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Alexander Denissoff

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To Ella, Aatos and Elina;

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ALEXANDER DENISSOFF: Psychiatric sequelae of adolescent cannabis use in the Northern Finland 1986 Birth Cohort
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ABSTRACT

Adolescence is a time of significant brain development, and this maturation process is thought to represent a time of heightened vulnerability to the adverse effects of environmental risk factors such as cannabis. While the association of adolescent cannabis use and subsequent psychosis and depression has received considerable attention in the existing literature, very few prospective studies have focused on the association of early cannabis exposure with severe self-harm or suicide, bipolar disorder, or anxiety disorders. Moreover, though there are reports focusing on the prognostic effect of cannabis use in patients at high risk for psychosis, population-based studies examining the prognosis of non-treatment-seeking adolescents with both psychotic-like experiences (PLEs) and cannabis exposure are scarce.

The aim of this thesis was to examine the association of early cannabis use with severe self-harm requiring medical attention, bipolar disorder, and depressive or anxiety disorders (studies I–III). Secondly, the prognosis of adolescents with PLEs with or without cannabis exposure was examined with respect to several psychiatric sequelae (study IV). A prospective general population-based Northern Finland 1986 Birth Cohort (N=9432) was utilized. Data on substance use including cannabis use and early psychopathology including PLEs were gathered in a field study in 2001–02 when the participants were aged 15–16 years. The participants were followed for 18 years (until the year 2018, when they were 33 years). Data on diagnoses made in clinical practice from nationwide registers were utilized as outcome measures.

Early cannabis use was found to be associated with severe self-harm (Study I). While an independent association of this exposure was seen with depressive/anxiety disorders (Study II), the association with a bipolar disorder attenuated to non-significance after adjusting for types of other substance use (Study III). In study IV, participants with both PLEs and early cannabis exposure were found to display a greater odds for adverse psychiatric sequelae than participants with only PLEs.

In summary, the findings support the proposal that early cannabis use is an adverse prognostic marker for other psychiatric sequelae in addition to psychosis.

KEYWORDS: cannabis, self-harm, bipolar disorder, depressive disorders, anxiety disorders, psychosis

TURUN YLIOPISTO
Lääketieteellinen tiedekunta
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ALEXANDER DENISSOFF: Nuorten kannabiksen käytön mielenterveydellinen ennuste Pohjois-Suomen 1986 syntymäkohortissa
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TIIVISTELMÄ

Nuoren kehittyvien aivojen arvellaan olevan erityisen haavoittuvia kannabiksen kaltaisille ympäristöriskitekijöille. Kannabiksen käytön ja psykoosin välistä yhteyttä on tutkittu monimuotoisesti, mutta varhaisen kannabikselle altistumisen ja itsensä vahingoittamisen, kaksisuuntaisen mielialahäiriön sekä ahdistuneisuushäiriöiden välistä yhteyttä on tutkittu merkitsevästi tätä vähemmän. Lisäksi siinä missä kannabiksen ennustevaikutusta psykoosiriskissä olevilla potilailla on jonkin verran tietoa, lievempien psykoosin kaltaisten oireiden ja samanaikaisen kannabiksen käytön mielenterveydellistä ennustetta nuorilla ei ole juuri kartoitettu yleisväestöpohjaisissa pitkittäistutkimuksissa.

Väitöskirjatyön tarkoitus oli tutkia varhaisen kannabiksen käytön ja vakavan itsensä vahingoittamiskäyttäytymisen, kaksisuuntaisen mielialahäiriön ja masennus- ja ahdistuneisuushäiriöiden välistä yhteyttä (tutkimukset I–III). Lisäksi varhaisen kannabiksen käytön vaikutusta mielenterveydelliseen ennusteeseen tutkittiin nuorilla, joilla oli psykoosin kaltaisia kokemuksia ja varhaista kannabiksen käyttöä. Aineistona käytettiin yleisväestöön pohjautuvaa Pohjois-Suomen 1986 syntymäkohorttia (N=9432). Kannabiksen ja muiden päihteidenkäyttöä ja psykoosin kaltaisia kokemuksia kartoitettiin kenttätutkimuksessa vuosina 2001–02 nuorten ollessa 15–16-vuotiaita. Tutkittavia seurattiin 18 vuoden ajan (vuoteen 2018 ja 33 vuoden ikään asti). Vastemuuttujat muodostettiin kansallisista rekistereistä saatavista diagnoositiedoista.

Nuoruusiän Varhainen kannabiksen käyttö oli yhteydessä vakavaan itsensä vahingoittamiskäyttäytymiseen (tutkimus I). Yhteys nuoruusiän kannabiskäytön ja masennus- ja ahdistuneisuushäiriöiden välillä havaittiin (tutkimus II), mutta yhteys kaksisuuntaiseen mielihäiriöön ei jäänyt tilastollisesti merkitseväksi monimuuttujamalleissa (tutkimus III), kun muu päihdekäyttö otettiin huomioon. Sekä psykoosin kaltaisia kokemuksia että kannabiksen käyttöä raportoineilla nuorilla oli suurempi riski erilaisiin mielenterveyshäiriöihin kuin niillä nuorilla, joilla oli psykoosin kaltaisia kokemuksia ilman varhaista kannabiksen käyttöä.

Tutkimuslöydökset viittaavat siihen, että varhainen kannabiksen käyttö on riskitekijä myöhemmille mielenterveyden häiriöille.

AVAINSANAT: kannabis, itsensä vahingoittaminen, kaksisuuntainen mielialahäiriö, mielialahäiriöt, ahdistuneisuushäiriöt, psykoosi

Table of Contents

Abbreviations

ADHD	Attention deficit hyperactivity disorder
ALSPAC	Avon Longitudinal Study of Parents and Children
AUD	Alcohol use disorder
ATP	Australian Temperament Project
CB1/2	Cannabinoid receptor type 1/2
CBD(A)	Cannabidiol(ic) (acid)
CHDS	Christchurch Health and Development Study
CIDI	Composite Diagnostic Interview
COMT	Catechol-o-methyl transferase
CUD	Cannabis use disorder
DSE	Depolarization-evoked inhibition of excitation
DSH	Deliberate self-harm
DSI	Depolarization-evoked inhibition of inhibition
DSM-5	Diagnostic and Statistical Manual of Mental Disorders 5th Edition
ECS	Endocannabinoid system
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
ESPAD	European School Survey Project on Alcohol and Other Drugs
FEP	First episode of psychosis
HCL-32	Hypomania checklist
HR	Hazard Ratio
ICD-10	International Classification of Diseases 10th Revision
IPW	Inverse probability weighting
MDD	Major depressive disorder
MRI	Magnetic resonance imaging
MUSP	Mater-University of Queensland study of Pregnancy
MTF	Monitoring the Future Study
NEMESIS	Netherlands Mental Health Survey and Incidence Study
NESARC	National Epidemiologic Survey on Alcohol and Related Conditions
NFBC1986	Northern Finland1986 Birth Cohort
NSDUH	National Survey of Drug Use and Health
NSSH	Non-suicidal self-harm

NSSI	Non-suicidal self-injury
OR	Odds ratio
PAF	Population attributable fraction
PET	Positron emission tomography
PFC	Prefrontal cortex
PLE	Psychotic-like experience
SD	Standard deviation
SP-NAP	Screen positive for non-affective psychosis
SUD	Substance use disorder
THC(A)	Tetrahydrocannabinol(ic) (acid)
VAHCS	Victoria Adolescent Health and Development Study
VIF	Variance inflation factor
YRBS	Youth Risk Behavior Survey
YSR	Youth Self Report

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Denissoff Alexander, Niemelä Solja, Scott James G, Salom Caroline L. Hielscher Emily, Miettunen Jouko, Alakokkare Anni-Emilia, and Mustonen Antti. (2021). Does cannabis use in adolescence predict self-harm or suicide? Results from a Finnish Birth Cohort Study. Acta Psychiatrica Scandinavica, 145(3):234–243.

II Mustonen Antti, Hielscher Emily, Miettunen Jouko, Denissoff Alexander, Alakokkare Anni-Emilia, Scott James G, and Niemelä Solja. (2021). Adolescent cannabis use, depression and anxiety disorders in the Northern Finland Birth Cohort 1986. British Journal of Psychiatry Open, 7(4).

III Denissoff Alexander, Mustonen Antti, Alakokkare Anni-Emilia, Scott James G., Sami Musa B, Miettunen Jouko, and Niemelä Solja. (2022). Is Early Exposure to Cannabis Associated with Bipolar disorder? Results from a Finnish Birth-Cohort Study. Addiction, 117(8):2264–2272.

IV Denissoff Alexander, Mustonen Antti, Miettunen Jouko, Alakokkare Anni-Emilia, Veijola Juha, Scott James G, Sami Musa B, and Niemelä Solja. (2022). Trajectories of adolescent psychotic-like experiences and early cannabis exposure: Results from a Finnish Birth Cohort Study. Schizophrenia Research, 246:95–102.

1 Introduction

The maturing adolescent brain is thought to be exceptionally vulnerable to the harms posed by environmental risk factors such as substance use. Thus, it is of paramount importance to examine the impact of cannabis exposure during adolescence in relation to subsequent psychiatric sequelae. To date, studies examining the association of early cannabis use with subsequent psychiatric disorders have been somewhat heterogenous in terms of sample characteristics, exposure and outcome variables used, covariates included in multivariable models, and the lengths of follow-up. Hence, it is extremely challenging to draw definitive conclusions from the existing evidence base.

Importantly, knowledge regarding the sequelae of cannabis use is markedly unequally distributed among the different outcomes that have been examined. A considerable body of research has certainly already accumulated regarding the association between cannabis use and psychosis with multiple complementary lines of evidence. These include adequately powered population-based prospective observational studies even with evidence of a dose-response (Marconi, Di Forti, Lewis, Murray, & Vassos, 2016; Robinson et al., 2022; Zammit, Allebeck, Andreasson, Lundberg, & Lewis, 2002), large multicenter case-control studies assessing the risk attributable to high-potency cannabis (Di Forti et al., 2019), high-quality register-based studies providing population attributable risk estimates (Hjorthoj, Larsen, Starzer, & Nordentoft, 2021; Hjorthøj, Posselt, & Nordentoft, 2021), and Mendelian randomization studies (Gage et al., 2017; Vaucher et al., 2018). Moreover, numerous preclinical laboratory studies with healthy volunteers on the psychotic symptoms induced by cannabis and its constituents (Hindley et al., 2020) emphasize the plausibility of this association. Thus while it might be already plausible to cautiously assert that cannabis is a component cause of psychotic disorders (D'Souza et al., 2022), the evidence if there is a causal association between cannabis use and other psychiatric sequelae such as self-harm, suicide or mood and anxiety disorders is far from conclusive. In addition, while there is a considerable body of research regarding the prognostic effect of concomitant cannabis use in patients found to be at a clinically high risk for psychosis (Kraan et al., 2016), little

is known about the mental health trajectories of non-help-seeking individuals with both subclinical psychotic-like experiences (PLEs) and cannabis exposure.

This thesis aims to narrow the knowledge gaps concerning these understudied questions pertaining to early cannabis exposure such as its associations with self-harm, depression, anxiety disorders and bipolar disorder as well as the prognosis of non-help-seeking adolescents with PLEs and cannabis exposure. A large population-based birth cohort (Northern Finland 1986 Birth Cohort) with prospective data and a long follow-up period was available for evaluation which enhances the generalizability of the results and mitigating concerns of reverse causality. As the incidence of most mental disorders is known to peak by the third decade of life (Solmi, Radua, et al., 2021), the follow-up period of the studies included in this thesis covers the period during which the respective outcomes of interest are most likely to emerge. Lastly, the use of register-based data for the outcomes studied instead of symptom scales as proxy measures or questionnaire-based data enhances the validity of the results.

2 Review of the Literature

2.1 Adolescence

The Latin root of the word adolescence, *adolescere*, to grow into maturity, aptly reflects the nature of the developmental phase heralded by pubescence and lasting until the individual achieves adulthood. By convention, adolescence is defined as the interval between puberty and the attainment of a stable role in society (Sawyer, Azzopardi, Wickremarathne, & Patton, 2018). Three distinct phases have been discerned, namely early, mid and late adolescence corresponding to ages of 11–13, 14–18 and 19–21 years approximately (Chulani & Gordon, 2014). By mid-adolescence, mid-puberty has been typically achieved, a shift from concrete to abstract thinking has occurred in terms of cognitive development, and an inclination is established towards peer-influence in the context of psychological detachment from the parents (Christie & Viner, 2005).

The psychological developments that occur in adolescents have been characterized by the so-called 'dual systems' model, which posits there to be an incongruity between the developmental trajectories of sensation-seeking and impulse control functions (Steinberg et al., 2008). This theory has been backed by empirical evidence suggesting that while propensity for risk-taking peaks at the age of 19 and declines thereafter, the capacity for impulse control only develops gradually until the age of 25 (Steinberg et al., 2018). Importantly, adolescence is a period of significant brain development with volumetric and qualitative changes occurring in cortical gray matter, white matter and subcortical structures (Arain et al., 2013). The volume of the cortical gray matter peaks in late childhood and declines thereafter (Giedd et al., 2015; Mills et al., 2016; Tamnes et al., 2017), putatively due to synaptic pruning (Huttenlocher & Dabholkar, 1997; Petanjek et al., 2011; Whitford et al., 2007). Conversely, the cerebral white matter volume continues to increase well into emerging adulthood, reflecting increases in myelinization (Giedd et al., 2015; Mills et al., 2016). Importantly, the cerebral cortex matures in a back-to-front manner; thus, the prefrontal cortex (PFC), a key area for cognitive control functions, is one of the last regions to become fully developed (Gogtay & Thompson, 2010). In contrast to the protracted development of the PFC, structures responsible for emotional and reward processing such as the amygdala and the

nucleus accumbens mature fully during adolescence (Galvan, 2010; Mills, Goddings, Clasen, Giedd, & Blakemore, 2014; Somerville, Jones, & Casey, 2010). This mismatch between the developmental trajectories of cortical and subcortical structures has been speculated as a crucial underpinning of pertinent features of adolescent psychological development (Somerville et al., 2010).

It has been hypothesized that this ongoing brain development confers vulnerability to psychiatric disorders (Paus, Keshavan, & Giedd, 2008) and there is epidemiological evidence suggesting that mental disorders most often emerge in adolescence (Kessler et al., 2005; Kessler & Wang, 2008; Powers & Casey, 2015). In a recent meta-analysis, 62.5% of the first mental disorders were estimated to occur before the age of 25 and most mental disorders were found to have their peak age of onset in young adulthood (Solmi, Radua, et al., 2021). Moreover, evidence from population-based surveys such as the U.S. National Survey of Drug Use of Drug Use and Health (NSDUH) and the Finnish Drug Habits Survey suggests that the peak ages of onset of substance use are in adolescence and young adulthood (NSDUH, 2019; THL, 2019). Furthermore, early exposure to substances is not uncommon as revealed by the European School Survey Project on Alcohol and Other Drugs (ESPAD), with a lifetime prevalence of cannabis use of 2.4% by the age of 13 years (EMCDDA, 2019). In fact, it has been postulated that initiating substance use in adolescence might pose a particularly high risk to mental health (Arseneault et al., 2002; Chen, Storr, & Anthony, 2009; Hingson, Heeren, & Winter, 2006; Jordan & Andersen, 2017; Marconi et al., 2016; S. McCabe, West, Morales, Cranford, & Boyd, 2007; Stefanis et al., 2013).

2.2 Cannabis as an intoxicant

Cannabis is a botanical term for a genus comprising of C. Sativa, C. Indica and C. Ruderalis (Greydanus, Kaplan, Baxter, Patel, & Feucht, 2015). The plant has been known to produce over 500 different compounds including over 120 phytocannabinoids (Morales, Hurst, & Reggio, 2017), the most significant of which are delta-9-tetrahydrocannabinolic acid (THCA) and cannabidiolic acid (CBDA). These compounds are decarboxylated to their active forms delta-9-tetrahydrocannabinol (THC), the most significant psychoactive component present in cannabis, and cannabidiol (CBD) by heating (Ujváry & Hanuš, 2016). Importantly cannabis research has suffered from a standard unit-dose for THC, which is presently an important topic of discussion (Arkell, Hayley, & Downey, 2021; Freeman & Lorenzetti, 2020; Volkow & Weiss, 2020). The propensity to produce different phytocannabinoids varies in the different cannabis strains; there seems to be an inverse relationship between the capacity of the plant to produce THC and CBD (De Meijer et al., 2003). Notably, the average THC content and THC:CBD ratio of

cannabis products have increased in the US and Europe (Chandra et al., 2019; ElSohly et al., 2016; Manthey, Freeman, Kilian, Lopez-Pelayo, & Rehm, 2021). In a recent study conducted by Freeman et al., the average THC content of herbal cannabis in Europe was found to have increased from 5% in 2006 to 10% in 2010 (Freeman et al., 2019). In the same vein, according to a fresh meta-analysis, also from Freeman et al. (2021), concentrations of delta-9-tetrahydrocannabinol (THC) in herbal cannabis have increased annually by 0.27% from 1970 to 2017 while cannabidiol (CBD) concentrations have remained relatively static (Freeman et al., 2021). This trend has been perceived as posing a threat to adolescent health since inexperienced users are less likely to titrate their doses according to the potency of the product consumed (Wilson, Freeman, & Mackie, 2019). Along the same line, in a recent placebo-controlled trial with a within-subjects design, adolescents were found to be more sensitive than adults to the acute behavioral and cognitive effects of THC (C. H. Murray, Huang, Lee, & de Wit, 2022).

