavy use (p=0.124). Because of the presence of heterogeneity, we report the ORs from random effects models.

Fig. 3 presents 6 studies that reported some form of epidemiological measure of the association between any chronic/distal cannabis use and suicide attempt, and Fig. 4 presents 6 studies that reported estimates for heavy cannabis use and suicide attempt. Three studies reported crude ORs for any cannabis (but (Roberts and Roberts, 2010), reported a point OR of 4.7 for the adjusted ORs that was claimed to be statistically significant), but many more reported adjusted estimates for heavy cannabis use. We found one case-control study on any cannabis and suicide attempt, and one case–control study for heavy cannabis and suicide attempt, with many more estimates derived from longitudinal studies. As seem from Fig. 3, pooled ORs estimate for any cannabis use and suicide attempt was 2.23 (1.24–4.00) and for any heavy use was 3.20 (1.72–5.94) in Fig. 4. Among all reports for cannabis use and suicide attempt, there was only one OR below 1 (non-significant). In both meta-analyses, there is evidence of heterogeneity in the OR/RR and asymmetry as well (p=0.004 and 0.002, respectively).

Next, the specifics of two recent studies are important to highlight. After 30 years of follow-up of a population based cohort (Van Ours et al., 2013), 327 participants had suicide ideation (cumulative incidence of ideation was 38% in females and 31% in males). After extensive adjustment of potential confounding variables using proportional hazard models, a large dose-response relation of cannabis with onset of suicidal ideation was found, suggesting that intense cannabis use is associated with a faster onset of suicidal ideation. Next, (Silins et al., 2014), reported on a merged Australian-New Zealand sample and 78 suicide attempts were found. After an extensive adjustment of potential confounding variables (53 potential covariates were used in models) a dose–response association for frequency of cannabis use (never to+daily use) before age 17 and suicide attempts between ages 17–25 was found.

3.2.2. Suicide death

We found 6 reports (4 non-overlapping) investigating whether chronic use of cannabis is associated with suicide (Andréasson and Allebeck, 1990; Kung et al., 2003, 2005; Palacio et al., 2007; Price et al., 2009; Arendt et al., 2013). Table 3 displays all studies that provided OR/RR estimates for the relation between cannabis use and suicide death.

Fig. 5 displays cannabis OR/RR estimates with pooled common OR/RR. Two studies were case-control, psychological autopsy studies, and two were longitudinal. While most studies suggested an association between any cannabis use and suicide, with pooled OR=2.56 (95% CI=1.25–5.27; presenting both heterogeneity and asymmetry) the only population-based longitudinal study, which also included dose-response estimates (Price et al., 2009), followed male conscripts for 33 years and reported a crude cannabis RR (any lifetime use of cannabis) and dose–response (cannabis used from none up to+50 times) associations with death by suicide (459 confirmed suicides). Notably, these associations disappeared after adjustment by an extensive list of control variables (e.g., alcohol, tobacco, other drugs, psychiatric disorders). Generalization of these findings is limited given the investigators' focus on male conscripts.

4. Discussion

4.1. Overall summary and limitations of acute cannabis-suicidality relations

The acute cannabis-suicidal ideation and behavior literature is small and spans multiple countries. It mostly includes case-series and descriptive toxicology reports, and only a handful of studies include a between-subject control group, or a within-subject control period that provide essential information regarding whether an association exists. The vast majority of studies reviewed use toxicology tests where a positive test can indicate last use which was weeks prior to suicidal behavior. Only a single case study is suggestive that acute cannabis use can induce suicidal ideation, and we found only one case-crossover study and the results suggest that cannabis may acutely decrease risk for a suicide attempt, which may be a protective effect, or may be explained by a withdrawal effect. In terms of death by suicide, the average cannabis detection rate was 9.50% for studies sampling from the general population of suicide decedents, and there is evidence that there are higher cannabis detection rates amongst suicide decedents by non-overdose methods (compared to overdose methods) and that males have higher rates than females within suicide decedents using non-overdose methods. Further, there is preliminary evidence suggesting that individuals who die by homicide have higher cannabis-positive rates than suicide decedents (except within adolescent/young adult samples), and that accidental deaths may have lower cannabis-positive rates than suicide decedents within adolescent/young adult samples. Notably, having homicide and accidental deaths as control groups are arguably not ideal, compared to natural death given that cannabis could be related to interpersonal violence and accidental deaths could be related to transit deaths were cannabis could be involved.

Table 3
Estimates of chronic cannabis use and suicide ideation, attempts and suicide death.

