

APPENDIX 3

Table A.3.1. Baseline Characteristics of Eligible Studies

Study Identification	Population Characteristics	Study Design	Exposure	Outcome	Mean Age at Initiation of Cannabis Use (Years)	Mean Length of Follow-Up	Covariates	Results
Andreasson et al. (1987)	45,570 Swedish conscripts Sweden % Male: 100 Mean age: NR ¹ (Age range: 18 to 20)	Cohort	Self-reported cannabis use	Schizophrenia at 15-year follow-up	NA ²	15 years	Socioeconomic status, prior psychiatric diagnosis, other substance abuse, father's alcohol abuse, parental divorce, disturbed conditions of upbringing, police contact	A dose-response relationship between cannabis use at age 18 and greater future risk for developing schizophrenia at follow up; Higher relative risk (RR) for schizophrenia among high consumers of cannabis (> 50 times) compared to non-users (RR = 6.0; 95% CI = [4.0, 8.9])
Arseneault, (2002)	759 % Male: NR Mean Age: NR New Zealand Recruitment as part of the Dunedin Multidisciplinary	Cohort	Drug use at ages 15 and 18 Controls vs. Cannabis users by age 15 and age 18	Psychiatric symptoms (Symptoms of schizophrenia, depression, Diagnosis of schizophreniform disorders, depression)	NA	Follow-up at age 26	Psychotic symptoms at age 11, use of other drugs during adolescence	All participants were male Cannabis users by age 15 and by age 18 had more schizophrenia symptoms than controls at age 26, which remained significant after controlling for psychotic symptoms at age 11, Cannabis use by age 15 did not predict depressive

¹ Not reported

² Not available

	Health and Development Study							outcomes at age 26 No sex differences reported
Bechtold et al. (2015)	506 boys in seventh grade (249 included in follow-up) USA % Male: 100 Mean Age at start: 14 Data taken from the oldest cohort of the Pittsburgh Youth Study	Cohort	Different developmental patterns of cannabis use from early-adolescence to young adulthood (mid-20s)	Psychosis (among other physical and mental health outcomes)	NA	From age 15 to age 26 (Every 6 months for 2.5 years, then annually for an additional 10 assessments Final assessment at age 36)	Socioeconomic status, co-occurring use of other substances, prior physical/mental health, access to medical care	The various cannabis trajectory groups were not significantly different from one another in terms of physical and mental health outcomes in the mid-30s All participants were male, thus sex differences not investigated
Cloak et al. (2015).	122 participants (80 cannabis users and 42 controls) between the ages of 13 to 23 years recruited from a community in Hawaii Controls – used cannabis less than 5 times	Case-control	Cannabis use vs non-use measured through self-report	Psychiatric symptoms measured through Symptoms Checklist-90R and Brief Psychiatric Rating Scale	Controls: 18.5 (SD = 0.8) Light cannabis users: 15.7 (SD = 0.4) Heavy cannabis users: 13.9 (SD = 0.4)	NA	Number of tobacco cigarettes smoked in lifetime, alcohol use	Younger age at initiation of cannabis use was associated with more psychiatric symptoms: Paranoid ideation ($r = -0.24$ $p = .031$) No sex difference reported
Degenhardt et al. (2012)	1756 adolescents followed to	Cohort	Cannabis use and dependence	Major depressive episode (MDE) and anxiety	NA	15-year with 9 waves (adolescence to age 29)	Sex, neither parent having completed secondary	Daily cannabis use associated with anxiety disorder at 29 years [Adjusted OR = 2.5, 95%