Phytocannabinoids such as THC and CBD exert their effects on the *endocannabinoid system* (ECS) which consists of the cannabinoid receptors (CB1 and CB2) (Lucas, Galettis & Schneider 2018), the endocannabinoids, the enzymes involved in the synthesis and degradation of the endocannabinoids, and relevant intracellular second-messenger systems (Fezza et al., 2014; Lucas, Galettis, & Schneider, 2018; Mechoulam, Hanuš, Pertwee, & Howlett, 2014). THC is a partial agonist of the CB1 and CB2 receptors (Mechoulam et al., 2014; Morales et al., 2017). CBD is a promiscuous compound having multiple other targets in addition to the ECS (Crippa, Guimarães, Campos, & Zuardi, 2018). Cannabinoid receptors are widely expressed in different key areas of the brain such as the prefrontal cortex, amygdala, hippocampus, ventral tegmental area and nucleus accumbens (Curran et al., 2016). The endocannabinoids are released from the postsynaptic membrane and bind to cannabinoid receptors on the presynaptic terminal, a function known as retrograde neurotransmission. This leads to a reduction of neuronal excitability of either excitatory (glutamatergic) or inhibitory (GABAergic) neurons, resulting in depolarization-evoked inhibition of excitation (DSE) or depolarization-evoked inhibition of inhibition (DSI) (Castillo, Younts, Chávez, & Hashimotodani, 2012; Ohno-Shosaku & Kano, 2014; Zachariou, Alexander, Coombes, & Christodoulou, 2013). Thus, the endocannabinoid system fine-tunes the activity of other major transmitter systems. (Alger & Kim, 2011; Felder, Dickason-Chesterfield, & Moore, 2006). Acute ingestion of THC induces a characteristic intoxidrome comprising of symptoms such as euphoria or anxiety and alterations of cognition and perception, as evidenced by a trial conducted on healthy volunteers (D'Souza et al., 2004). To achieve these desired effects in recreational use, cannabis can be consumed in a myriad of ways including smoking, vaping, dabbing i.e. vaporizing concentrated THC extracts or ingesting edibles (Hilderbrand, 2020). The latent period between consumption and onset of effects and the duration of effects varies

greatly according to the mode of consumption, with smoked and vaped products yielding faster and higher peak-concentrations of THC than edibles (Foster, Abramovici, & Harris, 2019; Spindle et al., 2018). Survey and longitudinal data indicate that using cannabis by multiple consumption methods is common among adolescents (Knapp et al., 2019; Zuckermann, Gohari, Romano, & Leatherdale, 2021), and that it might have more deleterious effects on mental health than unimodal use (Swan, Ferro, & Thompson, 2021).

Cessation of the protracted use of THC or cannabis is associated with withdrawal symptoms as evidenced in preclinical trials and observational studies, and the criteria for cannabis withdrawal syndrome have been formulated and included as a diagnostic entity in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (Hasin, 2017). In a recent-meta-analysis, 47% of regular cannabis users were reported to experience withdrawal symptoms (Bahji, Stephenson, Tyo, Hawken, & Seitz, 2020).

2.3 Cannabis use and the developing brain

2.3.1 Cannabis use, the endocannabinoid system and brain development

The endocannabinoid system (ECS) has been postulated to play a key role in synaptic pruning, neuronal development and stress responsivity (Dow-Edwards & Silva, 2017; Lee & Gorzalka, 2015; Meyer, Lee, & Gee, 2017), and preclinical evidence suggests that early exposure to THC might perturb these neurodevelopmental processes (Figure 1) (Bara, Ferland, Rompala, Szutorisz, & Hurd, 2021; Rubino & Parolaro, 2016). Specifically, the ECS is thought to have an important fine-tuning function as a modulator of other major neurotransmitter systems such as the glutamatergic and GABAergic systems (Ohno-Shosaku & Kano, 2014; Zachariou et al., 2013). Evidence from animal models indicates that early exposure to exogenous cannabinoids may cause dysregulation of these major neurotransmitter systems and also alter synaptic pruning, an important brain development process occurring in adolescence (See Section 2.1) (Rubino & Parolaro, 2016).

Structural brain alterations have been frequently reported in cross-sectional imaging studies comparing adolescents with or without cannabis use, with the alterations most consistently reported in the frontostriatal, frontoparietal, frontolimbic regions and the cerebellum. (Lichenstein et al., 2021). However, studies with imaging data both pre- and post-cannabis initiation provide a crucially important research avenue of studying the impact of cannabis use on neurodevelopment. In the IMAGEN study in which MRI images were obtained from a cohort of initially cannabis-naïve adolescents at 5 year intervals, cannabis use was

negatively associated with the thickness of the prefrontal cortices, with evidence of a dose-response effect (Albaugh et al., 2021). Furthermore, landmark studies have been conducted by the group of Jacobus et al. in the University of San Diego in which MRI images and data on cognitive performance have been obtained pre- and post-cannabis initiation with a six-year interval in-between, yielding results suggestive of altered cortical thinning and perturbations of cognitive domains of processing speed, cognitive inhibition and memory (Jacobus, Courtney, Hodgdon, & Baca, 2019). However, it is important to bear in mind that polydrug use among cannabis-consuming adolescents is common and may confound or modify the association between cannabis use and altered brain development (Halladay et al., 2020; Roche et al., 2019).

2.3.2 Cannabis use and impulse control

Early cannabis exposure has also been postulated to have an especially deleterious effect on impulse control functions. Namely, Wrege et al. reviewed studies assessing the acute effects of administered THC or cannabis as well as the non-acute effects of significant cannabis exposure on psychometric tasks assessing impulsivity and cerebral blood flow as measured by fMRI or PET (Wrege et al., 2014). There are also four reports assessing only structural changes that were included in the qualitative synthesis. The authors concluded that neuroimaging data provide evidence of the detrimental effects of cannabis on inhibitory control and that this is possibly mediated by region-specific reduced volume and white matter integrity of the prefrontal cortex. It is of particular interest that the structural brain alterations were more distinct in those subjects who had initiated cannabis use before the age of 16.

2.3.3 Cannabis use and cognition

While it is an established fact that cannabis intoxication is associated with a transient cognitive impairment (Broyd, Van Hell, Beale, Yücel, & Solowij, 2016; Zhornitsky et al., 2021), whether or not cannabis use may lead to a persistent cognitive decline in adolescents or adults is still unclear (Duperrouzel, Granja, Pacheco-Colón, & Gonzalez, 2020). In a meta-analysis of cross-sectional studies conducted on small adult samples, chronic cannabis use was found to be associated with impairments in several domains of cognitive functioning (Figueiredo, Tolomeo, Steele, & Baldacchino, 2020), and a recent meta-review focusing on both adult and adolescent samples concluded that there was some evidence for a cannabis-induced protracted impairment of verbal memory (Dellazizzo, Potvin, Giguère, & Dumais, 2022). The magnitudes of these neurocognitive effects reported in adult studies have been moderate at most, and longitudinal data is lacking, raising concerns pertaining to the possibility of reverse

causality. However, in one study with a 25-year follow-up conducted with a sample of young adults, cumulative cannabis use was associated with a deterioration in the domain of verbal memory by middle age, even after excluding current users and confounder control. Specifically they found verbal memory to be 0.13 standard deviation (SD) units lower per each 5 year interval of cumulative cannabis exposure (Auer et al., 2016). Lastly, an important birth cohort study addressing this issue was recently published (Meier et al., 2022); in that, the association between cannabis use and IQ and functioning in specific cognitive domains was examined with information on these variables at multiple time points during adulthood. Cannabis use and dependence were assessed at ages 18, 21, 26, 32, 38, and 45 years and IQ was assessed at ages 7, 9, 11, and 45. Regular cannabis use was defined as using cannabis ≥ 4 times a week. Both protracted regular use and cannabis dependence were associated with a decline in IQ, even after extensive confounder control for many factors including sex, tobacco, alcohol, other illicit drugs, low childhood socioeconomic status, low childhood self-control, and family history of substance dependence.

Specifically, adolescent cannabis use appears to exert an effect on cognition which persists beyond the acute intoxication (Lorenzetti, Hoch, & Hall, 2020). However, studies on the long-term effects of early cannabis exposure have yielded dramatically mixed findings. Namely, in the seminal study of Meier et al. utilizing prospective data from the Dunedin birth cohort, early cannabis use was associated with a general cognitive decline of 8 IQ points (Meier et al., 2012). However these findings were not replicated in twin studies (Jackson et al., 2016; Meier et al., 2018), which were suggestive of a confounding bias introduced by family factors associated with both modest cognitive achievement and the initiation of cannabis use. There is also some evidence for a reverse causality, i.e. that the cognitive delay is associated with the initiation of cannabis use (Debenham et al., 2021). Importantly, in a meta-analysis focusing on adolescent and young adults, cannabis use was not associated with impaired cognition, when only studies requiring an abstinence period of at least 72 hours were included in the quantitative analysis (Scott et al., 2018). On the other hand, in a recent meta-analysis of longitudinal studies, adolescent cannabis use was associated with a decline of 2 IQ points (Power et al., 2021).

In conclusion, the endocannabinoid system is thought to fine tune the activities of other neurotransmitter systems, and this function is believed to be crucial during the developmental phase of adolescence, as revealed by studies in experimental animals (Rubino & Parolaro, 2016). Moreover, landmark studies with imaging data obtained both pre- and post-cannabis initiation support the hypothesis of early cannabis exposure leading to altered brain development (Albaugh et al., 2021; Jacobus et al., 2019). Thus, it is reasonable to postulate that early cannabis use can lead to adverse sequelae such as self-injurious behaviors, psychiatric disorders and altered cognitive functioning.

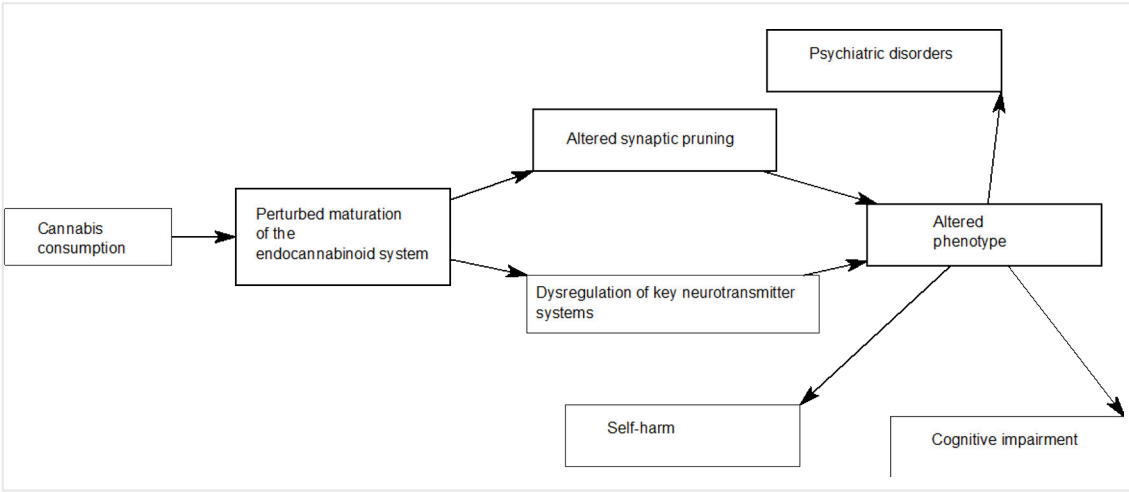

Figure 1. Effects of cannabis use on neurodevelopment, adapted with permission from Elsevier from Rubino, T., & Parolaro, D. (2016). The Impact of Exposure to Cannabinoids in Adolescence: Insights From Animal Models. *Biological Psychiatry*, *79*(7), 578–585.

2.4 Epidemiology of adolescent cannabis use

2.4.1 Prevalence of adolescent cannabis use

According to the most recent United Nations Office for Drugs and Crime (UNODC) World Drug Report, cannabis is the most widely used drug worldwide with 4% of the global population aged 15–64 having used cannabis during the past year (UNODC, 2021). The past-year and past-month prevalences for European youth aged 15–24 were 15.7% and 8.6% respectively, according to a recent study based on European Monitoring Centre for Drugs and Drug addiction (EMCDDA) data gathered in 2019 (Manthey et al., 2021). Early-onset, lifetime and past-year cannabis use estimates for adolescents have remained quite stable in major surveys conducted in Europe and the United States at regular intervals such as the European School Survey Project on Alcohol and Other Drugs (ESPAD), Monitoring the Future (MTF), Youth Risk Behavior Survey (YRBS) and the National Survey of Drug Use and Health (NSDUH) (EMCDDA, 2019; NIDA, 2020; NSDUH, 2019; YRBS, 2019). However there has been a significant change in the perception of the harmfulness of weekly use among adolescents (NSDUH, 2019). Even so, the most recent WDR encouragingly suggests that the strength of the inverse correlation between adolescent perceived harmfulness of cannabis and past-month prevalence of cannabis use has diminished during the past 20 years (UNODC, 2021).

The ESPAD is a pan-European survey conducted at regular intervals that provides information on substance use habits of adolescents aged 15/16 years

(EMCDDA, 2019). In the 1999 ESPAD conducted one year before the field study of the Northern Finland 1986 Birth Cohort study (NFBC1986), the prevalence of lifetime cannabis use in Finland was 10% whereas the average of all European countries was 16% (EMCDDA, 1999.; Oulu, 1986).

In the ESPAD 2003 study conducted two years after the 2000–01 field study of the Northern Finland 1986 Birth Cohort, the prevalence measures of cannabis use in Finland were as follows: 11 % of the participants reported lifetime cannabis use with 8 % of participants reported having used cannabis on 1–5 occasions and 3% on more than 5 occasions. The respective estimates for the whole ESPAD 2003 sample where 22% for lifetime use, 12% for lifetime use up to 1–5 occasions and 11% for more than 5 occasions. The lifetime cannabis use prevalence for both sexes were similar. However 2% of boys vs 0% girls reported having used cannabis on at least 20 occasions (EMCDDA, 2003).

The prevalence estimates for cannabis use according to the most recent ESPAD survey conducted in 2018 are summarized in Figure 2. On average 2.4% of the participants of the whole sample had initiated cannabis use aged 13 years or younger. The corresponding figure for Finnish participants was 1.5%; 16% of the whole sample and 11% of Finnish participants reported lifetime use. A total of 7.1% of the whole sample reported having used cannabis during the last 30 days (boys 8.5% vs girls 5.8%) and a sex difference was observed in the same direction in Finland with 4.9% boys vs. 3.2% girls ($p < 0.001$) reporting cannabis use during the last 30 days with 13 % of the whole sample and 10% of Finnish participants reporting use in the past year. With respect to the past-year users, cannabis was reported to have been used 9.9 times on average. Finnish past-year users reported having used cannabis 9.1 times on average during the past year, with boys using cannabis more frequently than girls (10 times vs. 7.5 times, $p = 0.02$). When one considered the whole sample, then 4.0% of participants were classified as high-risk cannabis users according to their Cannabis Abuse Screening Test (Legleye, 2018) score. The situation in Finland was that 3.0% were classified as high-risk users with a statistically significant sex difference 3.5 vs 2.5 ($p = 0.04$).

In conclusion, Finnish adolescents seem to consume somewhat less cannabis than their peers in other European countries. Moreover, the prevalence of lifetime use of cannabis among Finnish adolescents seems to have remained quite stable during the past two decades. However findings from the most recent drug habits survey conducted by the Finnish National Institute of Health and Welfare indicate that the prevalence of lifetime use among the 25–44 year age group has increased significantly from 19% in 2002 to 44% in 2018 (Rönkä & Markkula, 2020). This implies that Finns tend to initiate cannabis use later than their peers in other European countries.

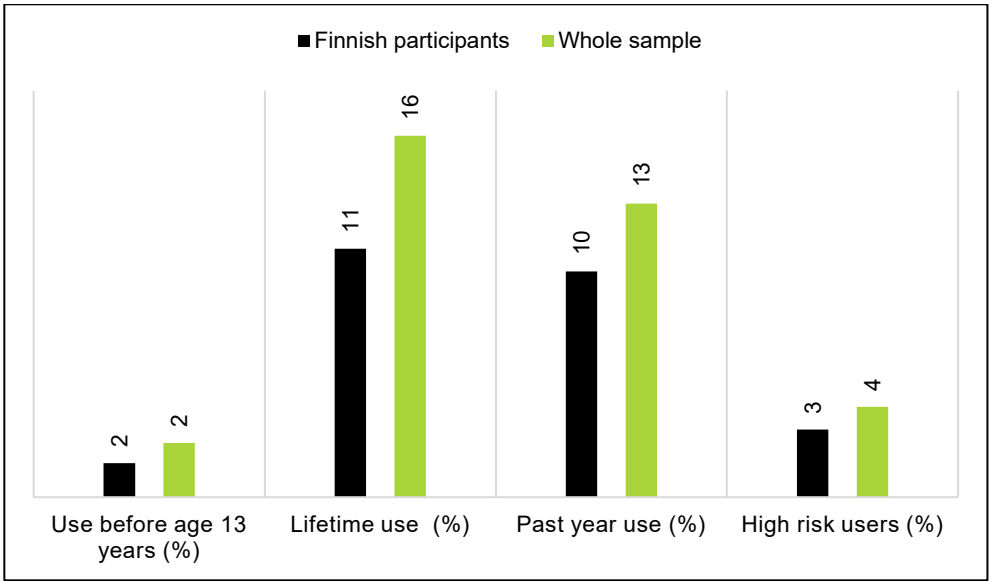

Figure 2. Cannabis use in the ESPAD 2019 survey. EMCDDA. (2019). ESPAD Report 2019. Available from http://www.espad.org/espad-report-2019.