Author, year	Place	Study type (longitudinal, case–control)	Exposure definition	Outcome (ideation, attempt, suicide)	Sample size and demographics	Estimate type/subpopulation/note	Point estimate	CI	Adjustment variables
Petronis et al. (1990)	US-ECA, all sites.	Case-control. prevalent and incident cases within one year.	Any marijuana use	Attempts	13,673 Participants; 40 CA; 160 NC. > 18 y/o.	OR	1.06	(0.38–2.97)	Crude only
Juon and Ensminger (1997)	US-Chicago, IL.	Longitudinal. Approx. 17 yrs. FU.	Adolescents used +40 times; adults used lifetime (; baseline non-exposed was 40+times used 0 – 39 Times).	Ideation lifetime; attempt lifetime	939 Ado; 953 adults; 86 ideation; 39 att. African-Americans.	Ado males ideation	1.21	(0.54–2.70)	Crude OR only
						Ado males att	0.34	(0.04–2.85)	
						Ado females ideation	0.64	(0.14–2.83)	
						Ado females att	1.84	(0.50–6.82)	
						Adult males ideation	3.01	(1.12–8.14)	
						Adult males att	4.22	(0.51–34.80)	
						Adult females ideation	3.69	(1.44–9.42)	
						Adult females att	3.16	(0.99–10.00)	
Beautrais et al. (1999)	New Zealand	Case-control. CA from a general Hospital, Co from the community.	DSM-IIIR abuse/dependence in the prior month	Serious att requiring medical intervention	302 att; 1028 *Co*. 18 y/o and older.	OR	2.00	(0.97–5.30)	Age and sex, lack of formal educational qualifications, low SES, childhood sexual abuse parental alcohol, mood disorder in prior month, substance disorder (alcohol OR drug other than cannabis) in prior month, antisocial disorder.
Borowsky et al. (2001)	US–National	Longitudinal. 11 months FU.	7 Categories of use from never to > =6 times past month at W1. OR's are for never vs. > =6 Times.	Attempts within 11 months after baseline	13,110 Students grades 7–12; 474 att. all by 3 ethnicities and sex.	Girls black	10.30	(4.80–22.20)	ORs adjusted for age, family structure and welfare. by ethnicity.
						Girls Hispanic	4.50	(2.10–9.70)	
						Girls whites	3.40	(2.20–5.30)	
						Boys black	5.90	(2.10–16.60)	
						Boys Hispanic	2.90	(1.10–7.50)	
						Boys whites	6.80	(3.60–12.80)	
Bovasso (2001)	US-ECA Baltimore, MD.	Longitudinal. Approx. 15 yrs. FU.	CIDI cannabis abuse at baseline (free of depression)	Depression and symptoms of ideation	1920 Adults > 18 y/o. 97 CA of ideation.	Ideation OR-No RC for depression	4.55	(1.37–15.12)	Sex, age, married, white race, education, income, stressful events, chronic illness, psychopathological symptoms (mania, OC, panic, phobia, schizophrenia, antisocial personality), treatment for mental health, alcohol, amphetamines, barbiturates, opioids.
Kung et al. (2003)	US–National	Case-control. suicide decedents, natural causes of deaths as Co	Death certificate & proxy psychological autopsies any marijuana last year	Suicide	1463 Suicides; 7392 natural deaths. 15–64 y/o.	Males OR	2.28	(1.54–3.37)	Age, race, education, living alone, depression, excessive alcohol use, access to firearms, mental health services.
						Females OR	4.82	(2.47–9.39)	
Wilcox and Anthony (2004)	US-Baltimore, MD.	Longitudinal. Approx. 15 yrs. FU.	Use before OR at age 15	Ideation last year; attempt last year; within CIDI	2311 Adolescents; 218 ideation; 155 attempts. young adults.	Female ideation RR	2.90	(1.40–6.10)	Race, sex, cohort, free lunch, intervention, major depression disorder, early onset drug use, early aggression, drug use, deviant peers, parental psychiatric disturbance. the association held in several
						Male ideation RR	1.10	(0.40–2.70)	

Table 3 (*continued*)