								No difference in association according to sex
Di Forti et al. (2014)	410 first episode psychosis patients UK % Male: 66 Mean age: NR (Age range: 18-65) Recruitment as part of the Genetics and Psychosis (GAP) Study	Cohort	Patterns of cannabis use	Age of Onset of Psychosis (AOP)	16.04 (<i>SD</i> = 4.3)	NA	Ethnicity, gender	The patients who started cannabis use at age 15 or younger had an earlier onset of psychosis (Mean years = 27.0, <i>SD</i> = 6.2, Median Years = 26.9) than those who had started after 15 years of age (mean years = 29.1, <i>SD</i> = 8.5, median years = 27.8; <i>HR</i> = 1.40, 95% <i>CI</i> = [1.06, 1.84]) Within each gender, cannabis use was associated with earlier onset of psychosis
Estrada et al. (2011)	157 Caucasian psychiatric inpatients Classified into 2 groups: 80 with schizophrenia-spectrum disorders 77 with non-psychotic disorders	Cross-sectional	Cannabis use vs non-use measured through a semi-structured interview	Age at onset of admission for psychosis measured through interviews with patients, information provided by relatives, and review of medical records	Schizophrenia-spectrum group: 14.6 years (<i>SD</i> = 1.61) Non-psychotic disorders group: 13.8 years (<i>SD</i> = 1.44)	NA	NA	age at first cannabis use correlates with age at onset in both schizophrenia-spectrum and other psychiatric disorder groups No gender differences were reported.

	Mean age = 17.01 SD = 3.6							
Faiman & Anthony (2012)	173,775 community-dwelling adult participants USA % Male: NR Mean age: NR Data from the National Surveys on Drug Use and Health (NSDUH) (2005-2009)	Cross-sectional	Early onset cannabis use (≤ 18)	Incident depression spell during adulthood	NA	NA	Sex, age, race/ ethnicity, years of cannabis involvement, tobacco cigarette onset, alcohol onset	Both early-onset (≤ 18 years) and adult-onset (> 18 years) cannabis smokers had a modest excess odd of a depression spell compared to never cannabis smokers, even with covariate adjustment ($OR = 1.7$ and 1.8 , respectively; both $p < .001$) Estimates for early- and adult-onset cannabis smokers did not statistically differ from one another No sex differences reported
Fergusson et al. (1996)	927 children recruited as part of Christchurch Health and Developmental Study, New Zealand, % Male: NR Mean age: NR (Age range: 14-15)	Cohort	Cannabis users (Identified from self-report or parental reports) vs. non-users	Depression and anxiety (Self-reports using the Diagnostic Interview Schedule for Children, DISC)	NA	1 year	Family and social background (Family social position, family functioning, family history of alcohol or drug abuse), individual characteristics (childhood behavioural problems and cognitive abilities, commitment to education at age 15, peer affiliation at age 15, adjustment at age 15)	After adjustment for confounders including family disadvantages, early adjustment problems, substance using and delinquent peers, no more significant differences in risk between the cannabis users and non-users: (Depression: $OR = 1.4$, $95\% CI = [0.7, 2.7]$; Anxiety: $OR = 1.2$, $95\% CI = [0.5, 2.8]$) No sex differences reported

Study-based recruitment								
Fergusson et al. (2003)	1025 adolescents and young adults % Male: NR Mean Age: NR New Zealand Data taken from longitudinal study of Christchurch Health and Development Study (CHDS)	Cohort	Cannabis dependence at ages 18 and 21	Rates of psychotic symptoms	NA	NA	Pre-existing psychotic symptoms, substance use, anxiety and major depression in the preceding 12 months, deviant peers, adverse life events, age of leaving the family home sociodemographic factors, family functioning, parental adjustment, individual characteristics, prior mental health, adjustment measures,	Following adjustment for confounding factors, those with cannabis dependence still had an increased rate of psychotic symptoms (rate ratio: 1.8; 95% CI: [1.2-2.6]; $p < .005$) No sex differences reported
Galvez-Buccollini et al. (2012)	57 people aged 18 to 39 years with non-affective psychosis USA % Male: 82.5 Mean age: 25.2	Cross-sectional	History of cannabis use (Heavy cannabis use was defined as a history of using cannabis 50 or more times in one year)	Age at onset of psychosis (the age when the patient first experienced delusions, hallucinations, disorganized speech, disorganized or catatonic behavior)	15.4 ($SD = 3$)	NA	Age, sex, lifetime diagnosis of alcohol abuse or dependence, family history of schizophrenia in a first degree relative	Found a significant association between age at initiation of cannabis use and age at onset of psychosis ($\beta = 0.4$, 95% $CI = [0.1, 0.7]$, $p = .004$) as well as age at first hospitalization following psychosis onset ($\beta = 0.4$, 95% $CI = [0.1, 0.8]$, $p = .008$) after adjustment for confounders No sex differences reported