2.4.2 Risk factors of adolescent cannabis use

Several constitutional and environmental factors have been found to predispose towards early exposure to cannabis. Externalizing disorders or traits (Colder et al., 2013; Cox et al., 2021; Miettunen et al., 2014) and atypical emotional perception (Fishbein et al., 2016) have been found to be associated with an early initiation of cannabis use. Furthermore, longitudinal studies conducted utilizing the Mater University of Queensland (MUSP) birth cohort have detected associations between early pubertal maturation, family status and adverse childhood experiences and cannabis use in young adulthood (Hayatbakhsh, Najman, Bor, O'Callaghan, & Williams, 2009; Hayatbakhsh, Najman, McGee, Bor, & O'Callaghan, 2009). In Finnish school-based surveys conducted biennially in students aged 14–16 years, cannabis use has been associated with parental unemployment in the past year, low parental education, and not living with both parents (Knaappila, Marttunen, Fröjd, Lindberg, & Kaltiala, 2020).

A genetic predisposition has also been hypothesized to confer a risk of cannabis initiation as evidenced by the meta-analysis of twin studies by Verweij et al. in which a heritability estimate of 48% was reported for the initiation of cannabis use (Verweij et al., 2010) and alleles conferring a risk towards the initiation of use have been identified in a study with a large meta-analytic sample (Stringer et al., 2016). However, in another meta-analysis, it was estimated that common genetic variants explained only 6% of the variation of cannabis initiation (Verweij et al., 2013).

Furthermore, a large twin study claimed that age of initiation of cannabis use was only moderately heritable (Minică et al., 2018). In a recent study, the transmission liability index, an aggregate index of adolescent behavioral and temperamental traits that are established harbingers of substance use disorders, was found to be an early indicator of repeated cannabis use in early adulthood (Brick et al., 2021). In addition, the risk for schizophrenia and lifetime cannabis use have been found to involve shared heritable factors in a Mendelian randomization study and other genetic studies (Pasman et al., 2018; Song, Lin, Yu, & Zhao, 2022).

2.5 Self-harm and suicide

2.5.1 Nomenclature of self-injurious behaviors

Self-injurious behaviors are complex phenomena involving both constitutional risk factors and acute stressors (Hawton, Saunders, & O'Connor, 2012; Hawton & van Heeringen, 2009; O'Connor & Nock, 2014; Turecki & Brent, 2016). Suicidology, the study of suicidality and other forms of intentional self-injury, suffers from a lack of a standard nomenclature with self-injurious behaviors being operationalized by a myriad of mutually overlapping entities to which varying definitions have been attached by different conventions (O'Carroll et al., 1996; Silverman, Berman, Sanddal, O'Carroll, & Joiner, 2007) For example, deliberate self-harm (DSH) encompasses a suicide attempt in some contexts but not in others (Samari et al., 2020). Moreover, for an outcome to be regarded as a suicide attempt (SA), a preceding intent to die has been only variably included as a necessary criterion (Michel et al., 2000; Posner, Oquendo, Gould, Stanley, & Davies, 2007). It does seem that the terms *non-suicidal self-injury* (NSSI) and *non-suicidal self-harm* (NSSH) are used interchangeably in the literature to denote an intentional self-injury without an intent to die, whereas self-harm and *deliberate self-harm* (DSH) can be regarded as almost synonymous since in most contexts neither accounts for the preceding objective, i.e. whether or not an intent to die is tied to the event of self-injury (Fontanella et al., 2021; Moran et al., 2012; Samari et al., 2020). By established convention, a *suicide attempt* is defined as an event of self-injury with a preceding intent to die (Posner et al., 2007), whereas suicide is defined as intentionally engaging in attempt to end one's life with a resulting lethal outcome.

2.5.2 Cannabis use and self-injury: putative intermediaries

The mechanisms by which cannabis use might predispose to subsequent self-harm probably involve a network of mutually linked factors as demonstrated in Figure 3 adapted from Bartoli et al (2018). Namely, borderline or antisocial features, or

externalizing features, predispose to cannabis use (Miettunen et al., 2014) and also by their very nature are often characterized by impulsivity and subsequent self-injurious behavior (Soto-Sanz et al., 2019). Furthermore, cannabis use has been associated with depressive and psychotic symptoms and disorders (Gobbi et al., 2019; Hindley et al., 2020; Lev-Ran et al., 2014; Marconi et al., 2016; Moore et al., 2007), all of which are independently associated with an elevated risk of self-harm, and thus may mediate the association of cannabis use with intentional self-injury. Cannabis use has also been associated with impaired impulse control (Ansell, Laws, Roche, & Sinha, 2015; Trull, Wycoff, Lane, Carpenter, & Brown, 2016), which in turn has been linked with self-harm (Klonsky & May, 2010; Liu, Trout, Hernandez, Cheek, & Gerlus, 2017). The neurobiological changes underpinning the association of cannabis use and impaired impulse control were reviewed by Wrege et al. as discussed in section 2.2.2 of this thesis (Wrege et al., 2014).

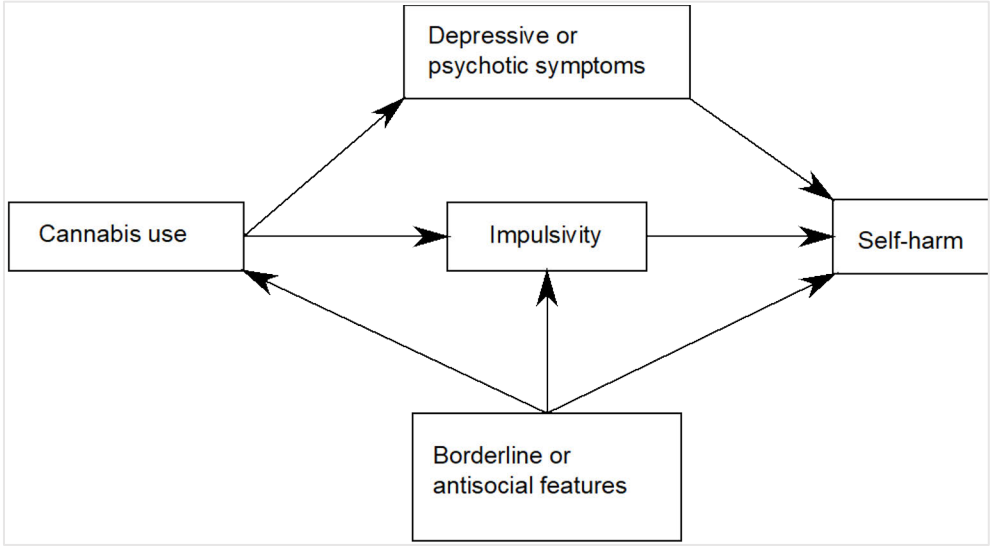

Figure 3. Putative mechanisms: cannabis use and self-harm, adapted with permission from Pacini Editore from Bartoli, Francesco, Lev-Ran, S., Crocamo, C., & Carrà, G. (2018). The interplay between cannabis use and suicidal behaviours: Epidemiological overview, psychopathological and clinical models. *Journal of Psychopathology*, *2018*, 180–186.

2.5.3 Adolescent cannabis use and subsequent self-harm

In the only available meta-analysis examining the association between cannabis use and self-harm, Escelsior et al. pooled nine methodologically heterogenous studies and reported a significant positive finding (odds ratio, OR=2.57; 95%, confidence interval, CI=2.03–3.26) (Escelsior et al., 2021). Three of the studies (Mars et al., 2019; Moran et al., 2012; Spears, Montgomery, Gunnell, & Araya, 2014) included

in this meta-analysis utilized adolescent cohorts. However, it should be noted that the study of Mars et al. assessed specifically the association between cannabis use and suicide attempt (Mars et al., 2019), which in a strict sense, is a different entity than self-harm. Furthermore, a recent register-based longitudinal study assessing the association of adolescent cannabis use disorder and subsequent severe self-harm requiring medical attention added to the evidence base concerning cannabis use and self-harm (Fontanella et al., 2021). These three studies of interest are summarized in Table 1. Lastly, a Norwegian population-based adolescent study assessing risk factors of self-harm with prospective data did include information on cannabis use, but all substance use was pooled together as one variable in the main analyses (Wichstrøm, 2009).

Knowledge regarding the association of cannabis use and subsequent self-harm is limited by the sample characteristics of the three studies conducted thus far. Only Moran et al. utilized a population-based sample of school pupils aged 14–15 years (Moran et al., 2012). The two other studies utilized high-risk cohorts of socio-economically deprived adolescents (Spears et al., 2014), and patients with a mood disorder receiving treatment (Fontanella et al., 2021). In the latter study, further confounding might be induced by inclusion bias-related issues, as data from insurance registries were utilized. In Moran et al., (2012) the length of follow-up was 15 years at most, but only 51% of the study sample participated in every wave of the study. In Spears et al., (2014) the follow-up was only 6 months, with a participant retention of 81%. The subsample of those with no incident self-harm was used in the main analyses. Fontanella et al. (2021) did not report attrition, which was possibly very limited due to the register-based outcome data used. The follow-up time in that study was only one year.

In conclusion, there are rather few prospective longitudinal studies assessing the association of adolescent cannabis use and subsequent self-harm. Moreover, only one population-based study examining this association has been published. Thus, it is not possible to draw any definitive conclusions of the implications of the existing research findings for non-help-seeking youth. Conversely, self-harm in adolescence was associated with weekly cannabis use in young adulthood in a population based study with prospective data, implying that there is a possible reciprocal relationship between cannabis use and self-injurious behaviors (Borschmann et al., 2017). Moreover, recent Mendelian randomization studies reported associations between cannabis use and self-harm (Hodgson et al., 2020; Lim et al., 2020) and a suicide attempt (Orri et al. 2021), opening a key new avenue of research of the association between cannabis use and intentional self-injury.

Table 1. Longitudinal studies assessing the association between adolescent cannabis use and self-harm.

STUDY	SAMPLE	SAMPLE SIZE	AGE AT BASELINE (YEARS)	FOLLOW UP (YEARS)	CANNABIS USE VARIABLE	POINT ESTIMATE (95 % CIS)	COVARIATES
MORAN ET AL. (2012)	VAHCS, Australia	1802	14-15	≤ 15	Any use during past 6 months	aHR **1.8** (1.0–3.1)	Sex, family structure, depression/ anxiety, risk alcohol use, smoking
SPEARS ET AL. (2014)	Socially deprived adolescents, Chile	1582	…	0.5	Exposure (never/at least once)	aOR 1.43 (0.83–2.49)	BDI, anxiety, school connectedness, rational problem solving, suicidal thoughts, **alcohol, smoking**
FONTANELLA (2021)	Medicaid data, Mood disorder patients US	204780	17.2 (mean)	1	Cannabis Use Disorder	aOR **3.28** (2.55–4.22)	Age, sex, ethnicity, health, insurance status, residence, Psychiatric comorbidities including **SUD**

Statistically significant findings and substance use covariates in bold. aHR = adjusted hazard ratio, aOR = adjusted odds ratio, BDI = Beck depression inventory, Victoria Adolescent Health Cohort Study, SUD = substance use disorder.

2.5.4 Adolescent cannabis use and subsequent suicide attempt

In the meta-analysis published by Borges et al. pooling prospective studies utilizing both adolescent and adult populations, significant positive findings were reported both for cannabis use (OR=2.23; 95% CI 1.24–4.00) and heavy cannabis use and a suicide attempt (OR=3.20; 95% CI 1.24–4.00) (Borges, Bagge, & Orozco, 2016). The current evidence base for an association between specifically adolescent cannabis use and subsequent suicide attempt comprises 16 studies (Agrawal et al., 2017; Guilherme Borges, Benjet, Orozco, Medina-Mora, & Menendez, 2017; Borowsky, Ireland, & Resnick, 2001; Clarke et al., 2014; Fergusson, Horwood, & Swain-Campbell, 2002; Hengartner, Angst, Ajdacic-Gross, & Rössler, 2020; Juon & Ensminger, 1997; Mars et al., 2019; Newcomb, Scheier, & Bentler, 1993; Pedersen, 2008; Rasic, Weerasinghe, Asbridge, & Langille, 2013a; Roberts, Roberts, & Xing, 2010; Silins et al., 2014; Thompson & Light, 2011; Weeks & Colman, 2017; Wilcox & Anthony, 2004) of which eight (Guilherme Borges et al., 2017; Borowsky et al., 2001; Clarke et al., 2014; Fergusson et al., 2002; Mars et al., 2019; Roberts et al., 2010; Silins et al., 2014; Wilcox & Anthony, 2004) reported an association between cannabis use and suicide attempt. The only meta-analysis published so far focusing specifically on early cannabis exposure pooled three of these studies (Roberts et al., 2010; Silins et al., 2014; Weeks & Colman, 2017) and reported a significant positive finding (OR=3.46; 95% CI 1.53–7.84) (Gobbi et al., 2019).

Three studies have examined the association between cannabis use and a suicide attempt using prospective birth cohort data. Fergusson et al. utilized a sample from the Dunedin birth cohort study with cannabis use assessed at multiple time points. They reported a statistically significant association in a multivariable analysis including alcohol abuse as a substance use covariate (Fergusson et al., 2002). A significant association was also reported in the Avon Longitudinal Study on Parents and Children (ALSPAC) birth cohort study by (Mars et al., 2019) in which, however only sex and socioeconomic position were used as covariates. Furthermore, the hypotheses in that study concerned transitioning from non-suicidal self-harm or suicide ideation to actually attempting suicide. The use of these high-risk subsamples of the original birth cohort limits the generalizability of the findings to the general population. In contrast, Silins et al. used a non-selective sample and controlled for other substance use (Silins et al., 2014). However, this study examined a sample composed of adolescents from both the Christchurch Health and Development Study (CHDS) birth cohort as well as the Victorian Adolescent Health Cohort Study (VACHS) – a cohort of students aged 14-15 years at baseline (Coffey & Patton, 2016). Thus, it cannot be regarded as a birth-cohort study in the strictest sense.

In all, the studies are quite heterogenous in terms of measurement of suicidal behaviors, sample sizes and characteristics, lengths of follow-up and which factors

were considered as covariates to be controlled. One study (Juon & Ensminger, 1997) reported only a crude estimate whereas some investigators have only included some measure of other forms of substance use in adolescence as a covariate (Clarke et al., 2014; Rasic, Weerasinghe, Asbridge, & Langille, 2013b; Silins et al., 2014; Wilcox & Anthony, 2004). In one report (Hengartner et al., 2020), a suicide attempt was assessed as a composite "suicidality" outcome, which did not discern between ideation and attempt. In three studies, the sample was formed by high-risk individuals i.e. individuals with a suicidal ideation (Clarke et al., 2014), individuals with suicidal ideation and with a history of non-suicidal self-harm (Mars et al., 2019) and individuals regarded as having a high genetic predisposition to alcohol use disorders (Agrawal et al., 2017). One study focused on a specific ethnic group, namely, African Americans (Juon & Ensminger, 1997).

There is one key confounder which should be assessed i.e. other forms of substance use as polysubstance use is common in adolescents (Halladay et al., 2020) and both illicit substance use (Wong, Zhou, Goebert, & Hishinuma, 2013) and heavy alcohol drinking in adolescence (Aseltine, Schilling, James, Glanovsky, & Jacobs, 2009) have been found to associate with suicide attempts. Of the eight prospective longitudinal studies reporting a statistically significant positive association between adolescent cannabis use and a subsequent suicide attempt (Borges et al., 2017; Borowsky et al., 2001; Clarke et al., 2014; Fergusson et al., 2002; Mars et al., 2019; Roberts et al., 2010; Silins et al., 2014; Wilcox & Anthony, 2004), four did not adjust for any other substance use in adolescence (Guilherme Borges et al., 2017; Borowsky et al., 2001; Mars et al., 2019; Roberts et al., 2010). Lastly, as these studies used self-reported measures for the suicide attempt, the outcome incidences tend to be quite high. For example, Wilcox and Anthony (2004) reported 9% of the re-interviewed participants stated that they had attempted suicide.

To conclude, noticeably more research has been conducted on the prospective association of early cannabis use with a suicide attempt as compared to self-harm. However, the results of these studies are markedly inconsistent. Most importantly, the source of confounding bias introduced by other substance use has been insufficiently addressed in previous research.

Table 2. Longitudinal studies assessing the association between adolescent cannabis use and suicide attempt.