Author, year	Place	Study type (longitudinal, case–control)	Exposure definition	Outcome (ideation, attempt, suicide)	Sample size and demographics	Estimate type/subpopulation/note	Point estimate	CI	Adjustment variables
				depression		Female att RR	2.10	(0.90–4.70)	models; only in full model was non-significant.
						Male att RR	2.30	(0.70–7.50)	
McGee et al. (2005)	New Zealand	Longitudinal. 3–6 yrs. FU.	Used at school at age 15	Ideation at ages 18–21 (first time measured)	764 With full information; 130 ideators. Dunedin study, child from adulthood.	OR	1.10	(0.58–2.07)	Sex, disadvantage, impulse, depressed, stress, low parent attach, alcohol and smoking.
Palacio et al. (2007)	Colombia-Medellín	Case-control. suicide decedents, deceased in accidents as Co.	Cannabis disorder by DSM-IV-TR	Suicide	108 Suicides; 108 deceased in accidents. 19–44 y/o.	Matched OR	2.85	(1.31–6.24)	Age and sex in matched analyses
Pedersen (2008)	Norway	Longitudinal. 13 yrs. FU.	Ever & last 12 months: no; 1–10 times; 11+	Ideation; attempts at 16–21 y/o; attempts at 22–27 y/o.	2033 Ado 12–16 y/o at baseline. ideation at 21 y/o=110; ideation at 27 y/o=101; Att at 16–21 y/o=118; Att at 22–27 y/o=111.	RR for ideation 11+Times*	2.70	(1.10–6.40)	Age, gender, parental educational level, parents unemployed OR receiving social welfare benefits, parental divorce, smoking OR alcohol problems, parental support and monitoring, early puberty, maturation, school marks, conduct problems and daily smoking, alcohol intoxication and problems, depression, impulsivity, level of education, unemployment and income, marriage ◆ cohabitation and being a parent.
						RR att 11+Times	2.90	(1.30–6.10)	
						No relationship for early use/onset but RR for cannabis at 21 y/o and ideation and att at 27 y/o. No RC was found.			
Tekin and Markowitz (2008)	US–National school survey	Longitudinal. Approx. 6–7 yrs. FU.	Ever use at time 1	Ideation at time 3 last 12-months	15,170 Students; 895 ideators (using a % of 0.059-Table 1).*	OR*	1.29	(1.13–1.48)	Crude, none for ideation.
Price et al. (2009)	Sweden	Longitudinal. 33 yrs. FU.	Cannabis at conscription: no; 1–10 times; 11–50; 50+Times	Suicide	50,087 Male conscripts. 459 suicides; 141 undetermined.	RR ever	0.88	(0.65–1.20)	Problematic behavior in childhood, psychological adjustment, social relations, parental psychotropic medication, alcohol, smoking, psychiatric diagnosis at conscription, IQ, and either use of other drugs.
Roberts and Roberts (2010)	US-Houston, TX.	Longitudinal. youths in health care maintenance 1 yr. FU.	Use of marijuana in the last year	Attempts	3134 Youths 11–17 y/o. No number of att, incidence of 0.95%. Approx. 30 CA.*	Incidence OR	4.81	(1.82–12.66)	Crude
						Incidence OR (No CI reported)	4.70	p ≪ =0.05	Age and gender of youths, family income, prior suicide attempts by youths and by their caregivers, pre-existing youth psychiatric disorders, personal and social resources, and life stress.
Arendt et al. (2013)	Denmark	Longitudinal. treatment sample 1–10 yrs. FU. (mean 4.1 yrs.)	Diagnoses of cannabis disorders at entry into treatment as a primary substance	Suicides	6445 Patients; 21 deaths by suicide in 26,584 P–Y. adults.	SMR No users of opioid, cocaine, amphetamine	4.80	(2.40–8.90)	"Adjusted" By other drugs only, but not alcohol.
Rasic et al. (2013)	Canada-Nova scotia school survey	Longitudinal-panel. Multimeasure, about 2 yrs. FU.	Cannabis use past 30 days:: any use; 10+Times	Ideation/planning; attempts last 12 months	976 With 2 time-points; ideation time 1 and time 2, 194 and 154 persons; Att time 1 and time 2, 55 and 35 CA.	Ideation OR	1.00	(0.94–1.07)	Time dynamic. living arrangement, alcohol, school mark.
						Ideation OR	1.04	(0.96–1.11)	
						Att OR	1.03	(0.98–1.09)	
						Att OR	1.04	(0.98–1.10)	
						No association with frequency of use			
Van ours	New	Longitudinal.	Year uptake and intensity	Ideation	938 Participants; 327 ideation.	Males monthly HR*	20.49	(10.66–	Characteristics of the individual, their parents and

et al. (2013)	Zealand (with Fergusson)	30 yrs. FU.	of marijuana (monthly, weekly,+weekly, daily, ever) since age 14		young adults.	Females several times/ week HR* Proportional hazards. No RC was found.	2.66	39.38) (1.43–4.95)	the socio-economic background of the family. parental mental disorders (including alcohol and drugs), child abuse and sexual abuse family SES at birth, stressful events at age 15, childhood conduct problems, anxiety, shyness, depression and related behaviors.
Clarke et al. (2014)	Dublin-Ireland	Longitudinal. Approx. 7 yrs. FU.	Ever used cannabis at age 12–15 y/o.	Attempt ever at ages 19–24 y/o.	N=168; 17 att. young adults.	OR	7.50	(1.20–43.80)	Family psychiatric history, childhood trauma, alcohol and other psychopathology.
Silins et al. (2014)	Australia & New Zealand (with Fergusson)	Longitudinal. FU time for both samples not available.	Frequency of use before 17 years (never, less monthly, monthly OR+, weekly OR+; daily).	Attempts between ages 17–25 y/o	2615 Young adults. 78 att.	Daily use/OR	6.83	(2.04–22.90)	53 covariates, including: school problems, conduct disorder, attentional problems, smoking, drinking and illicit drug use, depression, sex, ethnicity, SES, parental substance use, mental health and parental demographics, deviant peer affiliation.
Zhang and Wu (2014)	US–National	Longitudinal-panel. Multi-measure, about 13 yrs. FU.	Ever used at W1 ages 11–21 used last 12 months at W2-4	Ideation last 12 months (multiple measured)	W1=20,745 adolescents. W1-4=3342 young adults. ideation 13.4% at W1 (n=447) to a low 6.4% W4 (n=214). large attrition.	OR* Reverse OR's reported and are significant	1.51	(1.26–1.80)	Models includes cannabis and ideation in all four data points allowing for multiple bi-directional influences. other variables are not explicitly mentioned.

US:United States; ECA:Epidemiologic Catchment Area; yrs.:years; FU:Follow-up; W:Wave; OR:Odds Ratio; RR:Risk Ratio; SMR:Standardized Mortality Ratio; y/o:years old; Ca:Cases; Co:Controls; NC:non-cases; Ado:adolescents; Att:attempts; P–Y:Person-years; HR:Hazard Ratio; RC:Reverse Causality; SES:socio-economic status.

**Estimates provided by the corresponding author.

* Computed from tables information.

Research on the acute relation between cannabis and suicidal behavior is in its nascent stage. The pharmacological properties of cannabis are not usually viewed as toxic agent of death by suicide (e.g., (Bjornaas et al., 2010)). No symptoms of suicide ideation or attempt are inherently present during cannabis intoxication and withdrawal. It is possible that euphoria, a cannabis acute intoxication symptom (American Psychiatric Association, 2013), may immediately decrease risk for a suicide attempt. However, some cannabis withdrawal symptoms (e.g., irritability, anger or aggression, anxiety, depressed mood, restlessness, sleep difficulty (American Psychiatric Association, 2013), and deficits in planning/ response inhibition as consequence of cannabis use (Crean et al., 2011), are also broadly considered imminent warning signs for suicidal behavior (Rudd et al., 2006), and thus could conceivably lead to self-harm.