Green & Ritter (2000)	1941 young men USA % Male: 100 Mean age: NR Data from the 1985 wave of the Young Men and Drugs Survey (a nationally representative sample of men from the 1944-1954 birth cohort)	Cross-sectional	Age of cannabis initiation (Obtained retrospectively, age ≤ 16 as early users), Frequency of current cannabis use	Depressive symptomatology	21 (and 7 months) 15.4 ($SD = 3$)	NA	Educational attainment, employment status, marital status, frequency of cannabis use, number of other drugs in the last year, frequency of use of other drugs including tobacco and alcohol	Early cannabis initiation (≤ 16 years) was weakly associated with higher depression in adulthood and this relationship was mediated by educational attainment, employment status, marital status and other drug use mainly alcohol and tobacco use All participants were male
Hayatbakhsh et al. (2007)	Data used from Mater University Study of Pregnancy participants followed from birth to age 21	Cross-sectional	Age at initiation of cannabis use and frequency of cannabis use measured using self-report	Anxiety and depression at age 21 measured using the Young Adult Self-Report version of the Child Behavior Checklist Anxiety and depression symptoms were measured using the Youth Self-Report	15.9 years ($SD = 1.9$ years)	21 years	Gender, age, mother's age and education, maternal marital status and quality, family income, maternal and adolescent's mental health, maternal substance abuse, adolescent tobacco and alcohol use	Early age of cannabis initiation and frequent cannabis use during adolescence was associated with symptoms of anxiety and depression at age 21 $OR = 3.4, CI = [1.9, 6.1]$ No sex differences reported
Henquet et al. (2004)	2437 young people 14 to 24 years of age	Cohort	Cannabis use, and predisposition	Psychotic symptoms at follow-up	NA	4 years after baseline	Age, sex, socioeconomic status, urbanicity, childhood trauma, predisposition for psychosis at	After adjustment for the potential confounders, cannabis

	Germany		for psychosis at baseline				baseline, use of other drugs, tobacco, and alcohol	use at baseline increased the cumulative incidence of psychotic symptoms at follow up (Adjusted <i>OR</i> = 1.67, 95% <i>CI</i> = 1.13 to 2.46)
	% Male: 51.3 %							
	Mean age: 18.3							
	Population-based sample							No sex differences reported
Konings et al. (2008)	431 participants aged 12 to 23	Cross- sectional	Early cannabis use	Psychotic symptoms	13.3 (<i>SD</i> = 2.3, <i>range</i> = 7- 19)	NA	Age, School type, ethnicity, sex, current use of cannabis, use of other drugs	Exposure before but not after the age of 14 years predicted psychotic symptoms (Respectively <i>b</i> : 0.71, 95% <i>CI</i> = [0.22, 1.19], <i>p</i> = 0.004 and <i>b</i> : 0.11, 95% <i>CI</i> = [0.57, 0.36], <i>p</i> = 0.66)
	Trinidad							No sex differences reported
	% Male: 45							
	Mean age: 16							
	Population-based recruitment							
Manrique-Garcia et al. (2012)	45,087 Swedish conscripts with data on cannabis usage at ages 18- 20	Cohort	Cannabis use	Depression and other affective outcomes	NA	35-year follow-up	Diagnosis of personality disorders, IQ score, disturbed childhood behavior, social adjustment, risky use of alcohol, smoking, early adulthood socioeconomic position, use of other drugs, being brought up in a city	Only subjects with the highest level of cannabis use had an increased crude hazard ratio for depression (<i>HR</i> = 1.5, 95% <i>CI</i> = [1.0, 2.2]), the association disappeared after adjustment for confounders
	Sweden							No evidence for an increased risk of depression among cannabis users
	% Male: 100							All participants were male
	Mean age: NR (age range: 18-20)							
	Data taken from 1969-1970 Survey							