STUDY	SAMPLE	SAMPLE SIZE	AGE AT BASELINE	FOLLOW-UP (YEARS)	CANNABIS USE VARIABLE	POINT ESTIMATE (95% CIS)	COVARIATES
AGRAWAL ET AL. (2017)	High genetic risk for AUDs, USA	3277	22–26	10	Use before age 15 yrs	aOR 1.13 (0.76–1.67)	Gender, ethnicity, parental AUD, MDD, externalizing disorders
BOROWSKI ET AL. (2001)	USA	13110	Grades 7.–12.	0.92	Cannabis use	**ORs stratified by ethnicity, significant finding**	Age, family structure, welfare status, ethnicity
BORGES ET AL. (2017)	Mexico	1071	12–17	8	Use > 1–3 times during past 12 months	aRR **4.60** (1.03-20.60)	Gender, age, education, attending school, anxiety/mood/impulse control/eating disorders
CLARKE ET AL. (2014)	Dublin, Ireland	168	12–15	≈ 7	Ever used at age 12–15 years	aOR **7.50** (1.20-43.80)	Family psychiatric history, childhood trauma **alcohol**, psychopathology
FERGUSSON ET AL. (2002)	Dunedin, New Zealand	1063	14	7	annual frequency no, 1-11, 12-50, 50 + times	β 0.34 (SE 0.13)	Adverse life events, deviant peers, **alcohol abuse**, age at leaving school/home
HENGARTNER ET AL. (2020)	Zurich, Switzerland	591	19–20	30	Use at age < 20 years	aOR **1.64** (1.09–2.48)	Assessment year, sex, family climate, social support, parental income, education level, **drug abuse, alcohol abuse**
JUON & ENSMINGER (1997)	African Americans, Chicago, IL USA	953	15–16	≈ 17	Lifetime use: more or less than 4o times	OR male 0.34 (0.04–2.85) OR female 1.84 (0.50-6.82)	Crude only

MARS ET AL. (2019)	ALSPAC, UK	456 (ideators) 569 (with DSH)	16	5	At least occasional use	aORs ideators **2.61** (1.11–6.14) With DSH **2.14** (1.04–4.41)	Gender, socioeconomic position
NEWCOMB ET AL. (1993)	Los Angeles, USA	487	7th-9th grade students	12	Never-regularly	B- 0.1	Not reported
PEDERSEN ET AL. (2008)	Norway	2033	21	6	≥ 15 times	**aOR2.9** (1.3–6.1)	Age, gender, parental education, depression, impulsivity, education, unemployment, income on welfare, cohabitation, parenthood, **daily smoking, alcohol intoxications/problems**
RASIC ET AL. (2013)	Nova Scotia, Canada	976	grade 10.	2	use past 30 days ≥ 10 times	aOR 1.04 (0.98–1.10)	School marks, living arrangement, **alcohol, other drug use,** depression
ROBERTS ET AL. (2010)	Houston, Texas USA	3134	11–17		use in last year	aOR **4.70**	Age, gender, family income, prior suicide attempt self/caregiver, psychiatric disorders, personal/social resources, life stress
SILINS ET AL. (2014)	CHDS, VAHCS New Zealand, Australia	2537	< 17	not available	daily	aOR **6.83** (2.04–22.90)	Age, sex, baseline depression, **alcohol use, smoking**

THOMPSON & LIGHT (2011)	USA	10828	grades 7.–12.	7	use (yes/no)	aOR 1.03 (0.97–1.10)	All factors reaching significance in bivariate analyses
WEEKS & COLMAN (2017)	Canada	6788	14–15	2	use ≥ 1–2 times/month	aOR **1.87** (1.09–3.22)	Depression, socio-economic status, family dysfunction, stressful life event, disease in childhood, behavior problems
WILCOX & ANTHONY (2004)	Mid-Atlantic region, USA	2311	8–15	≈ 15	use before age 15 years	aOR**1.8** (1.0–3.3)	Ethnicity, MDD, **alcohol, tobacco, illicit drugs,** aggression, parental psychiatric disturbance, deviant peers

Statistically significant findings and substance use covariates in bold. aOR = adjusted odds ratio, aRR = adjusted risk ratio, β = linear regression, SE = standard error, MDD= major depressive disorder, AUD = alcohol use disorder, VAHCS = Victoria Adolescent Health Cohort study, DSH = deliberate self-harm.

2.5.5 Adolescent cannabis use and subsequent suicide

As summarized in our recent review, only a few longitudinal studies have been published on cannabis use and subsequent suicide death and the conclusions reported have been mixed (Denissoff, Levola, Niemelä, & Mustonen, 2022). Borges et al. 2016 pooled four methodologically heterogenous studies in their meta-analysis on cannabis use and a subsequent suicide death and reported a statistically significant association (OR 2.55; 95% CI 1.25–5.27). The only population-based prospective study available for analysis was performed by Price et al., in which young Swedish male-conscripts were followed for 33 years (Price, Hemmingsson, Lewis, Zammit, & Allebeck, 2009). Both lifetime use and dose-response (up to at least 50 times) were studied, but the associations attenuated to statistically nonsignificance after control for confounders. A recent prospective register-linkage study encompassing the whole Swedish adult population examined the association between different SUDs including cannabis use disorder (CUD) and suicide death (Crump, Sundquist, Kendler , Edwards & Sundquist, 2021). In that report, CUD was associated with a 3.10-fold risk of suicide as compared to the general population after extensive confounder control including substance use disorder (SUD) comorbidities. Six other register-linkage studies with prospective data assessing the association of cannabis use and suicide death have examined special cohorts such as people receiving treatment for drug use disorders (Arendt, Munk-Jørgensen, Sher, & Jensen, 2013; Hesse, Thylstrup, Seid, & Skogen, 2020), patients diagnosed with psychiatric disorders (Fontanella et al., 2021; Østergaard, Nordentoft, & Hjorthøj, 2017), veterans (Bohnert, Ilgen, Louzon, McCarthy, & Katz, 2017) and heroin users reported to the authorities for cannabis possession (Pavarin et al., 2015).

With the exception of the work of Fontanella et al. (2021), no studies have focused on early cannabis use and subsequent death by suicide. There, a crude association between CUD and suicide was reported, which attenuated to statistically non-significance after adjustments despite the high-risk nature of their sample consisting of mood disorder patients including those with prior history of self-harm, a formidable sample size ($n = 204780$) and a robust exposure variable (CUD). However, due to the short follow-up period of one year, only 30 suicide deaths were captured (Fontanella et al., 2021). Thus, further research with adequate sample sizes and longer durations of follow-up are needed to clarify this association.

2.6 Mood and anxiety disorders

2.6.1 Definitions and significance

Mood disorders can be seen as a spectrum from a unipolar disease, in which only depressive episodes occur, to the bipolar form, in which episodes of abnormally elevated mood are also evident during the course of the illness (Grande, Berk, Birmaher, & Vieta, 2016; Malhi & Mann, 2018; McIntyre et al., 2020; Vieta et al., 2018). Anxiety disorders are syndromes characterized by excessive fear or worrying and resulting avoidance behaviors (Craske & Stein, 2016; Craske et al., 2017; Penninx, Pine, Holmes, & Reif, 2021). If one considers all psychiatric disorders and mental disorders, then mood disorders are the leading causes of disability with a substantial proportion of the impairment impacting on adolescence and early adulthood (Baxter, Scott, Vos, & Whiteford, 2013; Erskine et al., 2015; Ferrari et al., 2013; Vos et al., 2017; Whiteford et al., 2013). Importantly, mood disorders are associated with excess mortality (Crump, Sundquist, Winkleby, & Sundquist, 2013; Hayes, Miles, Walters, King, & Osborn, 2015; Kessing, Vradi, & Andersen, 2015; Laursen, Munk-Olsen, Nordentoft, & Mortensen, 2007; Nordentoft et al., 2013; Ösby, Brandt, Correia, Ekbom, & Sparén, 2001) and thus research on potentially modifiable environmental factors predisposing to these disorders is of major significance.

2.6.2 Adolescent cannabis use and subsequent depressive disorders

To date, two meta-analyses focusing on both adolescent and adult populations assessing the association of cannabis use and depression have been published. In the first meta-analysis assessing cannabis use and the subsequent appearance of depression, weekly cannabis use or CUD was associated with a 49% increased risk of subsequent depression (Moore et al., 2007). In the meta-analysis conducted by the group of Lev-Ran, cannabis use was associated with a 17% increased odds of subsequent depression; for frequent cannabis use, the value was greatly elevated to 69% (Lev-Ran et al., 2014).

The association of adolescent cannabis use with depression seems to have been one of the most studied domains of all observational cannabis research focusing on early exposure, as Gobbi et al. identified over 30 prospective studies addressing this issue in their systematic review and meta-analysis (Gobbi et al., 2019). They identified seven studies (Brook, Lee, Brown, Finch, & Brook, 2011; Degenhardt et al., 2013; Gage et al., 2015; Ganguli, Dodge, & Mulsant, 2002; Georgiades & Boyle, 2007; Marmorstein & Iacono, 2011; Silins et al., 2014) which were found to be

suitable for quantitative analysis (Gobbi et al., 2019). Cannabis use in adolescence was found to increase the risk of depression in young adulthood by 37%. An earlier meta-analysis also detected a positive correlation between adolescent cannabis use and depressive symptoms (r = 0.118) (Cairns, Yap, Pilkington, & Jorm, 2014).

While an ample amount of prospective data exists on this association, the number of general population-based and birth cohort studies addressing the issue is more moderate. To date, six longitudinal studies assessing the association of adolescent cannabis use and subsequent depression have examined a prospective birth cohort data, specifically from the ALSPAC study (Gage et al., 2015), the Christchurch Health and Development Study (CHDS) (Fergusson & Horwood, 1997; Fergusson et al., 2002; Fergusson, Lynskey, & Horwood, 1996; Silins et al., 2014), and the Dunedin birth cohort (Arseneault et al., 2002) (Table 4). The results of these studies are mixed with half of them reporting a significant positive finding (Arseneault et al., 2002; Fergusson & Horwood, 1997; Fergusson et al., 2002). While all of the studies had data on other substance use as well as cannabis, the follow-up times were moderate, ranging from two (Fergusson & Horwood, 1997; Fergusson et al., 1996) to eight (Silins et al., 2014) years. Depression diagnoses were constructed from clinical interviews or self-report measures in all of these studies. Thus, further studies with register-based outcomes and longer durations of follow-up are warranted.

Table 3. Prospective birth cohort studies assessing the association between adolescent cannabis use and depression.

STUDY	BIRTH COHORT	SAMPLE SIZE	AGE AT BASELINE (YEARS)	FOLLOW-UP (YEARS)	CANNABIS USE VARIABLE	POINT ESTIMATE (95% CI)	COVARIATES
ARSENEAULT ET AL. (2002)	Dunedin, New Zealand	759	18	8	Use by age 18 years	aOR **1.59** (1.01–2.49)	Childhood psychotic symptoms, **other drug use**
FERGUSSON & HORWOOD (1997)	Dunedin, New Zealand	935	15–16	2	Frequency of use in last year ≥ 10 times	**No point estimate given**	Maternal age, ethnicity, age, family size/functioning, conduct problem, IQ, self-esteem, baseline mood and anxiety disorder, **alcohol use, smoking**
FERGUSSON ET AL. (1996)	Dunedin, New Zealand	927	14–16	2	Use (never/ever)	1.4 (0.7-2.7)	Family functioning, adverse life events, delinquent or drug using peers**,** sex, **alcohol use,** depression/anxiety/suicidality at baseline
FERGUSSON ET AL. (2002)	Dunedin, New Zealand	953–1025	14–15 17–18 20–21	1	At least weekly use	aRR **1.7** (1.0–2.7)	Adverse life events, deviant peer affiliations, **alcohol use**, baseline depression, age of leaving school/home
GAGE ET AL. (2015)	ALSPAC, UK	1791	16	2	Frequency of use 0,1–20, 21–60, > 60 times a year	aOR 1.30 (0.98–1.72)	Family history of depression, maternal education, urban living, IQ, childhood mental conditions, borderline personality, victimization, peer problems, conduct disorder, sex**, alcohol use, other illicit drug use**
SILINS ET AL. (2014)	CHDS, New Zealand ATP &VAHCS, Australia	2537	< 17	18	Daily use	aOR 1.02 (0.52–2.01)	Age, sex, baseline depression, **alcohol use, smoking**

Statistically significant findings and substance use covariates in **bold**. aOR = adjusted odds ratio, aRR = adjusted risk ratio, ALSPAC = Avon longitudinal study of parents and children CHDS = Christchurch health and development study, ATP = Australian temperament project, VAHCS = Victoria Adolescent Health Cohort Study, CI = confidence interval.

2.6.3 Adolescent cannabis use and subsequent anxiety disorders

To date, three meta-analyses focusing on both adolescent and adult populations assessing the association of cannabis use and anxiety disorders have been published. Twomey et al. reported a negative finding on the association of cannabis use and anxiety symptoms (Twomey et al., 2017). In contrast, in the recent meta-analysis conducted by Xue et al., cannabis use was associated with a 1.25-fold odds of the development of a subsequent anxiety disorder (Xue, Husain, Zhao, & Ravindran, 2021). However, due to power issues in the statistical analyses, non-significant findings were reported for all separate meta-analyses conducted for different anxiety disorder types. Lastly, a meta-analysis pooling data from both cross-sectional and prospective studies found both cannabis use and a cannabis use disorder to increase the odds of anxiety by 24% and 68% respectively (Kedzior & Laeber, 2014).

Compared to the extensive evidence on the link between adolescent cannabis use and depression, the association of early cannabis exposure and anxiety disorders has been less extensively studied. To date, five longitudinal studies assessing anxiety-disorder-related outcomes have been published (Brook, Cohen, & Brook, 1998; Brook et al., 2011; Degenhardt et al., 2013; Fergusson et al., 1996; Suzanne H. Gage et al., 2015) (see Table 3) with only two of them reporting a significant positive finding (Brook et al., 1998, 2011). Two of these studies utilized birth cohort data (Fergusson et al., 1996; Gage et al., 2015); in those studies, the sample sizes ranged from modest (n=173) (Brook et al., 1998) to moderate (n= 1943) (Degenhardt et al., 2013). In the meta-analysis reported by Gobbi et al. on adolescent cannabis use and anxiety disorders, three studies (Brook et al., 2011; Degenhardt et al., 2013; Gage et al., 2015) were found to be suitable for quantitative analysis, which yielded a negative result (OR= 1.18; 95% CI 0.84–1,67) (Gobbi et al., 2019). Interestingly in a recent study utilizing cross-sectional data from the ALSPAC cohort, use of high-potency cannabis was found to associate with an anxiety disorder but not with depression (Hines et al., 2020). In conclusion, a significant knowledge gap exists concerning the relationship of early cannabis use and subsequent anxiety disorders. The few studies addressing this issue have reported mixed findings, and most importantly, might have been underpowered to detect this association.

Table 4. Prospective studies assessing association between adolescent cannabis use and anxiety disorders.

STUDY	SAMPLE	SAMPLE SIZE	AGE AT BASELINE (YEARS)	FOLLOW-UP (YEARS)	CANNABIS USE VARIABLE	POINT ESTIMATE (95% CIS)	COVARIATES
BROOK ET AL. (1998)	United States	168	16	6	Daily use	aOR **1.16** (1.00–1.35)	Age, sex, depression, anxiety, disruptive behavior disorder
BROOK ET AL. (2011)	United States, African American & Puerto Rico	837	14	15	Chronic use from adolescence to adulthood	aOR 2.3 (1.3-4.0)	Depression at baseline
DEGENHARDT ET AL. (2013)	Australia	1943	15–17	14	Weekly use	aOR **1.4** (0.84–2.5)	Baseline depression/anxiety, sex, school location, parental education, family structure. **alcohol use**
FERGUSSON ET AL. (1996)	Dunedin, New Zealand	927	14–16	2	Use (yes/no)	aOR 1.2 (0.5–2.8)	Family functioning, delinquent or drug using peers, **alcohol use**, sex, depression/anxiety/suicidality at baseline
GAGE ET AL. (2015)	ALSPAC, UK	1791	16	18	Use: 0, 1-20, 21-60, > 60 times a year	aOR 0.96 (0.75–1.24)	See table 3 for list of covariates

Statistically significant findings and substance use covariates in bold. aOR = adjusted odds ratio, ALSPAC = Avon longitudinal study of parents and children CI = confidence interval.

2.6.4 Adolescent cannabis use and subsequent bipolar disorder

To date, ten prospective longitudinal studies investigating the association between cannabis use and the first onset of manic symptoms or a bipolar disorder have been published. The majority of published adult studies (Table 5) have used either data from either NESARC or the NEMESIS cohorts with the lengths of follow-up ranging from three to five years (Bach et al., 2021; Cougle, Hakes, Macatee, Chavarria, & Zvolensky, 2015; Feingold, Weiser, Rehm, & Lev-Ran, 2015; Gilman, Dupuy, & Perlis, 2012; Henquet, Krabbendam, de Graaf, ten Have, & van Os, 2006; Van Laar, Van Dorsselaer, Monshouwer, & De Graaf, 2007). Four studies have utilized a sample of adolescents or young adults (Table 6) (Duffy et al., 2012; Marwaha, Winsper, Bebbington, & Smith, 2018; Ratheesh et al., 2015; Tijssen et al., 2010), of which three have reported significant positive associations (Duffy et al., 2012; Marwaha et al., 2018; Tijssen et al., 2010). The sole meta-analysis published thus far on the subject reported cannabis use to be associated with a threefold elevated odds for the onset of mania symptoms (Gibbs et al., 2015). However, only two studies (Henquet et al., 2006; Tijssen et al., 2010) were included in analysis.

Only one study assessing the association between cannabis use and a bipolar disorder-related outcome has examined a prospective birth cohort data (Marwaha et al., 2018). Utilizing data from the ALSPAC, Marwaha et al. found an association between of cannabis use at least 2–3 times per week and hypomania (Marwaha et al., 2018). In two studies, small high risk samples were utilized: one sample comprised 211 probands of individuals with type 1 bipolar disorder (Duffy et al., 2012) and another was a clinical at-risk sample of 52 individuals (Ratheesh et al., 2015). These special population studies used Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnoses as their primary outcome measure but neither controlled for other substance use. The two general-population-based studies had sample sizes of 3370 (Marwaha et al., 2018) and 543 (Tijssen et al., 2010). While the former controlled for hazardous alcohol use and other drug use, the latter evaluated alcohol use only as a separate exposure. Notably, none of the previous studies had included daily smoking as a covariate.

Importantly, in all four studies published to date on early cannabis use and the subsequent development of a bipolar disorder, the durations of follow-up were moderate, at most ranging from one year only (Ratheesh et al., 2015) to eight years (Tijssen et al., 2010) raising concerns pertaining to self-medication and reverse causality. Moreover, the two population-based studies examining this association used proxy-measures as outcomes, namely hypomania symptoms as assessed by the Hypomania Checklist (HCL-32) (Marwaha et al., 2018) and mania symptoms evaluated by the Composite International Diagnostic Interview (CIDI) (Tijssen et al., 2010). Complementing these longitudinal observational studies are the

genetically based approaches which have tried to elucidate this association. For example, in a very recent study examining probands with type II bipolar disorder and their first degree relatives, an association between proband type II bipolar disorder and a cannabis use disorder in a first degree relative was reported suggesting that there may be a shared heritable basis for these conditions (Quick et al., 2022). On the other hand, a recent Mendelian randomization study provided some evidence for an association between bipolar disorder and lifetime cannabis use but no evidence was found for the counter directional association (Jefsen, Speed, Speed, & Østergaard, 2021).