4.2. Overall summary of chronic cannabis-suicidality relations

In evaluating the evidence it is important to keep in mind that several estimates are based on a small number of cases that endorsed suicide ideation and even smaller number for suicide attempt. All results from meta-analyses suggested that any cannabis use and heavy cannabis use were associated with suicidality, but we also found heterogeneity and publication bias in these results. With few exceptions, most point estimates for the risk of suicide ideation and attempt after exposure to cannabis are above the null and while most are modest in size (point RRs/ORs between 1–3) some are larger. Very few estimates were below the null and none statistically significant. There was a general tendency for higher risk of suicidal ideation and attempt among those that were heavy cannabis users. Newer studies with a larger series of cases, much more exhaustive control of variables and dose-response analyses are also suggestive of this association. A matter of caution is needed for the results on cannabis exposure and death by suicide. While our meta-analysis was suggestive of an association, the only population-based longitudinal study (that also included dose-response estimates) did not find a cannabis- death by suicide association after full adjustment in this sample of male conscripts.

4.3. Current critics on the association between cannabis and suicidal behavior

Some reviews on the distal/chronic cannabis use-suicidality relation are available (Moore et al., 2007; Calabria et al., 2008, 2010; Degenhardt and Hall, 2012; Degenhardt et al., 2013; Ferrari et al., 2014; Hall and Degenhardt, 2014). In general these reviews, with exceptions (Serafini et al., 2012, 2013), concluded that an overall association, or the lack of it, could not be established given the current investigations to date. From these reviews, two main arguments are put forward to substantiate such a conclusion: (1) there is a lack of adjustment of important control variables, especially adjustment by depression and alcohol; and (2) there is no determination that observed results are not due to reverse causality (suicidal behavior causing cannabis use). We discuss these two issues next.

Regarding the argument of control variables, most of the current estimates for cannabis-suicidality do control for several important confounding influences. While studies varied across number and type of selected controls (e.g., one study reported to control for as many as 53 variables (Silins et al., 2014)), most studies included theoretically important control variables (such as depression, alcohol and other drug use) within their models. We compared studies that reported both crude and adjusted effects of chronic cannabis use and suicidality, in order to facilitate an evidenced-based comparison (Fergusson et al., 1996, 2002; Beautrais et al., 1999; Bovasso, 2001; Wilcox and Anthony, 2004; Pedersen,

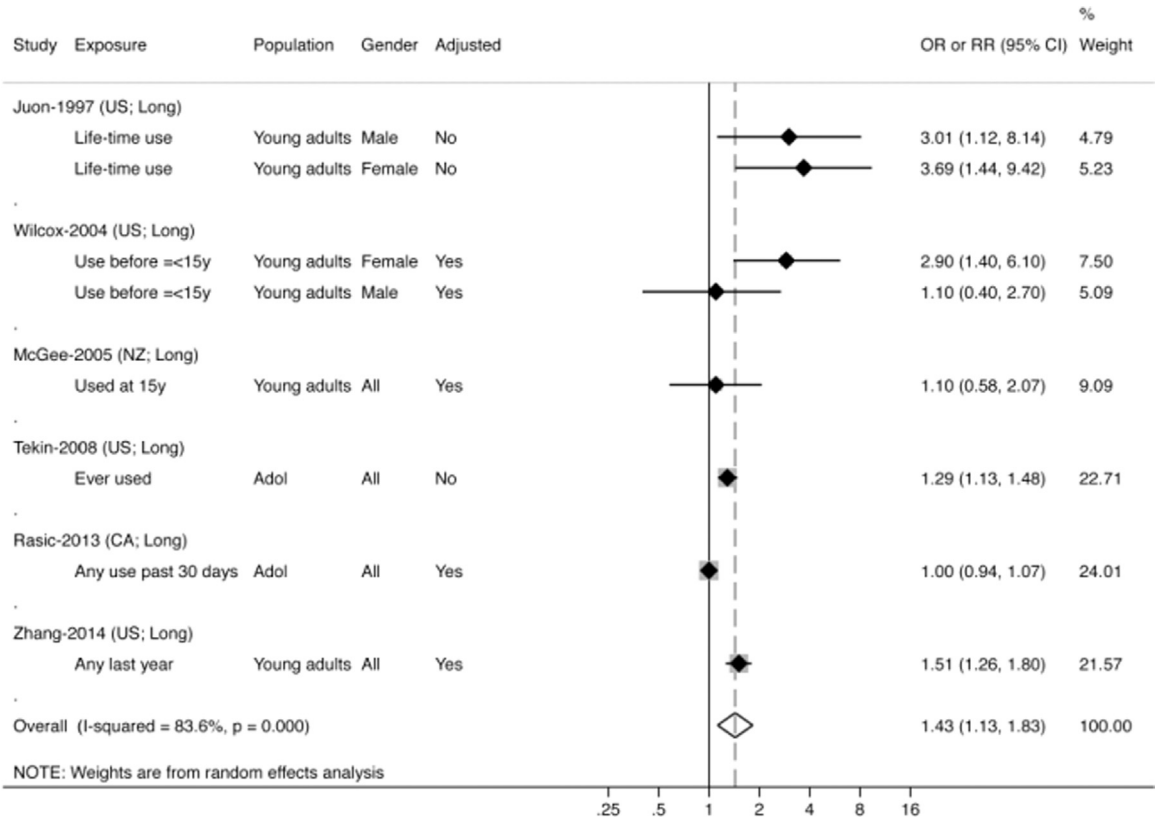

Fig. 1. Forest plot showing effect sizes for suicidal ideation according to any cannabis use in individual studies (random effects). Heterogeneity Q=42.8 (7 df); $p < 0.001$. Egger's test bias=2.26; 90%CI=(0.56–3.96); p=0.042. Abbreviations: CA-Canada, NZ-New Zealand, US-United States, Long:Longitudinal, Adol:Adolescents.