	of Swedish Conscripts)							
McGrath et al. (2010)	3801 young adults (228 sibling pairs) Australia % Male: 47.5 % Male: 60 male sibling pairs Mean age: 20.1 Sibling pair analysis nested within a prospective birth cohort	Case- Control	Cannabis use	Psychosis related outcomes	NA	NA	Sex, age, parental mental illness, hallucinations at age 14	Duration since first cannabis use was associated with psychosis- related outcomes For duration since first cannabis use of 6 or more years, there was a significantly increased risk of (1) non-affective psychoses (aOR = 2.2; 95% CI = [1.1, 4.5]), (2) being in the highest quartile of Peters et al Delusions Inventory score (Adjusted OR = 4.2; 95% CI = [4.2, 5.8]), (3) hallucinations (Adjusted OR: 2.8; 95% CI = [1.9, 4.1]) No sex differences reported
Medina et al. (2007)	16 cannabis user aged 16 to 18 years USA % male: 72 Mean age: 18 Recruitment from schools through ads	Cross- sectional	Cannabis use,	Depression	NA	NA	Alcohol use, other drug use	Cannabis users demonstrated more depressive symptoms than controls Cannabis use and smaller white matter volume each predicted higher levels of depressive symptoms on the Hamilton Depression Rating Scale

								Cannabis use interacted with white matter volume in predicting depression scores on the Beck Depression Inventory
								No sex differences reported
Patton et al. (2002)	1601 students aged 14-15 Australia % Male: 45.6 Mean age: 14.5 (at wave 1) A statewide secondary school recruitment	Cohort	Cannabis use in adolescence	Rates of depression and anxiety	NA	6 years (7 waves)	Concurrent use of other substances including alcohol, tobacco, and other illicit substances	Daily use in women associated with an over fivefold increase in the odds of reporting a state of depression and anxiety after adjustment for current use of other substances (<i>OR</i> = 5.6, 95% <i>CI</i> = [2.6,12]) Weekly or more frequent cannabis use in teenagers predicted an approximately twofold increase in risk for later depression and anxiety (<i>OR</i> = 1.9, 95% <i>CI</i> = [1.1,3.3]) after adjustment for confounders Daily cannabis use was associated with higher prevalence of depression and anxiety among females
Pedersen, (2008)	2033 young participants Norway % Male: NR Mean age: NR	Cohort	Cannabis use	Later depression	NA	13-year (From early teens to late twenties)	Socioeconomic status, parental relationships and family characteristics, pubertal development, education, school dropout, source of income, conduct problems, alcohol problems	Early adolescence use (< 16 years) had no associations with later depression No sex differences reported

	Population-based, Data from the Young in Norway Longitudinal Study							
Schubart et al. (2011)	17698 adolescents and young adults % Male: 51 Mean Age: 21.6 Netherlands	Cross-sectional	Age at initiation and amount of cannabis use	Subclinical psychosis symptoms, Top 10% scores in three symptom dimensions of self-reported psychiatric experiences	< 12 years	NA	NA	Cannabis use at age 12 or younger strongly associated with a top 10% score on psychotic experiences (<i>OR</i> 3.1, 95% <i>CI</i> : [2.1–4.3]) For heavy users (>25 Euro/week) for negative Symptoms: (<i>OR</i> = 3.4 (95% <i>CI</i> : [2.9–4.1]), For psychotic experiences: (<i>OR</i> = 3.0 (95% <i>CI</i> : [2.4–3.6]), For depressive symptoms: (<i>OR</i> = 2.8 (95% <i>CI</i> : [2.3–3.3]) No sex differences reported
Zammit et al. (2002)	50,053 Swedish conscripts UK % Male: 100 Mean age: NR (Age range: 18- to 20)	Cohort	Self-reported use of cannabis	Admissions to hospital for ICS-8/9 schizophrenia and other psychoses	NA	26 years (1970-96)	Personality traits related to social integration, psychiatric diagnosis at conscription, disturbed behaviour in childhood, IQ, history of alcohol abuse, family history of psychiatric illness, family financial situation, father's occupation, other sociodemographic factors	For subjects with sole cannabis use and no other drugs, this dose–response relationship was significant, and the overall adjusted <i>OR</i> was 1.3 (95% <i>CI</i> = [1.1–1.5], <i>p</i> < .015) For those who had used

Record linkage

(brought up in a city,
paternal age), cigarette
smoking

cannabis more than 50
times, the adjusted *OR* rose
to 6.7 (95%
CI = 2.1–21.7)

All participants were male

Table A.3.2. The Newcastle-Ottawa Scale for Assessing Quality of Observational Studies³*Cross-Sectional Studies (Psychosis as Study Outcome)*