In conclusion, there is rather limited evidence for the proposal that there is an association between early cannabis use and a subsequent bipolar disorder. The few studies which have assessed this issue are based on selective or high-risk samples, have used symptom scales rather than diagnoses as outcomes and may suffer from confounding bias and reverse causality.

Table 5. Prospective studies assessing the association between adolescent cannabis use and bipolar-disorder related outcomes.

STUDY	SAMPLE	SAMPLE SIZE	FOLLOW-UP (YEARS)	CANNABIS USE VARIABLE	OUTCOME	POINT ESTIMATE (95% CIS)	SUBSTANCE USE COVARIATES
DUFFY ET AL. (2012)	One percent with Type 1 BD, Ottawa/Halifax, Canada	211	5.2	SUD	Bipolar disorder	HR **3.40**	Crude only
MARWAHA ET AL. (2018)	ALSPAC, UK	3370	5	Use ≥ 2-3 times per week	Hypomania	aOR **2.21** (1.49-3.28)	Psychotic symptoms, depression, gender, family adversity, childhood abuse, **Other drug use, Hazardous alcohol use**
RATHEESH ET AL. (2010)	High risk clinical sample, Australia	52	1	CUD	Bipolar disorder	OR 1.7 (0.7-18.1)	Crude only
TIJSSEN ET AL. (2010)	Munich, Germany	543	8.3	At least 5 times	Mania symptoms	aOR **4.26** (1.42-12.76)	Age, sex, socioeconomic status

Statistically significant findings and substance use covariates in **bold.** aOR = odds ratio, HR = hazard ratio, BD = bipolar disorder, CI = confidence interval, ALSPAC = Avon longitudinal Study of Parents and Children, SUD = substance use disorder, CUD = cannabis use disorder.

Table 6. Prospective longitudinal adult studies assessing cannabis use and mania-related outcome.

STUDY	SAMPLE	SAMPLE SIZE	FOLLOW-UP (YEARS)	CANNABIS USE VARIABLE	POINT ESTIMATE (95% CIS)	COVARIATES
VAN DER LAAR ET AL. (2007)	NEMESIS, Netherlands	3381	3	Lifetime use (yes/no)	**aOR 4.98** (1.80–13.81)	Gender, age, education, urbanicity, employment, partner status, neurotic personality, parental psychiatric history, childhood trauma, **AUD/SUD**, psychotic symptoms, anxiety disorders
GILMAN ET AL. (2012)	NESARC, USA With past year MDD	2585	3	CUD	**aOR 2.12** (1.10–4.08)	Depression characteristics, lifetime psychiatric disorder
FEINGOLD ET AL. (2015)	NESARC, USA	32606	3	Weekly use	**aOR 2.47** (1.03–5.92)	Sex, age, education, income, marital status, urbanicity, **AUD/SUD (not CUD)**, baseline psychiatric diagnosis
HENQUET ET AL. (2006)	NEMESIS, Netherlands	4815	3	Daily use	**aOR 3.43** (1.42–8.26)	Age, sex, education, ethnicity, marital status, neuroticism**, other drug use, alcohol use**, baseline depression/mania
COUGLE ET AL. (2015)	NESARC, USA	34653	3	Weekly use	**2.62** (2.23–3.06)	**Weekly alcohol, weekly nicotine**, age at first assessment, income, marital status, gender, ethnicity, education, psychiatric comorbidity
DE LIMA BACH ET AL. (2021)	Pelotas, Brazil	1560	5 (mean)	Cannabis abuse (ASSIST)	**2.38** (1.15-4.89)	**crude**

Statistically significant findings and substance use covariates in **bold.** AUD=Alcohol use disorder**,** CUD = Cannabis use disorder, SUD = substance use disorder, aOR = adjusted odds ratio. ASSSIST = alcohol, smoking and drug use involvement screening test.

2.7 Psychotic-like experiences and psychosis

Psychotic-like experiences (PLEs) are defined as attenuated distortions of thought and perception resembling those experienced in psychosis (Hinterbuchinger & Mossaheb, 2021; Lee et al., 2016), and lie on the continuum formed from the normal to overtly psychotic phenomena (Johns & Van Os, 2001; Van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009). Most mental disorders are associated with an elevated risk of PLEs (Lancefield, Raudino, Downs, & Laurens, 2016; McGrath et al., 2016) and conversely, PLEs in childhood are associated with psychopathology in adolescence (Giocondo et al., 2021; Healy, Gordon, et al., 2019). While PLEs are differentiated from psychotic symptoms by the relative lack of distress or help-seeking behavior (Hinterbuchinger & Mossaheb, 2021), they are nevertheless associated with adverse sequelae even in non-help-seeking populations. These include psychotic disorders (Kaymaz et al., 2012), excess mortality (Sharifi et al., 2015), self-injurious behaviors (Honings, Drukker, Groen, & Van Os, 2016; Kelleher et al., 2013), depression (Calkins et al., 2014; Dolphin, Dooley, & Fitzgerald, 2015) and poorer social outcomes (Davies, Sullivan, & Zammit, 2018).

Importantly, early cannabis exposure has been associated with PLEs in several studies, some of which have utilized prospective birth cohort data (Bechtold, Hipwell, Lewis, Loeber, & Pardini, 2016; Gage et al., 2014; Miettunen et al., 2008; Schubart et al., 2011; Van Gastel et al., 2013). Moreover, also cigarette smoking has been associated with PLEs (Bhavsar et al., 2018; Gage et al., 2014). Lastly, while PLEs tend to be transient and self-resolving phenomena (McGrath et al., 2015; Zammit et al., 2013), a persistence of PLEs has been found to associate with both an increased risk of psychiatric disorders (De Loore et al., 2011; Downs, Cullen, Barragan, & Laurens, 2013; Klrll et al., 2019) and cannabis use (Kuepper et al., 2011; Wigman et al., 2011).

Psychosis is a syndrome characterized by gross distortions of thought and perception with impaired reality-testing as its defining feature (McClellan, 2018). While psychotic episodes are especially characteristic of schizophrenia and related disorders, psychosis may also emerge in severe affective disorders, as a complication of use of psychoactive substances, or in the context of general medical conditions. The association of cannabis and psychosis is discussed in section 2.6.2.

2.7.1 Prognosis of adolescent psychotic-like experiences

In the meta-analysis of prospective longitudinal studies performed by Healy et al. 2019, PLEs in childhood or adolescence were associated with an almost threefold elevation in the odds for both any mental disorder and non-psychotic mental disorder (Healy, Brannigan, et al., 2019). However, only three studies were available for analysis with respect to the latter outcome (Cederlöf et al., 2017; Dhossche,

Ferdinand, Van Der Ende, Hofstra, & Verhulst, 2002; Poulton et al., 2000). In the analyses in which outcomes were stratified by disorder type, PLEs were associated with psychosis and mood disorders, but not with anxiety disorders. Several prospective studies assessing the prognosis of PLEs in adolescence in terms of different psychiatric sequelae have been published (see Table 1). Birth cohort data from the MUSP (Connell et al., 2016; J. Scott et al., 2009; Welham et al., 2009), Dunedin birth cohort (Fisher et al., 2013; Poulton et al., 2000) and the ALSPAC cohort (Sullivan et al., 2015; Zammit et al., 2013) have been utilized in seven studies with two of them adjusting for cannabis use (Klrll et al., 2019; Welham et al., 2009) or substance use in general (Connell et al., 2016). However, while the prognostic effect of cannabis use on the outcomes of individuals classified as being at an ultra-high risk for psychosis has been studied to some extent (Auther et al., 2012; Buchy, Perkins, Woods, Liu, & Addington, 2014; Kraan et al., 2016; McHugh et al., 2017; Valmaggia et al., 2014), relatively little is known about the sequalae of cannabis exposure of non-help-seeking adolescents with PLEs. Lastly, two studies examining PLEs and early cannabis exposure have utilized data from the NFB86. Mustonen et al, determined a higher cumulative incidence of psychosis in those participants with both baseline PLEs and early cannabis use in comparison with those participants with baseline PLEs only (Mustonen et al., 2018). Moreover, an earlier cross-sectional study using NFBC 1986 data reported an association between adolescent cannabis exposure and prodromal symptoms (Miettunen et al., 2008).

Table 7. Longitudinal studies focusing on psychiatric prognosis of PLEs in adolescence.

STUDY	SAMPLE	SAMPLE SIZE	AGE AT BASELINE (YEARS)	FOLLOW-UP (YEARS)	PLE VARIABLE	OUTCOMES
CONNEL ET AL. (2012)	MUSP*, Australia	333	14 & 21	≤ 19 years	hallucinations	any psychiatric disorder, SUD, suicide attempt
CEDERLÖF ET AL. (2017)	Sweden	9242	15 or 18	2.7 (median)	PEs	SUD, suicide attempt
DHOSSCHE ET AL. (2002)	Zuid-Holland, Netherlands	779	11–18	9	auditory hallucinations	any psychiatric disorder, depressive disorders, SUD, specific phobia, PTSD
DOMINGUEZ ET AL. (2011)	Munich, Germany	845	14–17	8.4	persistence of PEs	psychotic disorder
FISCHER ET AL. (2013)	Dunedin birth* cohort, New Zealand	776	11	27	strong PEs	schizophrenia, anxiety, depression, PTSD, SUD, suicide attempt/suicide
KLRLL ET AL. (2021)	Turkey, community-based sample	187	39.6% of participants aged 15–30., 60.4% participants aged > 30	6	Persistent PEs	Any psychiatric disorder
POULTON ET AL. (2000)	Dunedin birth cohort*, New Zealand	1073	11	11	PEs	Schizophreniform diagnosis
SCOTT ET AL. (2009)	MUSP*, Australia	3617	14	14	Hallucinations	Delusional-like experiences
SULLIVAN ET AL. (2005)	ALSPAC*, UK	3171	12	12	PEs	Suicidal ideation/suicide attempt
WELHAM ET AL. (2009)	MUSP*, Australia	?	14	14	PEs	SP-NAP status
ZAMMIT ET AL. (2013)	ALSPAC*, UK	4724	12	6	PEs	Psychotic disorders

* Birth cohort, PLE = psychotic-like experience, PE = psychotic experience, ALSPAC = Avon longitudinal study of parents and children, MUSP = Mater-university of Queensland study of pregnancy. SP-NAP = screen positive for non-affective psychosis.

2.7.2 Cannabis and psychosis: lines of evidence

In a recent meta-analysis of experimental studies, THC was shown to cause transient positive and negative symptoms with large effect sizes (Hindley et al., 2020). However, it is yet far from clear whether cannabis use is causally related to psychotic disorders. As pointed out recently, several lines of evidence will be needed to establish whether cannabis is independently of other risk factors associated with the development of psychotic disorders (Gage, 2019). In the first meta-analysis examining the association between cannabis use and psychotic outcomes, lifetime use was associated with a 41% elevated risk of psychosis whereas heavy use increased doubled the risk (Moore et al., 2007). However, the studies available for analysis were mostly cross-sectional in design. In the meta-analysis published by Marconi et al., heavy cannabis use was associated with a 3.9-fold odds of risk of a subsequent psychotic outcome (Marconi et al., 2016). Recently, evidence for a dose-response relationship was reported in the meta-analysis performed by Robinson et al. in which daily users were found to be at the greatest risk for psychotic outcomes (RR = 1.76; 95% CI 1.47–2.12) (Robinson et al., 2022). In addition to heaviness of cannabis use, use of high potency cannabis has been an exposure of interest in observational research in attempts to determine if there is a dose-response with respect to psychosis with at least eight such studies published to date according to a recent systematic review (Petrilli et al., 2022).

Observational studies assessing the frequency of psychosis attributed to cannabis use at the population level provide an important complementary line of research. Di Forti et al. conducted a transnational case-control study on first episode psychosis (FEP) and specifically on high potency cannabis as defined as a THC content exceeding 10%. They reported a population-attributable factor for incident FEP of high-potency cannabis of 12.2% across all sites and up to 50% in Amsterdam (Di Forti et al., 2019). Using a large Danish register-based dataset, Hjorthøj et al. detected a fourfold increase in the population-attributable fraction (PAF) of cannabis use for schizophrenia, i.e. from 2% in 1995 to 8% in 2010 (Hjorthøj et al., 2021). The same group reported an increase in the incidence rate of cannabis-induced psychosis from 2.8 per 100 000 person years in 2006 to 6.1 per 100 000 person years in 2016 in Denmark (Hjorthoj et al., 2021). This is of crucial significance, as a large proportion of the patients initially diagnosed with an episode cannabis-induced psychosis had converted to schizophrenia spectrum disorders or a bipolar disorder (Kendler, Ohlsson, Sundquist, & Sundquist, 2019; Niemi-Pynttäri et al., 2013; Starzer, Nordentoft, & Hjorthøj, 2018). Furthermore, a recent meta-analysis reported a conversion rate of 34% from cannabis-induced psychosis to schizophrenia (Murrie, Lappin, Large, & Sara, 2020). These findings are in line with a longitudinal study reporting that cannabis use has a much stronger effect in those predisposed to psychosis (Henquet et al., 2005). Cannabis use might also precipitate the onset of

first episode psychosis as found in the meta-analysis performed by Large et al (Large, Sharma, Compton, Slade, & Nielssen, 2011). Lastly, three Mendelian randomization studies assessing this association have been conducted (Gage et al., 2017; Pasman et al., 2018; Vaucher et al., 2018), two of which reported a significant positive association between cannabis use and schizophrenia. Conversely, while also examining this association, one study found the counter-directional association between schizophrenia and subsequent cannabis use to be even stronger (Gage et al., 2017).

It has been speculated that vulnerability to cannabis induced psychosis could be conferred by variants of genes of significance impacting on the dopaminergic neurotransmitter system (Murray et al., 2017; Murray, Mehta, & Di Forti, 2014). In line with this theory, the association of early cannabis use and schizophreniform disorder stratified by catechol-o-methyl transferase (COMT) genotype was examined utilizing data from the Dunedin birth cohort (Caspi et al., 2005). However, in general these gene-environment interaction (GxE) studies assessing the interaction of cannabis exposure and alleles known to confer a risk for psychosis have yielded mixed findings and are heterogenous in terms of study design and outcomes examined (Hindocha et al., 2020; Wahbeh & Avramopoulos, 2021; Zammit et al., 2007). In contrast, an interaction between a high polygenic risk score for schizophrenia and cannabis use was found in a multicenter case-control study assessing risk factors for psychosis (Guloksuz et al., 2019). Furthermore, findings indicating a shared genetic vulnerability for cannabis use and schizophrenia were reported in a recent genomic structural equation modeling study (Song et al., 2022).

2.7.3 Adolescent cannabis use and subsequent psychosis

A recent systematic review and meta-analysis by Kiburi et al. (2021) focused specifically on adolescent cannabis use and psychosis. According to these investigators, cannabis use in adolescence was associated with a 71% elevated risk of subsequent psychotic outcomes. Moreover, a quantitative analysis was conducted in which the effect of cannabis exposure onset was studied. There, early onset cannabis use was associated with an increased risk of a subsequent psychotic outcome in comparison to the group with late onset cannabis use (Kiburi, Molebatsi, Ntlantsana, & Lynskey, 2021).

Several prospective population-based studies on the association between cannabis use and psychosis have been conducted (Table 7). The Swedish conscript cohort is of particular significance as it included >97% of the country's male population aged 18–20 in 1969–70, with information on psychotic disorders linked from nationwide registers which translates into exceptional generalizability of these results. Furthermore, its large sample size with more than 50,000 participants yielded

sufficient statistical power to study schizophrenia, a relatively rare outcome, separately from other non-affective psychoses. The seminal paper was published in 1987 with a follow-up of 15 years and reported cannabis use to be associated with a six-fold risk of schizophrenia after confounder control (Andréasson, Engström, Allebeck, & Rydberg, 1987). Zammit et al. published another study re-examining the same cohort (Zammit et al., 2002). The length of follow-up was extended to 26 years and the question of self-medication was addressed by conducting separate analyses with cases registered after 5 years of follow-up. Then, the issue of confounding by other substance use was examined by conducting separate analyses with a subsample of participants reporting cannabis use only at baseline. Significant positive findings were reported for the heavy use group (>50 times) in each analysis. While the association remained elevated by over six-fold for those reporting only heavy cannabis use at baseline, the effect size for heavy users in the un-stratified sample (OR = 3.1) was reduced to half of that reported by Allenbeck et al. Other longitudinal studies assessing cannabis use and cannabis use and psychosis have also been published (please see table 8 for details) (Manrique-Garcia et al., 2012; Edison Manrique-Garcia, Zammit, Dalman, Hemmingsson, & Allebeck, 2012; Zammit, Lewis, Dalman, & Allebeck, 2010).

While the Swedish conscript cohort represents an exceptional resource for studying cannabis exposure in late adolescence, other important prospective studies have provided useful data about early exposure to cannabis and the subsequent onset of psychosis (Arseneault et al., 2002; Bechtold, Simpson, White, & Pardini, 2015; McGrath et al., 2010; Mustonen et al., 2018). Three of these studies have used prospective birth cohort data (Arseneault et al., 2002; McGrath et al., 2010; Mustonen et al., 2018); two adjusted for psychotic experiences at baseline (Arseneault et al., 2002; Mustonen et al., 2018) but only one study used linkage to nationwide registers for the diagnoses of psychotic disorders (Mustonen et al., 2018). However, in the study by McGrath et al., information on early cannabis use was gathered retrospectively at the age of 21 introducing the possibility of recall bias (McGrath et al., 2010). With the exception of the publication from Bechtold et al., the aforementioned studies have uniformly reported findings suggesting that in particular early cannabis exposure is a risk factor for the onset of psychosis (See Table 8).