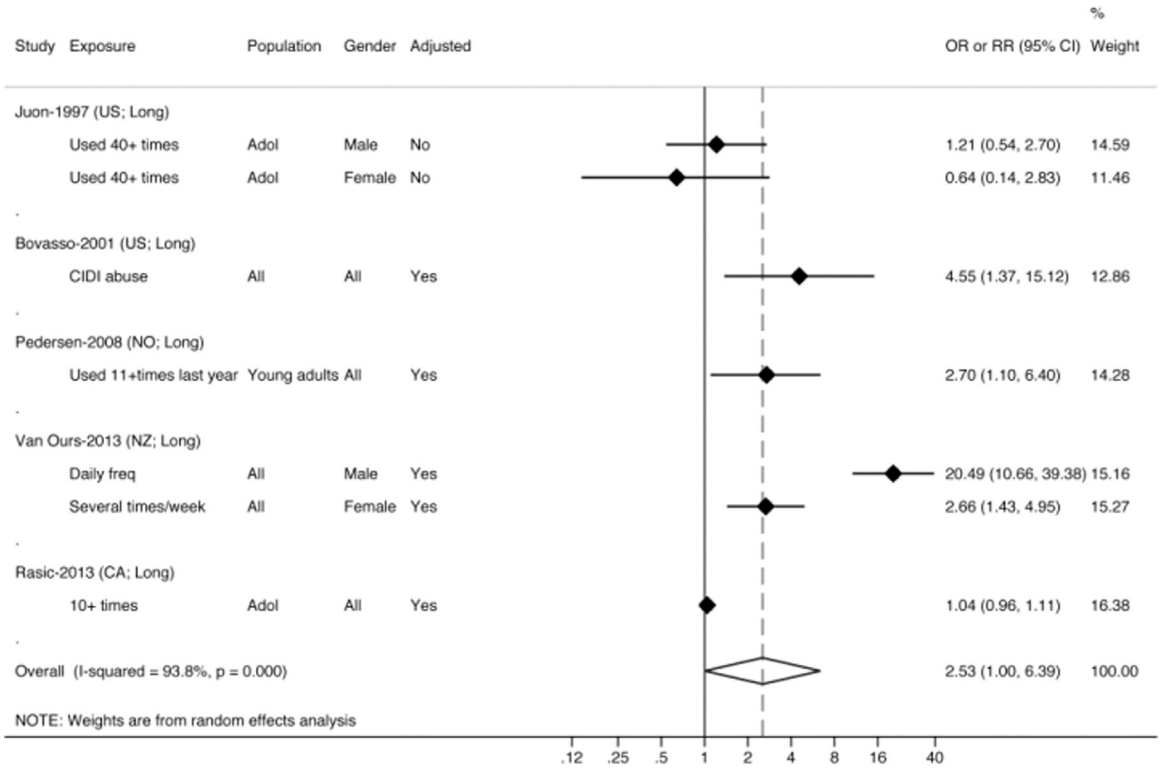

Fig. 2. Forest plot showing effect sizes for suicidal ideation according to heavy cannabis use in individual studies (random effects). Heterogeneity Q=96.95 (6 df); $p < 0.001$. Egger's test bias=2.86; 90%CI=(−0.26–5.96); p=0.124. Abbreviations: CA-Canada, NO-Norway, NZ-New Zealand, US-United States; Long:Longitudinal, Freq:Frequency, Adol:Adolescents.