Study Identification	Selection				Comparability of subjects in different outcome groups	Outcome		Total Score	Quality Characterization
	Representativeness of the sample	Sample size	Non-respondents	Ascertainment of exposure (Risk Factor)		Assessment	Statistical Test		
Estrada et al. (2011)	*	-	-	**	-	**	*	6	Medium
Galvez-Buccollini et al. (2012)	*	-	-	*	**	**	*	7	Medium
Konings et al. (2008)	**	-	-	*	*	*	*	6	Medium
Schubart et al. (2011)	**	-	-	*	-	*	*	5	Medium

³ An asterisk (*) indicates the study has the listed characteristic. A dash (-) indicates the above category is not applicable to that study. Studies can receive a maximum of ten stars. Studies are characterized based on scores. Some categories can receive a maximum of two asterisk: Ascertainment of exposure, comparability, outcome assessment (in cross sectional designs); comparability (in case-control and cohort designs).

Case-Control Studies (Psychosis as Study Outcome)

Study Identification	Selection				Comparability of cases and controls on basis of design/analysis	Outcome			Total Score	Quality Characterization
	Case Definition Adequate	Representativeness of the cases	Selection of Controls	Definition of Controls		Assessment of exposure	Method of ascertainment for cases and controls	Non-response rate		
McGrath et al. (2010)	*	*	*	*	**	-	*	-	7	Medium

Cohort Studies (Psychosis as Study Outcome)

Study Identification	Selection				Comparability of cohorts on the basis of design/analysis	Exposure			Total Score	Quality Characterization
	Representative of Exposed Cohort	Selection of Non-exposed cohort	Ascertainment of Exposure	Outcome Not Present at Baseline		Assessment of Outcomes	Sufficient Follow-up Duration	Adequate Follow-up		
Bechtold et al. (2015)	*	*	-	*	**	*	*	*	8	High
Fergusson et al. (2003)	*	-	*	*	**	*	-	-	6	Medium
Henquet et al. (2004)	*	*	*	-	**	*	*	*	8	High

Zammit et al. (2002)	*	*	-	*	**	*	*	*	8	High
Andreasson et al. (1987)	*	*	-	*	**	*	*	-	7	Medium
Di Forti et al. (2014)	*	*	*	*	*	*	*	*	8	High
Areseneault et al. (2002)	*	*	-	*	**	*	*	-	7	Medium

Cross-Sectional Studies (Depression and/or Anxiety as Study Outcome)

Study Identification	Selection				Comparability of subjects in different outcome groups	Outcome		Total Score	Quality Characterization
	Representativeness of the sample	Sample size	Non-respondents	Ascertainment of exposure (Risk Factor)		Assessment	Statistical Test		
Faiman & Anthony (2012)	*	*	*	*	**	*	*	8	High
Green & Ritter (2000)	*	-	-	*	**	*	*	6	Medium
Medina et al. (2007)	-	-	-	*	*	**	*	5	Medium

Case-Control Studies (Depression and/or Anxiety as Study Outcome)

Study Identification	Selection				Comparability of cases and controls on basis of design/analysis	Outcome			Total Score	Quality Characterization
	Case Definition Adequate	Representativeness of the cases	Selection of Controls	Definition of Controls		Assessment of exposure	Method of ascertainment for cases and controls	Non-response rate		
Cloak et al. (2015)	-	*	*	*	*	-	*	-	5	Medium
de Graaf et al. (2010)	-	*	*	*	**	-	*	-	6	Medium

Cohort Studies (Depression and/or Anxiety as Study Outcome)

Study Identification	Selection				Comparability of cohorts on the basis of design/analysis	Exposure			Total Score	Quality Characterization
	Representative of Exposed Cohort	Selection of Non-exposed cohort	Ascertainment of Exposure	Outcome Not Present at Baseline		Assessment of Outcomes	Sufficient Follow-up Duration	Adequate Follow-up		
Degenhardt et al. (2012)	*	*	-	-	*	*	*	*	6	Medium
Fergusson et al. (1996)	*	*	*	-	*	-	-	*	5	Medium
Hayatbakhsh et al. (2008)	*	*	-	*	**	-	-	*	6	Medium

Manrique-Garcia et al. (2012)	*	*	-	*	**	*	*	*	8	High
Patton et al. (2002)	*	*	-	-	*	*	*	*	6	Medium
Pedersen, (2008)	*	*	*	-	*	*	*	*	7	Medium