Table 8. Prospective studies assessing association of adolescent cannabis use and psychosis.

STUDY	SAMPLE	SAMPLE SIZE	AGE AT BASELINE (YEARS)	LENGTH OF FOLLOW-UP (YEARS)	CANNABIS USE VARIABLE	POINT ESTIMATE (95% CIS)	COVARIATES
ANDREASSON ET AL. (1987)	Swedish conscripts	50087	18–20	15	Heavy use	**aOR 6.0** (4.0–8.9)	**Other substance use, Abuse of solvents**
ARSENEAULT ET AL. 2002)	Dunedin, New Zealand	1037	15 & 18	11	Use by age 15	**aOR 11.38** (1.84–70.06)	**Childhood, psychotic symptoms, other drug use**
BECHTOLD ET AL. (2015)	Pittsburgh, USA	386	13.9 (mean)	21.9 (mean)	Use trajectory	No difference between trajectories	Socioeconomic status, Childhood psychopathology, **Use of alcohol, use of cigarettes**
CASPI ET AL. (2005)	Dunedin, New Zealand	1037	13 & 15	13	Lifetime use & Val/val genotype	**OR 10.9** (2.2–54.1)	**Crude**
MANRIQUE-GARCIA ET AL. (2012)	Swedish conscripts	50087	18–20	35	Heavy use	**aOR 3.7** (2.3–5.8)	Psychiatric diagnosis at baseline, IQ, **cigarette smoking,** disturbed behavior, urbanicity
MCGRATH ET AL. (2010)	MUSP, Australia	3801	14	7	Duration since first use ≥ 6 years	**aOR 2.1** (2.2-4.5)	Sex, age, parental mental illness, hallucinations at 14 year follow up
MUSTONEN ET AL. (2018)	NFBC86, Finland	6534	15–16	18	At least 5 times	**aHR 3.02** (1.14–7.98)	Baseline prodromal symptoms**, frequent alcohol intoxications, daily smoking, use of other illicit drugs,** parental psychosis
ZAMMIT ET AL. (2002)	Swedish conscripts	50087	18	27	Heavy use	**aOR 3.1** (1.7–5.5)	Diagnosis at conscription, IQ score, poor social integration, disturbed behaviour, **cigarette smoking**, and place of upbringing

Statistically significant findings and substance use covariates in **bold.** CI = confidence interval. aHR = adjusted hazard ratio aOR = adjusted odds ratio.

2.8 Adolescent cannabis use and subsequent substance use disorders

Substance use disorders (SUDs) are syndromes characterized by a compulsive preoccupation with substance use regardless of the possible adverse consequences and negative mood whilst not under the influence of the substance in question (Koob & Volkow, 2016). Substance use disorders tend to have an onset in early adulthood, with a mean age of onset of 25 years as reported in a recent large scale meta-analysis of observational studies (Solmi, Radua, et al., 2021). Furthermore early age of onset of alcohol, cannabis, or misuse of prescription drugs have been demonstrated to predict the development of SUDs (Hingson et al., 2006; Le Strat, Dubertret, & Le Foll, 2015; McCabe, West, Morales, Cranford, & Boyd, 2007).

While an umbrella review of five meta-analyses of observational studies found only limited evidence for risk-factors associated with substance use disorders (Solmi, Dragioti, et al., 2021), evidence on environmental risk factors in adolescence for substance use disorders in young adulthood has also been mixed (Stone, Becker, Huber, & Catalano, 2012). Nevertheless studies using prospective birth cohort data have reported associations between early environmental risk factors and different substance use disorders, e.g., childhood sexual abuse and nicotine use disorder (Al Mamun et al., 2007), early parental separation and alcohol use disorder (Hope, Power, & Rodgers, 1998), externalizing behavior in childhood/adolescence and cannabis use disorder (Hayatbakhsh, Najman, Bor, et al., 2009). Importantly, an association was reported in a meta-analysis on prospective studies between childhood attention-deficit and hyperactivity disorder (ADHD) and externalizing disorders and subsequent substance use disorders (Groenman, Janssen, & Oosterlaan, 2017).

The concept of cannabis being a gateway drug is backed by some evidence from observational studies. An association was reported between cannabis use and opioid use disorder in a recent meta-analysis (Wilson et al., 2021), and specifically adolescent cannabis use has also been associated with the subsequent abuse of prescription opioids (Fiellin, Tetrault, Becker, Fiellin, & Hoff, 2013). Moreover, a study examining the trajectories of adolescent cannabis use utilizing the ALSPAC birth cohort data found that those with early occasional or regular use were at an elevated risk for harmful alcohol use or nicotine dependence at the age of 21 years (Taylor et al., 2017).

3 Aims

The objective of this thesis was to study the association of early cannabis exposure with self-harm and suicide as well as mood- and anxiety disorders. In addition, we applied a longitudinal general population study design, to examine the mental-health trajectories of participants with psychotic-like experiences with or without cannabis exposure.

The objectives were as follows:

To study prospective associations between early cannabis exposure and psychiatric sequelae, specifically severe self-harm requiring medical attention (Study I), the onset of a depressive or anxiety disorder (Study II), and the onset of a bipolar disorder (Study III)

To study the impact of cannabis use on the mental health trajectories of adolescents with psychotic-like experiences (Study IV)

To assess the impact of confounding bias, namely baseline and parental psychopathology, and other types of substance use when studying the prognosis of adolescent cannabis use (Studies I-IV)

4 Materials and methods

4.1 Participants and data collection

The Northern Finland Birth Cohort 1986 is a population-based and ongoing birth cohort study including 99% of all births in the two northernmost provinces in Finland (i.e., Northern Ostrobothnia and Lapland) between July 1, 1985 and June 30, 1986 (Oulu, 1986). The original sample included 9,432 live-born children. A multidisciplinary follow-up study was conducted in 2001–2002 when study members were aged 15–16 years. First, self-report postal questionnaires were sent to the adolescents (n = 9215) in which they answered questions concerning their health and wellbeing (n = 7344). Then, all the participants were invited to a clinical study, as a part of which they completed self-report questionnaires including questions on emotional and behavioral problems and substance use habits. Sample inclusion is presented in Figure 3. The provision of informed consent (non-response, n=2) and answering questions on cannabis (non-response, n =210) use were fundamental inclusion criteria in all the studies included in this thesis. Additional exclusion criteria were as follows: having a diagnosis implying severe self-harm at age 15/16 (Study I, n = 5), having a psychiatric diagnosis at age 15/16 (Studies II and III, n=261) and not answering questions concerning psychotic-like experiences (Study IV, n=34). The follow-up study in 2001–2002 was approved by the Ethics Committee of the Northern Ostrobothnia Hospital District (17 May 2006).

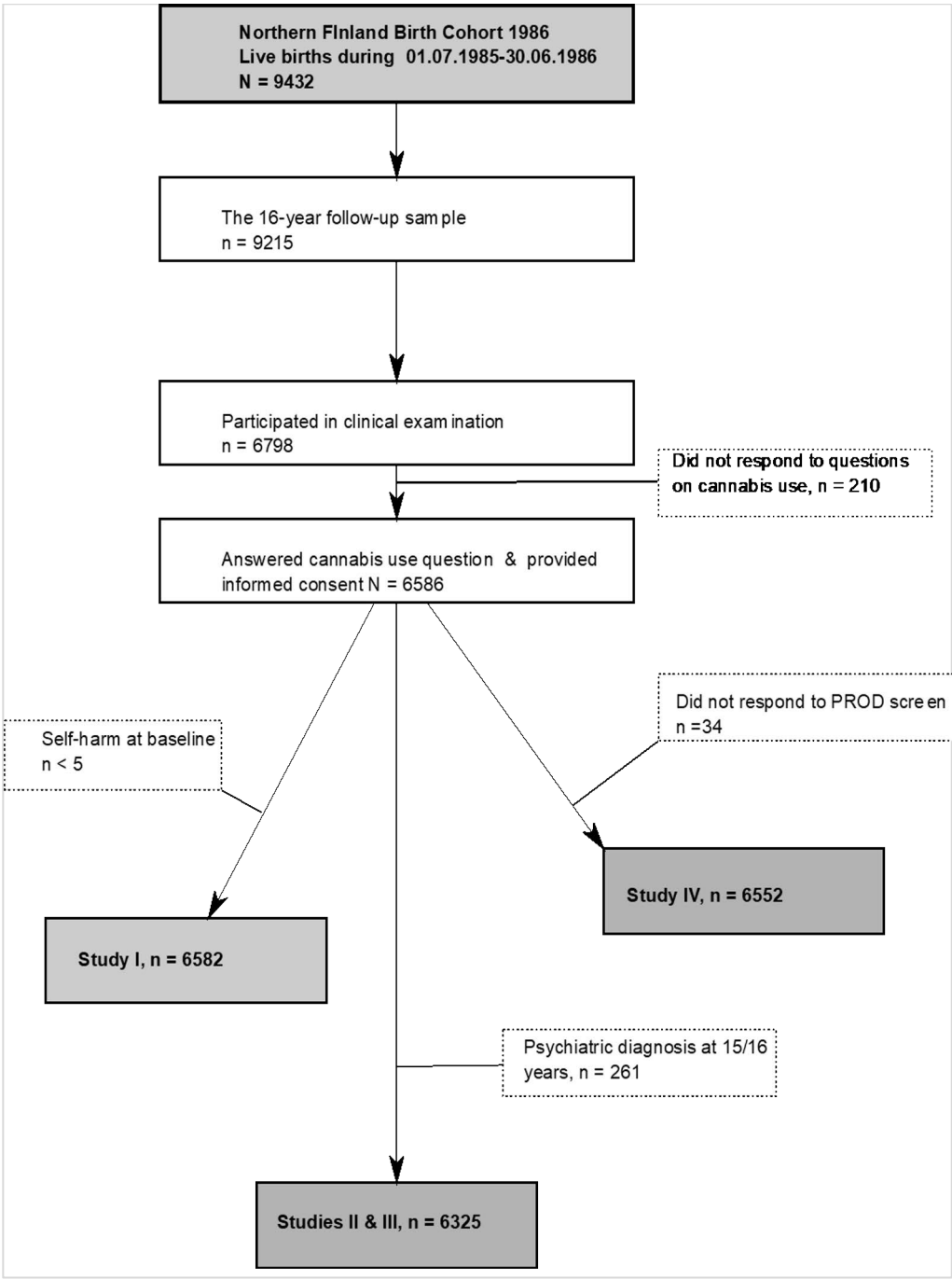

Figure 4. Representation of participant flow in the studies included in this thesis (modified from studies I-IV).

4.2 Early cannabis use

Data on lifetime adolescent cannabis use were collected during the clinical study when participants were aged 15–16 years. They were asked ‘Have you ever used marihuana or hashish?' with options ‘never, once, 2–4 times, 5 times or more, or I use regularly'. Cannabis use was categorized into four groups, and the two latter groups were pooled because of infrequent reporting (Study II). When outcome was rare (Study I and III) or the exposure variables included small cell sizes (study IV), cannabis use was studied dichotomously (never/ever). In addition, in Study III, cannabis use was assessed dichotomously in the main multivariable analyses, but univariable analyses were also performed utilizing a three-class cannabis variable (never, 1–4 times, at least 5 times).

4.3 Outcomes: register based ICD-10 diagnoses

For all outcome variables, linkage to the Care Register for Health Care 2001–2018, the Register of Primary Health Care Visits 2011–2018, the medication reimbursement register of the Social Insurance Institution of Finland 2001-05 and the disability pensions of the Finnish Center for Pensions was used to obtain information on clinician-rated diagnoses of relevance to the respective studies. The data were collected cumulatively from the participants´ age of 16 years until the end of 2018, when the participants were aged 33 years, yielding a follow-up of 18 years in each study. The Care Register contains data on patients discharged from inpatient care, and since 1998 also on specialized outpatient care. The Register of Primary Health Care Visits records information on outpatient primary health care.

The diagnostic codes utilized for the outcome variables in Studies I to IIII were as follows: self-harm-related diagnostic codes (Study I; ICD-10: X60-X84, Z91.5, Y87.0 and Z72.8 as well as ICPC-2: P77), anxiety disorders and unipolar depressive disorders (Study II; ICD-10 F40–44, F32.0–33.9, F34.1, F38.10), bipolar disorder (Study III F30.xx, F31.xx). In Study I, information on deaths by suicide was obtained from the Registry for Causes of Death until 2018.

In Study IV, data on diagnostic ICD-10 codes related to any psychiatric disorder (F00-F69, F80-F99), psychosis (F20-F25, F28, F29, F30.2, F31.2, F31.5, F32.3, F33.3), mood disorder (F30-F39), depression (F32, F33, F341, F38.10), anxiety disorder (F40-44) and substance use disorder (F1x.1-2) was used to construct the respective variables.

4.4 Covariates

4.4.1 Demographic characteristics

Parental education was operationalized as a dichotomous variable according to the highest educational level achieved by either parent (less or more than 12 years of schooling). Information on the parental education level was collected from a postal questionnaire from the parents in 2001–02. Information on family structure was studied in studies II–IV and was categorized into a binary variable (both parents living with participant/other type of family). Information on family structure was gathered from the parent at birth and from adolescents in the field study in 2001–02.

4.4.2 Parental psychopathology

Information on lifetime parental psychiatric diagnoses (ICD-10: F00-F69, F80-F99) that were included as covariates in all studies was obtained from the nationwide Registers of Health Care during the years 1972–2018 and Finnish Center for Pensions until 2016.

4.4.3 Baseline psychopathology in adolescence

In Study I, early psychopathology was operationalized as a binary variable (yes/no) of any psychiatric diagnosis (ICD-10: F00-F69, F80-F99) recorded in the national registries before the participants were aged 16 years. Data for this variable was obtained from the registries listed in section 4.3.

Information on adolescent mental health was collected in the field study when the participants were aged 15–16 years using the Youth Self Report (YSR) (Achenbach & Rescorla, 2013). The YSR consists of 118 items measuring symptoms of emotional and behavioral problems in adolescents aged 11–18 years. Responses to YSR items are scored on a three-point scale with statements being not true (0); somewhat/sometimes true (1); or very true (2) in terms of reflecting how the young person has felt within the past six months. In Study II, the subscales for internalizing and externalizing symptoms were included separately in the multivariable models. In Study III, the total score of the YSR was included as a covariate. As substance use was assessed utilizing separate variables in studies II and III, the YSR item “I use alcohol or drugs for nonmedical purposes” was removed from the YSR total sum score.

Data on psychotic-like experiences (PLEs) was collected during the clinical study and utilized in Study IV of this thesis. The participants were asked about the occurrence of psychotic-like experiences during the previous 6 months (no/yes)

using the PROD-screen (Heinimaa et al., 2003). The PROD-questionnaire has 12 dichotomized items (rated no/yes) assessing attenuated psychotic experiences such as mild paranoia or experiences resembling the so-called Schneiderian first rank symptoms. In the main analyses, a PROD threshold of 3 points was used, as this is the cutoff used by convention when screening at-risk patients in clinical practice (Mustonen et al., 2018). However, the aim of this study was to assess PLEs as experienced in the wider non-prodromal population and therefore the analyses were also conducted with a lower threshold of at least 2 points. Importantly, the construct validity of the PROD screen has been studied also with this threshold (Heinimaa et al., 2003). The participants were stratified into four groups according to PLE and cannabis exposure (CE) status: PLE/CE +/+, PLE/CE +/-, PLE/CE -/+, PLE/CE -/-. Due to the small subsample size (n=129, 1.9% of the sample), the group with cannabis exposure but not presenting with psychotic experiences (PLE/CE -/+) was not included in the main analyses.

4.4.4 Other substance use

Data on daily smoking, frequent alcohol intoxication and lifetime illicit substance use were collected at age 15–16 years using a questionnaire during the clinical study. The participants were asked: 'Have you used ecstasy, heroin, cocaine, amphetamine, LSD or other similar intoxicating drugs?' The information was categorized in the form of a binary variable (never/at least once) Frequent alcohol intoxication were questioned as 'Have you been drunk during the past year? (0, 1–2, 3–5, 6–9, 10–19, 20–39, or 40 times or more)', and this was dichotomized as 'Have you been drunk 10 times or more during the past year (no/yes)' based on the distribution of the data. Information on regular cigarette smoking was collected from postal questionnaires: adolescents were asked if they currently smoked cigarettes daily (at least 1 cigarette/day, no/yes).

4.5 Statistical methods

The statistical methods used in studies I–IV are presented in table 9. With respect to the covariate selection in studies I, III and IV, a fixed set of predictors were used based on previous prospective research on the psychiatric sequelae of early cannabis use (Heinze & Dunkler, 2017). In study II, univariable screening with cross-tabulation and Chi squared or Fisher's exact test was used to evaluate the relationship of the respective variables with cannabis use, depression and anxiety. Those variables achieving a significance level of $p<0.1$ for both cannabis use and the outcome under examination were included in the multivariable models.