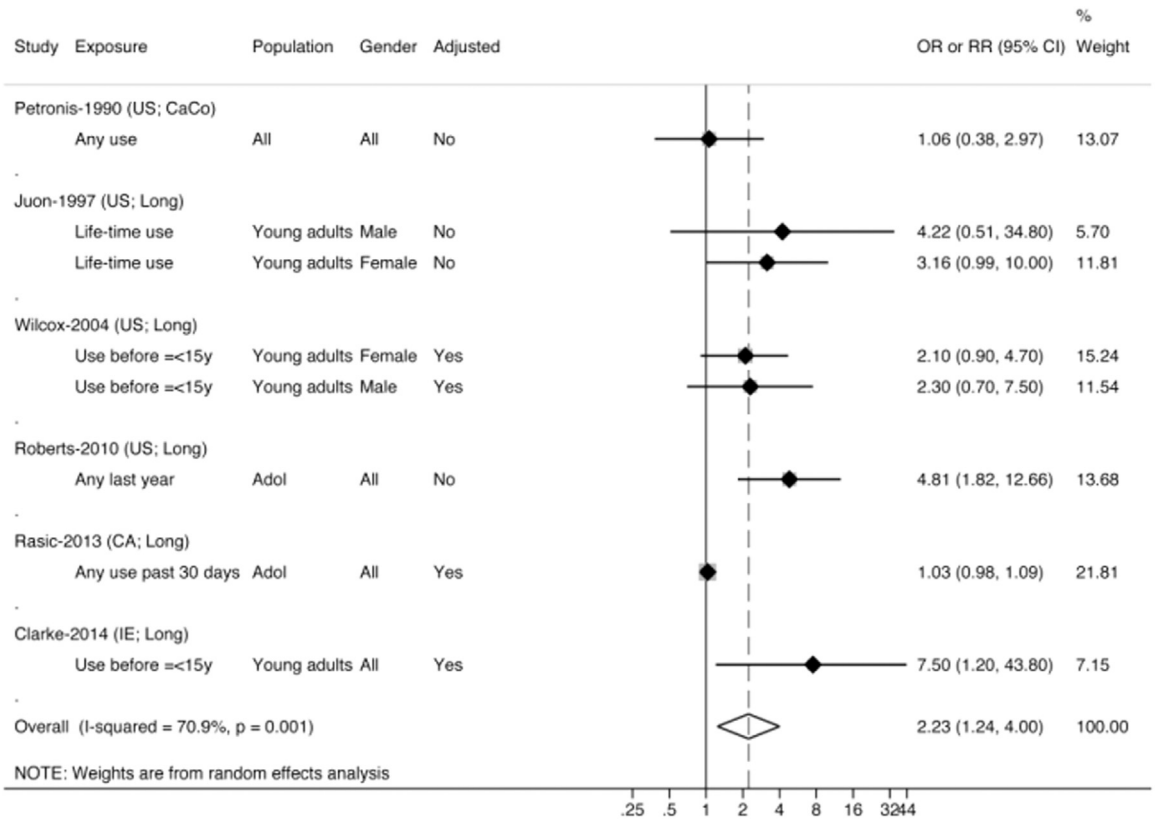

Fig. 3. Forest plot showing effect sizes for suicidal attempt according to any cannabis use in individual studies (random effects). Heterogeneity Q=24.05 (7 df); p=0.001. Egger's test bias=1.73; 90%CI=(1.00–2.45); p=0.004. Abbreviations: CA-Canada, IE-Ireland, US-United States; Long:Longitudinal, CaCo:Case-Control, Adol:Adolescents.

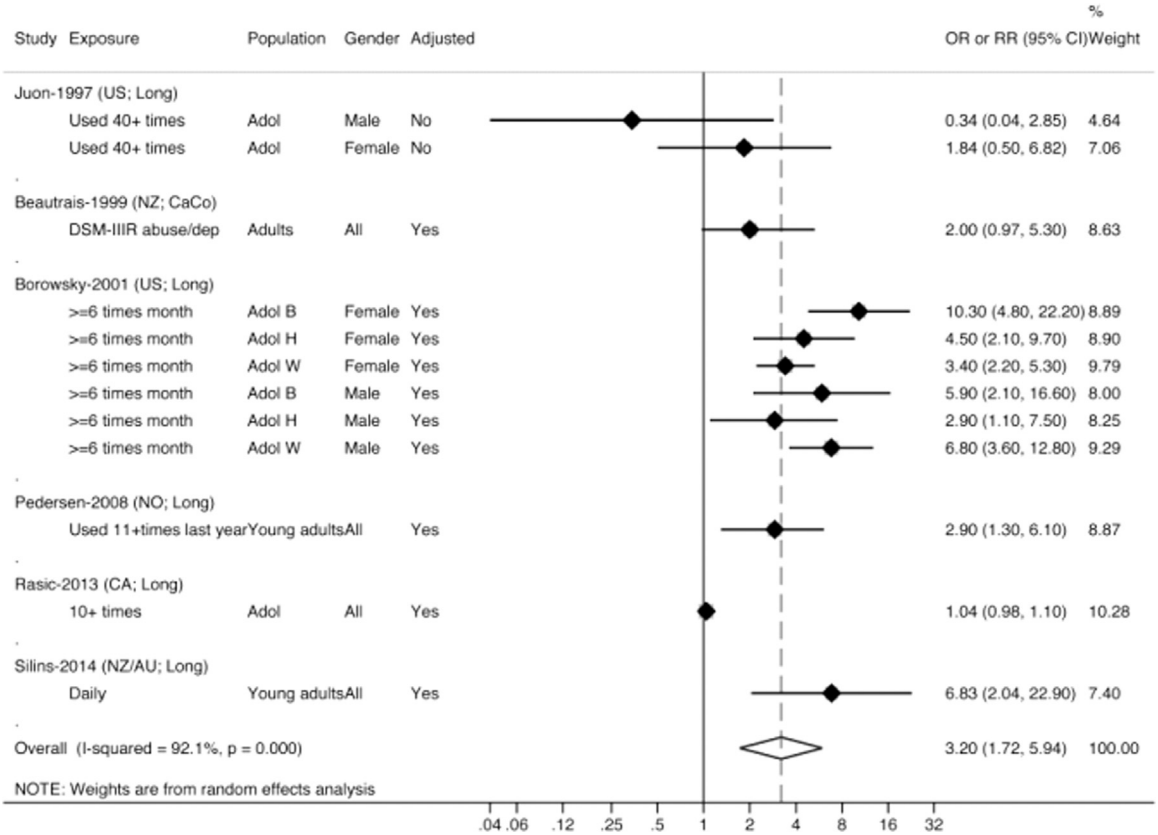

Fig. 4. Forest plot showing effect sizes for suicidal attempt according to heavy cannabis use in individual studies (random effects). Heterogeneity Q=138.5 (11 df); p < 0.001. Egger's test bias=3.14; 90%CI=(1.82–4.47); p=0.002. Abbreviations: AU-Australia, CA-Canada, NO-Norway, NZ-New Zealand, US-United States; Long:Longitudinal, CaCo: Case-Control, Adol B/H/W:Adolescents Black/Hispanic/White, dep:dependence.