In study IV, the association between cannabis use and the respective psychiatric diagnoses was assessed using logistic regression with odds ratios and 95% confidence intervals. A sensitivity analysis was conducted by performing each analysis with a sample from which those with a psychiatric disorder at baseline had been removed. In study II, a sensitivity analysis was conducted by performing the analyses with a sample from which those with a baseline psychiatric disorder had not been excluded. In studies I–III, Cox-regression with Hazard Ratios and 95% confidence intervals were used for the multivariable models. In studies I and III, the interactions between cannabis use and each variable included in the final model were also assessed. Dose-response was studied in studies I–III using a trend-test in which a categorical cannabis use variable was applied as a continuous variable using a Cox-regression (studies I and II) or a logistic regression (study III) model. Times at emigration (n=256) or death (n=50) were used as censoring points in the analyses. The proportionality of hazards and time-dependency assumptions were assessed using hazard logarithms, scaled Schoenfeld residuals and time-dependent covariates. In studies II and III, the data was visualized by computing survival curves, whereas in studies I and IV, Aalen-Johansen cumulative incidence curves were computed.

Linear regression and multicollinearity diagnostics with variance inflation factor (VIF) scores were used to detect the correlation between multiple covariates, with VIF >5 as a threshold of indicator of multicollinearity.

Inverse probability weighting (Haukoos & Newgard, 2007) was conducted as an attrition analysis in studies I and III, as previous publications utilizing this cohort have shown that fewer males (64% vs. 71%; $p<0.001$), individuals living in urban areas (66% vs. 71%, $p<0.001$) and individuals with parental psychiatric disorder (58% vs. 69%, $p<0.001$) participated in the 15–16 year follow-up study (Miettunen et al. 2014). Thus, the sample data of Studies I and III was weighted by sex, parental psychiatric disorder and urbanicity. Both the weighted and the unweighted data were analyzed with logistic regression analysis and odds ratios (OR). To account for missing data due to non-response in study III, multiple imputations with fully conditioned specification and ten data sets were conducted. Moreover, in Studies I–IV, when examining the effects of non-response on sample characteristics, descriptive statistics for the frequencies and proportions of different covariates cross-tabulated with both cannabis use and respective outcome variables were computed for both crude and final models.

In study III**,** post hoc tests with cross-tabulation and Mann-Whitney U-tests were conducted to assess the association of early cannabis use with both the age of onset of a bipolar disorder and transitioning from a unipolar major depressive disorder to a bipolar disorder.

Table 9. Statistical methods used in Studies I-IV.

METHOD	STUDY I	STUDY II	STUDY III	STUDY IV
CROSSTABULATION WITH CHI SQUARE TEST	x	x	x	x
CROSSTABULATION WITH FISHER'S EXACT TEST	x	x	x	
MANN-WHITNEY U-TEST			x	
LOGISTIC REGRESSION				x
COX REGRESSION	x	x	x	
HAZARD LOGARITHMS	x	x	x	
SCALED SCHOENFELD RESIDUALS	x	x	x	
TIME DEPENDENT COVARIATES	x		x	
IPW	x		x	
LINEAR REGRESSION & VIFS	x	x	x	
E VALUES		x		
MULTIPLE IMPUTATIONS			x	
AALE-JOHANSEN CUMULATIVE INCIDENCE CURVES	x			x

IPW = inverse probability weighting, VIF = variance inflation factor.

5 Results

5.1 Early cannabis use, self-harm and suicide

The sample characteristics are displayed in Tables 8 and 9. The sample size totaled 6582 participants with 5.7% (n=377/6582) presenting with early cannabis use. The cumulative incidences of self-harm and suicide death were 1.2% (n = 79/6582, 56% male) and 0.3% (n=22/6582, 91% male) respectively. Less than five individuals received both an ICD-10 diagnosis implying severe self-harm and death by suicide. No evidence of significant multicollinearity was seen (all VIF values < 5).

The results of the multivariable models are presented in Table 10. The association of cannabis use with suicide did not reach statistical significance even in the crude analysis (HR = 2.60; 95% CI 0.77–8.78). The results of the multivariable analyses for cannabis use and self-harm are summarized in Table 11. Regarding sex, evidence of time-dependency was seen both when examining the hazard logarithm curves and utilizing the time-dependent covariate. No violations of the proportionality of hazards assumption were detected concerning cannabis use or other covariates included in the final model.

A crude association was detected between adolescent cannabis use and the risk of self-harm. Adjusting for sex and psychiatric disorders at baseline, the association between cannabis use and subsequent self-harm attenuated but remained statistically significant (HR =3.75; 95% CI 2.13–6.61). The association attenuated further by 46 percent when adjusted for frequent alcohol intoxications and illicit drugs other than cannabis (HR 2.04; 95% CI 1.07–3.90). Statistical significance was still evident in the final model after further adjusting for parental psychiatric disorders (HR 2.06; 95% CI 1.07–3.95). No statistically significant interactions were observed between cannabis use and any of the covariates included in the final model (sex, psychiatric disorder at baseline, frequent alcohol intoxications, use of other illicit drugs and parental psychiatric disorders, Model 3). A dose-response for cannabis use and self-harm was observed in a trend test (HR = 1.87; 95% CI 1.17–3.00). In the inverse probability weighting analyses, statistical significance was retained in the weighted analyses of early cannabis use and subsequent severe self-harm for all those associations that were statistically significant in the unweighted analyses with the associations being similar in strength.

Table 10. Association of covariates with cannabis use in Study I.

		CANNABIS USE STATUS						
	Total	**n = 6582**		**No cannabis use, n = 6205**		**Once or more**		**p-value**
COVARIATES	**n**	**n**	**%**	**n**	**%**	**n**	**%**	
SEX	6582							
Male		3239	49.2	3073	49.5	166	44.0	0.038
Female		3343	50.8	3132	50.5	211	56.0	
PSYCHIATRIC DISORDER AT BASELINE	6582							
No		6325	96.1	5973	96.3	352	93.4	0.005
Yes		257	3.9	232	3.7	25	6.6	
CANNABIS USE	6582							
No		6205	94.3	6205	100.0	0	0.0	-
Yes		377	5.7		0.0	377	100.0	
OTHER ILLICIT DRUG USE	6554							
No		6519	99.5	6171	99.9	348	92.6	<0.001*
Yes		35	0.5	7	0.1	28	7.4	
ALCOHOL INTOXICATION ≥ 10 TIMES A YEAR	6419							
No		5227	81.4	5105	84.4	122	32.8	<0.001
Yes		1192	18.6	942	15.6	250	67.2	
PARENTAL PSYCHIATRIC DISORDER	6582							
No		4174	63.4	3949	63.6	225	59.7	0.123*
Yes		2408	36.6	2256	36.4	152	40.3	

* Fisher's exact test

Table 11. Association of covariates and cannabis use with self-harm and suicide in Study I.

		SELF-HARM					SUICIDE				
	Total	**No, n=6503**		**Yes, N =79**		**p-value**	**No**		**Yes**		**p-value**
COVARIATES	**n**	**n**	**%**	**n**	**%**		**n**	**%**	**n**	**%**	
SEX	6582										
Male		3195	49.1	44	55.7	0.259*	3219	49.1	20	90.9	<0.001
Female		3308	50.9	35	44.3		3341	50.9	2	9.1	
PSYCHIATRIC DISORDER AT BASELINE	6582										
No		6261	96.3	64	81.0	<0.001*	6304	96.1	21	95.5	0.584*
Yes		242	3.7	15	19.0		256	3.9	1	4.5	
CANNABIS USE	6582										
No		6141	94.4	64	81.0	<0.001*	6186	94.4	19	86.4	0.128*
Yes		362	5.6	15	19.0		374	5.7	3	13.6	
OTHER ILLICIT DRUG USE	6554										
No		6443	99.5	76	96.2	0.008*	6497	99.5	22	100.0	1.00*
Yes		32	0.5	3	13.8		35	0.5	0	0.0	
ALCOHOL INTOXICATION ≥ 10 TIMES A YEAR	6419										
No		5183	81.7	44	57.1	<0.001	5213	81.5	14	66.7	0.092*
Yes		1159	18.3	33	42.9		1185	18.5	7	33.3	
PARENTAL PSYCHIATRIC DISORDER	6582										
No		4147	63.8	37	34.2	<0.001	4166	63.5	8	36.4	0.008
Yes		2356	36.2	52	65.8		2394	36.5	14	63.6	

* Fisher's exact test

Table 12. The hazard ratios (HR) for the risk of self-harm according to the cannabis use status.

			NO CANNABIS USE AT BASELINE	CANNABIS USE AT BASELINE		
SELF-HARM		SAMPLE SIZE n	SELF-HARM n	SELF-HARM n	HR	95% CI
	Crude	6576	64	15	**3.93**	2.24–6.90
	Model 1	6576	64	15	**3.75**	2.13–6.61
	Model 2	6388	62	15	**2.04**	1.07–3.90
	Model 3	6388	62	15	**2.06**	1.07–3.95

Model 1: sex, psychiatric disorder at baseline; Model 2: sex, psychiatric disorder at baseline, frequent alcohol intoxications in past year, use of other illicit drugs; Model 3: sex, psychiatric disorder at baseline, frequent alcohol intoxications in past year, use of other illicit drugs, parental psychiatric disorder. Statistically significant results in **bold**. HR = hazard ratio. CI= confidence interval.

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5.2 Early cannabis use, depression, and anxiety disorders

The sample characteristics of Study II are presented in Table 12. The sample size totalled 6325 participants with 5.6% (n = 352/6325) presenting with early cannabis use. The cumulative incidences for depressive disorder were 9.2% (n = 583/6325) and were somewhat similar for any anxiety disorder i.e. 10.9% (n= 688/6325).

The results of the multivariable analyses for early cannabis use, depressive disorders and anxiety disorders are presented in Table 13. All of the confidence intervals of hazard ratios are listed in the table in the original publication. No violations of the proportionality of hazards assumptions or time-dependency were detected, neither was any significant multicollinearity evident (all VIFs <5). A crude association was seen between early cannabis use and depression in all cannabis use categories: Once (HR = 2.66, 95% CI 1.91–3.70), 2-4 times (HR = 2.51, 95% CI 1.62–3.88) and at least five times (HR = 2.56, 95% CI 1.45–4.54) Both ~~in both~~ full models (models 3a and 3 b) adjusted for daily smoking, frequent alcohol intoxications, other illicit substance use, family structure and parental psychiatric disorder. In addition to these covariates, Model 3a adjusted for internalizing and 3b for externalizing symptoms. Statistical significance was retained in both models in the categories consisting of those participants who had used cannabis only once or 2–4 times at baseline. The association between using cannabis 5 times or more and depression was attenuated to statistical non-significance.

A crude association between early cannabis use and anxiety was observed in all cannabis use categories: Once (HR = 1.62, 95% CI 1.11–2.35), 2–4 times (HR 1.88, 95% CI 1.19–2.97), and at least five times (HR = 3.36, 95% CI 2.10–5.37). Whereas the association between cannabis use and anxiety disorders attenuated to non-significance in the two lower categories, statistical significance was retained in both full models in the group consisting of participants having used cannabis at least five times at baseline (Model 3a, HR =2.20, 95% CI 1.18–4.08; Model 3b, HR=2.01, 95% CI 1.15–3.82). The results of the sensitivity analyses conducted with the sample including those with a baseline psychiatric disorder were similar to those of the main analyses.

Table 13. Association of covariates and cannabis-use in studies II and III.

COVARIATES	Total	CANNABIS USE FREQUENCY						
		n = 6325		**No cannabis use, n = 5973**		**Once or more N = 352**		**p-value**
	n	**n**	**%**	**n**	**%**	**n**	**%**	
SEX	6325							
Male		3089	48.8	2929	49.0	160	45.5	0.191
Female		3236	51.2	3044	51.0	192	54.5	
FAMILY STRUCTURE	5413							
Other		1102	20.4	1004	19.6	98	33.4	<0.001
Living with both parents		4311	79.6	4116	80.4	196	66.6	
PARENTAL EDUCATION	5504							
Less than 12 years		3382	61.4	3207	61.6	175	58.3	0.255-
12 years or more		2122	38.6	1997	38.4	125	41.7	
CANNABIS USE	6325							
No		5973	94.4	5973	100.0	0	0.0	-
Yes		352	5.6		0.0	352	100.0	
OTHER ILLICIT DRUG USE	6299							
No		6268	99.5	5942	99.9	326	92.9	<0.001*
Yes		31	0.5	6	0.1	25	7.1	
Alcohol intoxication ≥ 10 times a year	6167							

No		5024	81.5	4910	84.4	114	32.9	<0.001
Yes		1143	18.5	910	15.6	233	67.1	
Parental psychiatric disorder	6325							
No		4046	64.0	3836	64.2	210	59.7	0.083
Yes		2279	36.0	2137	35.8	142	40.3	
Daily smoking	5853							
No		5134	87.7	4960	89.7	174	54.2	<0.001
Yes		719	12.3	572	10.3	147	45.8	
Youth self-report		Mean	SD	MEAN	SD	MEAN	SD	
Total score	5849	26.5	15.6	25.9	15.2	36.2	19.0	<0.001**
Internalizing symptoms	5876	9.6	7.5	9.4	7.4	11.8	8.9	
Externalizing symptoms	5892	13.8	7.9	13.5	7.6	20.3	9.6	

* Fisher's exact test, Mann-Whitney U- test.

Table 14. The hazard ratios for risk of depressive and anxiety disorders according to cannabis use status (Study II).

USE FREQUENCY			NO USE	ONCE		2–4 TIMES		≥ 5 TIMES	
		SAMPLE SIZE	CASES	CASES	HR	CASES	HR	CASES	HR
DEPRESSION	Crude	6323	500	38	**2.66**	21	**2.51**	12	**2.56**
	Model 1a	5874	465	36	**2.40**	20	**2.26**	11	**2.14**
	Model 2a	5646	452	36	**2.06**	20	**1.88**	11	1.42
	Model 3a	5021	395	30	**2.01**	18	**2.02**	11	1.64
	Model 1b	5890	468	36	**2.11**	20	**2.02**	11	1.73
	Model 2b	5663	456	36	**1.97**	20	**1.88**	11	1.34
	Model 3b	5038	397	30	**1.93**	18	**2.02**	11	1.58
ANXIETY DISORDERS	Crude	6323	603	29	**1.62**	19	**1.88**	18	3.36
	Model 1a	5874	561	28	**1.56**	18	**1.77**	16	**2.98**
	Model 2a	5646	543	28	1.36	17	1.46	16	**1.94**
	Model 3a	5021	465	22	1.31	15	1.63	15	**2.20**
	Model 1b	5890	566	28	1.37	18	1.57	16	**2.53**
	Model 2b	5663	548	28	1.27	17	1.40	16	**1.81**
	Model 3b	5038	468	22	1.21	15	1.55	15	**2.01**

Models denoted with a or b conducted with internalizing/externalizing subscales respectively. Model 1x:YSR subscale, Model 2x: Model 1x + illicit drugs, frequent alcohol intoxications, Model 3x = Model 2x + family structure & parental psychiatric disorders. Statistically significant findings in **bold.**

5.3 Early cannabis use and bipolar disorder

The sample characteristics of Study III are presented in Table 12. The sample size totalled 6325 participants with 5.6% (n = 352/6325) presenting with early cannabis use. By the end of the follow-up, 1.0% (66/6325) had been diagnosed with a bipolar disorder. Importantly, of the participants diagnosed with a bipolar disorder, only 3/66 had used cannabis at least 5 times, 8/66 had used the drug less frequently i.e. 1–4 times.

The results of the multivariable analyses are summarized in Table 13. No violations of the Cox proportional hazard assumption were seen nor was there any significant sign of multicollinearity (all VIFs <5). A crude association was observed between early cannabis exposure and the risk of bipolar disorder (HR =3.46; 95% CI 1.81–6.61). When adjusted for sex, family structure, and parental psychiatric disorders, the association between cannabis use and a bipolar disorder diagnosis was somewhat attenuated but remained statistically significant (HR =3.00; 95% CI 1.47–6.13). Statistical significance persisted even after further adjusting for the YSR total score (HR =2.34; 95% CI 1.11–4.94). However, further adjustments for frequent alcohol intoxications, daily smoking and lifetime illicit drug use attenuated the associations to statistical non-significance. In unadjusted analyses, an association was also observed between cannabis use and bipolar disorder using a three-class cannabis variable 1-4 times (HR = 3.03; 95% CI 1.44–6.36), 5 times or more (HR = 5.55; 95% CI 1.74–17.73). This kind of dose-response was also seen with the trend test (OR =2.57; 95% CI 1.61–24.12). In the inverse probability weighting analyses, statistical significance was retained in the weighted analyses of early cannabis use and the subsequent onset of bipolar disorder for all those associations that were statistically significant in the unweighted analyses, and the associations were similar in strength. The results in the complete case sample were similar to those in the imputed sample.

The results of the post hoc tests were as follows: In the subsample of participants with unipolar major depression (n = 572), cannabis use was not associated with transitioning from a unipolar depressive disorder to a bipolar disorder (8.8% (n= 6) vs 5.6% (n= 28), p = 0.271). Furthermore, the mean of age of onset of bipolar disorder was similar in participants with or without early cannabis use at baseline (25.0 years (n= 11) vs 25.9 years (n= 55), p= 0.810).

Table 15. Hazard ratios for risk of bipolar disorder by cannabis use status (Study III).