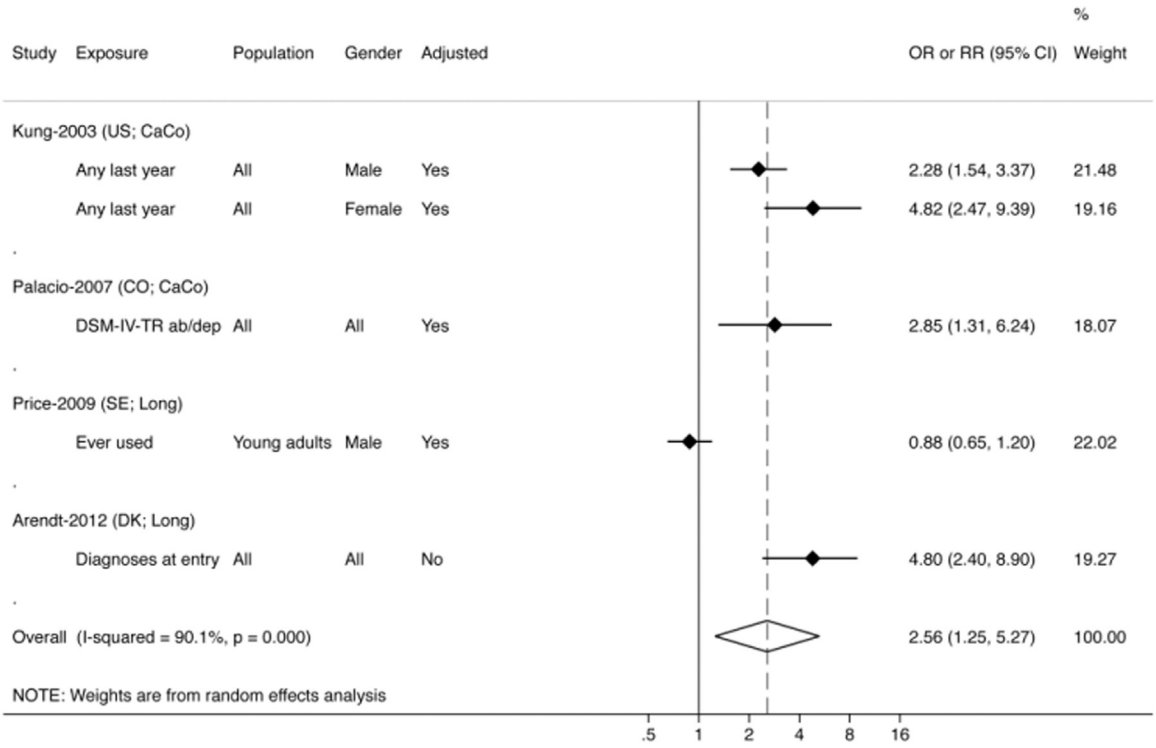

Fig. 5. Forest plot showing effect sizes for suicide according to cannabis exposure in individual studies (random effects). Heterogeneity Q=40.52 (4 df); $p < 0.001$. Egger's test bias=6.94; 90%CI=(1.26–12.61); p=0.064. Abbreviations: CO-Colombia, DK-Denmark, SE-Sweden, US-United States; Long:Longitudinal, CaCo:Case-Control, ab/dep: abuse/dependence.

2008; Price et al., 2009; Roberts and Roberts, 2010; Arendt et al., 2013; Rasic et al., 2013; Van Ours et al., 2013; Zhang and Wu, 2014; Silins et al., 2014). As expected, crude estimates were generally higher in magnitude and indicate mostly statistically significant associations. Adjusted estimates usually are lower than the observed crude (unadjusted) estimates and sometimes (but not always) result in confidence intervals that include the null value (i.e., below 1). In some instances (notably (Price et al., 2009), and (Beautrais et al., 1999), the adjustment of confounding variables results in non-significant cannabis-suicidality associations, but in other instances adjustments have a small impact (Roberts and Roberts, 2010; Silins et al., 2014). Because of the complexities related to the possible pathways and the large number of risk factors for suicidal behavior, including childhood trauma, impulsiveness, other substances and mental disorders, among others, whether confounding explains all the observed associations remains a question for further studies.

Second, beyond the usual limitations of using cross-sectional studies, results from longitudinal studies could still be attributed to reverse causality (suicidal ideation or attempt causing or increasing the use of cannabis) in longitudinal panel studies with repeated measures of suicidality. In our review, few studies actually tested for reverse causality. Of studies testing for reverse-causation, two studies concluded that reverse casualty was not found on ideation and attempt (Pedersen, 2008) and on ideation only (Van Ours et al., 2013); another study reported findings consistent with reverse causality: suicide ideation leading to cannabis use (Zhang and Wu, 2014). Other studies, investigating cannabis use and broad indicators of health (i.e., other than suicidal behavior; (Bovasso, 2001), and (Baggio et al., 2014)), did not find evidence of reverse causality (e.g., depression causes cannabis use). The current evidence to date, albeit small, does not suggest reverse-causality (suicidal behavior leading to cannabis use). However, this is an area that deserves future dedicated research.

4.4. Limitations of the chronic cannabis use-suicidality literature

The GBD estimate for the association of opioids, cocaine and amphetamine on death by suicide explicitly focuses on dependence of these drugs, not use of these drugs (Ferrari et al., 2014). We found only one study on cannabis use disorder and death by suicide (Palacio et al., 2007). We only found 3 studies that reported on diagnoses of abuse/dependence and suicide ideation or attempt (Newcomb et al., 1999; Beautrais et al., 1999; Bovasso, 2001). The bulk of studies is concentrated in a few countries by a small group of researchers. More importantly, most studies had a small number of cases (i.e., presence of ideation and attempts) and some used complex cannabis dose-response analyses adjusting for a long list of control variables thereby making estimates less precise/stable. Finally, for studies investigating chronic cannabis-death by suicide relations, there are only four studies, and the most modern study with a large follow-up period, included only young adult males (Price et al., 2009).

4.5. Suggestions for further studies of acute cannabis-suicidal behavior relations

The literature needs controlled studies, particularly studies that specifically assess acute use immediately prior to suicidal behavior (as opposed to only toxicology reports which may detect use weeks prior to testing) and that use within-person designs. New studies should better differentiate between acute and chronic use of cannabis and focus on study designs that help to disentangle the possible role of each one in their relation with suicidal behavior. Additional national and international studies that assess the presence of (1) cannabis use immediately prior to any suicide attempt (and not just for attempts deemed to be drug-related) and (2) during a comparative control period/group should be encouraged. Given substantial co-use of substances prior to an attempt, information regarding sole-use of cannabis and combined

use with specific non-cannabis substances would inform future reviews on this topic. Studies which include both acute use and the usual frequency of use/associated problems (cannabis use disorder) will also help to determine the boundaries of any observed acute cannabis-suicidal behavior association (i.e., effect modifier). Extensions of the case-crossover coupled with psychological autopsy methods may help to identify patterns of substance use (and provide control periods) that could inform effective interventions. Further, as discussed by (Karila et al., 2014), there are two main ingredients in cannabis, Delta-9-tetrahydrocannabinol (THC) and Cannabidiol (CBD). THC is believed to be responsible for the addictive potential of cannabis (e.g., subjective euphoria), and resulting anxiety/dysphoria, cognitive deficits, and psychotic symptoms, while CBD is the primary non psychoactive constitute, and has shown to mitigate potential resulting effects of THC (e.g., acute psychotic symptoms) and has anxioloytic properties. Importantly, levels of THC vary by mode of administration and by product. Given, divergent/competing psychopharmacological and psychiatric effects across specific types of marijuana, with varying levels of THC and CBD, each strain may have different implications for acute and chronic suicide risk, and this should be area of future study.

4.6. Future studies needed to determine chronic cannabis-suicidality relations

Based on this review, controlled studies of death by suicide and chronic cannabis use are a priority. Inclusion of both sexes, additional age groups, and diverse geographical areas is necessary in order to increase the scope of our knowledge. Since cannabis use and cannabis use disorder may affect suicidal behavior indirectly by affecting those with a prior disorder (Agrawal and Lynskey, 2014) studies among patients with and without a comorbid disorder are needed. Analyses of suicide among drug-related deaths among cannabis users may also shed additional insights (Vento et al., 2011). Another priority across all suicidality outcomes is to include measures of heavy cannabis involvement, probably using current classification systems of mental disorders (cannabis use disorders). More studies that target dose-response analyses are needed. This will require larger sample sizes to ensure an adequate number of incident cases of suicide ideation and especially of suicide attempt. Longitudinal study designs that avoid the possibility of confounding and reverse causality, or model the possibility of both cannabis leading to suicide ideation-attempt and suicidal ideation-attempt leading to cannabis pathways, are recommended. While cohort studies of large well-defined samples are preferable, they will take time to complete. One option is to actively identify prior cohort studies on death by suicide among users of other substances (alcohol, opioids, cocaine and other stimulants). Such studies may contain data on cannabis use for re-analysis. Another option is the identification and re-analysis of previous psychological autopsy studies, a study design which has been underutilized in this area.

4.7. Summary and implications for future research

We currently lack evidence that acute cannabis use increases imminent risk for suicidality and this is an area of high priority. When studying suicidal behavior, case-crossover studies are likely the most ideal design, given its focus on examining *within-person* transient (or short-term) changes, the ease of examining co-use and sole-use of substances, and integrating effect modifiers (e.g., usual frequency of cannabis use). Also, it would be beneficial to explore whether the case-crossover methodology could be used within psychological autopsy studies in order to better understand the role of acute cannabis in death by suicide.

The current evidence tends to support that chronic cannabis use can predict suicidality. The lack of homogeneity in the measurement of cannabis exposure, the small number of cases of suicidality included in these reports, the concentration of research in a few geographical areas, and in some instances the lack of measurement of other key risk factors (including other substances such as alcohol), tempered this conclusion. While new studies are recommended, older and current studies seem to under-use or under-report information that could inform a critical analysis for the potential of cannabis-suicidality relations. Re-analysis of prior reports is thereby recommended as a first step in understanding the role of chronic cannabis use on suicidality.

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