CANNABIS USE			NO CANNABIS USE AT BASELINE	ONCE OR MORE		
BIPOLAR DISORDER		Sample size	Cases	Cases	HR	95% CI
	Crude	6325	55	11	**3.46**	1.81–6.61
	Model 1	5413	49	9	**3.00**	1.47–6.13
	Model 2	5190	49	9	**2.34**	1.11–4.94
	Model 3	4992	47	9	1.70	0.73–3.98

Model1: sex, family structure, parental psychiatric disorder; Model 2: sex, family structure, parental psychiatric disorder, YSR total; Model 3: sex, family structure, parental psychiatric disorder, YSR total, frequent alcohol intoxications during the past year, daily smoking, other illicit drug use. Statistically significant findings in **bold.**

5.4 Trajectories of psychotic-like experiences and early cannabis exposure

The sample characteristics of Study IV are presented in Tables 14 and 15. The sample size totalled 6552 participants with 5.7% (n = 375/6552) presenting with early cannabis use. In all, 47.2% (3093/6552, 40.8% male) displayed PLEs defined as a score of 2 or more items on the PROD-screen. The cumulative incidences of the outcomes were as follows: 24.4% (1601/6552) for any psychiatric disorder, 2.4% (154/6552) for a psychotic disorder, 10.7% (702/6552) for a mood disorder, 10.2% (669/6552) for depression, 11.6% (758/6552) for anxiety disorder and 2.9% (190/6552) for substance use disorder.

The results of the logistic regression models are presented in Table 16. The full model was adjusted for sex, family structure, parental psychiatric disorder, frequent alcohol intoxications, daily smoking, other illicit substance use. After these adjustments, individuals with psychotic experiences and cannabis exposure (PLECE +/+) were at an increased risk of any psychiatric disorder (OR 2.59; 95% CI 1.82-3.68), psychotic disorders (OR 3.86; 95% CI 1.83–8.11), mood disorders (OR 4.07; 95% CI 2.74–6.04), depressive disorders (OR 4.35; 95% CI 2.93–6.48) and anxiety disorders (OR 2.06; 95% CI 1.34–3.17) and substance use disorders (OR 2.26; 95% CI 1.13–4.50) when compared to the reference group (PLECE -/-). The odds ratios of the PLE/CE +/- group were found to be uniformly smaller than in the PLECE +/+ group.

In the sensitivity analysis conducted by excluding the subjects diagnosed with a psychiatric disorder before the age of 15/16 (n = 255), as in the main analyses presented in the paragraph above, individuals with PLE/CE +/+ were at a greater risk than the PLE/CE +/- group for all of the subsequent outcomes. Importantly, similar results were obtained when a lower threshold of 2 points on the PROD scale were used in the multivariable analyses (for more detailed information, please see online supplement table of the original publication).

Table 16. Association of covariates and psychotic-like experiences and cannabis exposure status in the Northern Finland 1986 Birth Cohort (Study IV).

COVARIATES		TOTAL N = 6552		PLECE +/+ N = 205		PLECE -/+ N = 170		PLECE +/- N = 1795		PLECE -/- N = 4382		P-VALUE
		n	%	n	%	n	%	n	%	n	%	
SEX	6552											
Male		3221	49.2	75	36.6	90	52.9	681	37.9	2375	54.2	<0.001
Female		3331	50.8	130	63.5	80	47.1	1114	62.1	2007	45.8	
FAMILY STRUCTURE	5595											
Family with both parents		4419	79.0	114	67.1	94	66.7	1213	77.6	2998	80.6	<0.001
Other		1176	21.0	56	32.9	47	33.3	351	22.4	722	19.4	
DAILY SMOKING	6050											
No		5290	87.4	101	54.9	73	46.2	1494	88.4	3622	90.9	<0.001
Yes		760	12.6	83	45.1	85	53.8	196	11.6	396	9.1	
OTHER ILLICIT DRUG USE	6525											
No		6490	99.5	187	91.2	159	94.1	1783	99.7	4361	100	<0.001
Yes		35	0.6	18	8.8	10	5.9	6	0.3	1	0	
ALCOHOL INTOXICATION ≥ 10 TIMES A YEAR	6390											
No		5203	81.4	65	32.2	7	33.9	1431	81.1	3650	85.8	<0.001
Yes		1187	18.6	137	67.8	111	66.1	333	18.9	606	14.2	
PARENTAL PSYCHIATRIC DISORDER	6552											
No		4152	63.4	120	58.5	105	58.5	1104	61.5	2823	64.4	0.07
Yes		2400	36.6	85	41.5	65	41.5	691	38.5	1559	35.6	

PLE = psychotic-like experiences, CE = cannabis exposure.

Table 17. Distribution of outcomes by psychotic-like experience and cannabis exposure status in Northern Finland Birth Cohort 1986 (Study IV).

COVARIATES	TOTAL N = 6552		PLECE +/+ N = 205		PLECE -/+ N = 170		PLECE +/- N = 1795		PLECE -/- N = 4382		P-VALUE*
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	
ANY PSYCHIATRIC DISORDER											
No	4951	75.6	109	53.2	119	70.0	1263	70.4	3460	79.0	<0.001
Yes	1601	24.4	96	46.8	51	30.0	532	29.6	922	21.0	
PSYCHOTIC DISORDERS											
No	6398	97.6	189	92.2	165	97.1	1730	96.4	4314	98.4	<0.001
Yes	154	27.4	16	7.8	5	2.9	65	3.6	68	1.6	
MOOD DISORDERS											
No	5850	89.3	141	68.8	143	84.1	1538	85.7	4028	91.9	<0.001
Yes	702	10.7	64	31.2	27	15.9	257	14.3	354	8.1	
DEPRESSIVE DISORDERS											
No	5883	89.8	143	69.8	144	84.7	1547	86.2	4049	92.4	<0.001
Yes	669	10.2	62	30.2	26	15.3	248	13.8	333	7.6	
ANXIETY DISORDERS											
No	5794	88.4	156	76.1	142	83.5	1549	86.3	3947	90.1	<0.001
Yes	758	11.6	49	23.9	28	16.5	246	13.7	435	9.9	
SUBSTANCE USE DISORDERS											
No	6362	97.1	184	89.76	156	91.8	1743	97.1	4279	97.6	<0.001
Yes	190	2.9	21	10.24	14	8.2	52	2.9	103	2.4	

PLE = psychotic-like experiences, CE = cannabis exposure, * Chi-squared test

Table 18. Odds ratios of outcomes by PLE/CE status (Study IV).

	CRUDE N =6382 OR	95% CI	MODEL 1 N = 5454 OR	95% CI	MODEL 2 N = 5454 OR	95% CI	MODEL 3 N =5091 OR	95% CI
ANY PSYCHIATRIC DISORDER								
PLE/CE -/- (reference)	1	-	1	-	1	-	1	-
PLE/CE +/+	3.31	2.49–4.39	3.02	2.20–4.13	3.01	2.19–4.14	2.59	1.82–3.68
PLE/CE +/-	1.58	1.40–1.79	1.51	1.32–1.73	1.50	1.31–1.73	1.48	1.29–1.71
PSYCHOTIC DISORDERS								
PLE/CE -/- (reference)	1		1	-	1	-	1	-
PLE/CE +/+	5.37	3.06–9.44	5.46	2.91–10.25	5.31	2.82–10.01	3.86	1.83–8.11
PLE/CE +/-	2.38	1.69–3.36	2.52	1.74–3.67	2.49	1.71–3.62	2.41	1.61–3.62
MOOD DISORDERS								
PLE/CE -/- (reference)	1		1	-	1	-	1	-
PLE/CE +/+	5.17	3.77–7.08	4.56	3.21–6.47	4.59	3.22–6.53	4.07	2.74–6.04
PLE/CE +/-	1.90	1.60–2.26	1.74	1.44–2.10	1.73	1.43–2.10	1.68	1.38–2.05
DEPRESSIVE DISORDERS								
PLE/CE -/- (reference)	1		1	-	1	-	1	-
PLE/CE +/+	5.27	3.84–7.25	4.76	3.34–6.78	4.78	3.35–6.83	4.35	2.93–6.48
PLE/CE +/-	1.95	1.64–2.32	1.79	1.48–2.17	1.78	1.47–2.16	1.75	1.43–2.14
ANXIETY DISORDERS								
PLE/CE -/- (reference)	1				1	-	1	-
PLE/CE +/+	2.85	2.04–3.99	2.51	1.77–3.56	2.50	1.71–3.64	2.06	1.34–3.17
PLE/CE +/-	1.44	1.22–1.70	1.32	1.02–1.46	1.30	1.08–1.57	1.28	1.05–1.55
SUBSTANCE USE DISORDERS								
PLE/CE -/- (reference)	1		1	-	1	-	1	-
PLE/CE +/+	4.74	2.90–7.75	4.69	2.23–7.21	4.60	2.53–8.37	2.26	1.13–4.50
PLE/CE +/-	1.24	0.88–1.74	1.43	0.93–3.94	1.40	0.95–2.06	1.37	0.90–2.07

Model 1: sex, family structure; Model 2: sex, family structure, parental psychiatric disorder; Model 3: sex, family structure, parental psychiatric disorder, frequent alcohol intoxications, daily smoking, other illicit drug use PLE = psychotic-like experiences, CE = cannabis exposure,OR = odds ratio.

5.5 The association of covariates with outcomes

The adjusted association of covariates with respective outcomes in the full models are presented in Tables 18 (Studies I–III) and 19 (Study IV). Family structure, baseline psychopathology and parental psychiatric disorder consistently predicted subsequent outcomes in almost all of the final models. Frequent alcohol intoxications were a strong predictor of subsequent self-harm in the fully adjusted model (HR 2.46 95% CI 1.49–4.04). In Study IV, daily smoking retained its prognostic value in all models except for the model examining the link between anxiety disorder and any psychiatric disorder. Sex was found to predict all subsequent outcome in study IV and a bipolar disorder in study III.

Table 19. The hazard ratios (HR) of covariates for the outcomes examined in studies I–III.

COVARIATE	SELF-HARM	DEPRESSIVE DISORDERS$_{INT}$	DEPRESSIVE DISORDERS$_{EXT}$	ANXIETY DISORDERS$_{INT}$	ANXIETY DISORDERS$_{EXT}$	BIPOLAR DISORDER
SEX	0.76 (0.48–1.20)	-	-	-	-	**2.58** (1.33–5.01)
PSYCHIATRIC DISORDER BEFORE AGE 16	**5.05** (2.87–8.90)	-	-	-	-	-
OTHER ILLICIT DRUG USE	2.50 (0.72–8.64)	1.45 (0.62–3.38)	1.50 (0.66–3.42)	1.96 (0.90–4.26)	**2.15** (1.01–4.55)	1.67 (0.35–7.94)
FREQUENT ALCOHOL INTOXICATIONS	**2.46** (1.49–4.04)	1.21 (0.95–1.55)	1.12 (0.88–1.42)	1.10 (0.87–1.39)	1.02 (0.81–1.29)	1.85 (0.99–3.47)
PARENTAL PSYCHIATRIC DISORDER	**3.13** (1.93–5.05)	**1.62** (1.35–1.96)	**1.65** (1.37–1.99)	**1.65** (1.37–1.99)	**1.70 (1.43–2.02)**	**3.13** (1.93–5.05)
DAILY SMOKING	-	1.08 (0.82–1.42)	0.96 (0.73–1.27)	1.08 (0.82–1.40)	0.79 (0.96–0.74)	1.02 (0.49–2.13)
FAMILY STATUS	-	**1.30** (1.06–1.61)	**1.29** (1.05–1.60)	**1.23** (1.00–1.50)	1.21 (0.99–1.48)	1.09 (0.59–1.99)
YOUTH SELF-REPORT (YSR) SCALE	-	**1.06** (1.05–1.07)	**1.04 (1.03–1.05)**	**1.04** (1.02–1.05)	**1.03 (1.02–1.04)**	**1.02** (1.00–1.04)

HRs adjusted for all other covariates in column and cannabis use. Int/Ext = YSR internalizing/externalizing subscale

Table 20. Odds ratios (OR) of the covariates assessed in study IV, PROD-questionnaire with the two-point cutoff model.

COVARIATE	PSYCHOSIS	ANY DEPRESSION	ANY MOOD DISORDER	ANXIETY DISORDERS	ANY PSYCHIATRIC DISORDER	SUBSTANCE USE DISORDERS
SEX	**0.61** (0.42–0.90)	**1.61** (1.32–1.96)	**1.67** (1.38–2.02)	**1.69** (1.40–2.03)	**1.38** (1.21–1.58)	**0.33** (0.22–0.49)
OTHER ILLICIT DRUG USE	**4.64** (1.34–16.06)	1.45 (0.56–3.80)	1.76 (0.69–4.53)	2.00 (0.78–5.16)	**1.42** (1.21–1.66)	3.53 (0.97–12.83)
FREQUENT ALCOHOL INTOXICATIONS	1.18 (0.72–1.93)	1.13 (0.88–1.45)	1.14 (0.89–1.46)	1.07 (0.84–1.37)	1.66 (0.96–1.39)	**1.74** (1.12–2.71)
PARENTAL PSYCHIATRIC DISORDER	**2.46** (1.67–3.63)	**1.80** (1.49–2.17)	**1.86** (1.54–2.24)	**1.84** (1.54–2.20)	**1.65** (1.44–1.89)	**2.45** (1.67–3.60)
DAILY SMOKING	**1.63** (0.96–2.75)	**1.39** (1.06–1.84)	**1.39** (1.06–1.82)	1.20 (0.91–1.58)	1.23 (0.99–6.71)	**2.82** (1.80–4.42)
FAMILY STATUS	0.90 (0.57–1.41)	**1.48** (1.20–1.83)	**1.45** (1.18–1.78)	**1.34** (1.09–1.64)	**1.42** (1.21–1.66)	**1.95** (1.33–2.87)

Statistically significant findings in **bold**. Odds ratios adjusted for all other covariates included in the column for each outcome.

6 Discussion

6.1 Prospective associations of early cannabis use with subsequent mental health outcomes

A major aim of this PhD study was to assess the associations of early cannabis exposure with non-psychotic outcomes, which certainly have been examined less exhaustively in previous research than the respective associations with psychotic outcomes. We found a significant association between early cannabis use and self-harm, depression, and anxiety disorders. In contrast, the association between early cannabis use and bipolar disorder seems to be confounded by other substance use, and no association was seen with suicide death even in unadjusted analysis.

6.1.1 Self-harm and suicide

Adolescent cannabis use was found to be associated with a subsequent incident of severe self-harm requiring medical attention. This association remained statistically significant after extensive confounder control, i.e., adjusting for sex, baseline and parental psychiatric disorders, frequent alcohol intoxications and use of different illicit drugs other than cannabis at age 15/16 years. However, no association was evident between adolescent cannabis use and death by suicide even in the univariable analysis. Importantly, the association between early cannabis use and incident self-harm was attenuated by 46% after adjusting for frequent alcohol intoxications and other illicit drug use.

Studying the antecedents of severe self-harm by young-adulthood is of paramount importance as prior self-harm and/or suicide attempt are regarded as the strongest predictors of a subsequent suicide death (Bostwick, Pabbati, Geske, & McKean, 2016; Demesmaeker, Chazard, Hoang, Vaiva, & Amad, 2021). Particularly, self-harm requiring medical attention strongly predicts a subsequent suicide both in adolescence and adulthood (Geulayov et al., 2019; Goldman-Mellor, Olfson, Lidon-Moyano, & Schoenbaum, 2019; Hawton et al., 2020), and a meta-analysis found that one in 25 patients receiving medical treatment for self-harm will die by suicide in the next 5 years (Carroll, Metcalfe, & Gunnell, 2014).

To the best of my knowledge, this is the first study which has utilized a prospective birth cohort data; it is also only the second population-based study examining the association between early cannabis use and incident self-harm. Another population-based study evaluating this association was conducted by Moran et al., who used prospective data from the Victoria Adolescent Health Cohort, a stratified sample drawn from 44 schools (Moran et al., 2012). The two other studies examining this association have utilized specialized samples, namely a clinical sample of adolescents with mood disorders (Fontanella et al., 2021), and a sample of socio-economically deprived adolescents (Spears et al., 2014), limiting the generalizability of those results. Moreover, Fontanella et al. resorted to register-based data for all variables studied (Fontanella et al., 2021) and Spears et al. used data originally gathered for a randomized controlled trial (Spears et al., 2014).

In this PhD study, self-harm was operationalized by utilizing register-based data on ICD-10 diagnoses made in clinical practice referring to severe self-harm requiring medical attention. A similar outcome variable was used by Fontanella et al., who also reported a 1.0% incidence of self-harm (Fontanella et al., 2021). It should be noted that the length of follow-up in the above study was only 1 year, yielding a higher incidence rate compared to our values, in which the participants were followed for 18 years. However, our study the sample consisted of patients with mood disorders at baseline, and psychopathology has been associated independently with subsequent self-harm (Christoffersen, Poulsen, & Nielsen, 2003). The two studies which were based on self-report measures for their outcome variables described incidences of self-harm many-folds higher than in the present results (Moran et al., 2012; Spears et al., 2014). However, the focus was on self-harm requiring medical attention and these more severe cases are the tip of the iceberg of all behaviors classified as self-harm.

No significant association between cannabis exposure and suicide was observed even in the crude analysis. However, only a small number of cases of suicide deaths captured (n=20). Fontanella et al. 2021 reported a negative finding for cannabis use disorder and suicide despite utilizing a clinical sample of participants with baseline psychopathology, including those with a prior history of self-harm as well as a large sample size ($n = 204\ 780$). Moreover, a markedly more robust exposure variable (CUD) was used than in the present work (lifetime use). However, most probably due to the short follow-up period of one year, only 30 cases of suicide deaths were recorded. Nonetheless, as suicide is a rare event, no association between heavy cannabis use (at least 50 times) and suicide was found even in the large Swedish conscript study (Price et al., 2009).

6.1.2 Depressive disorders and anxiety disorder

Adolescent cannabis use was found to be associated with the onset of depression and anxiety disorders independently from baseline internalizing or externalizing disorders, daily smoking, frequent alcohol intoxications, use of other illicit drugs and family structure. In the full models, cannabis use once or 2–4 times was associated with depression, while this association attenuated to non-significance in the group using cannabis at least five times. In contrast, a statistically significant association between early cannabis use and anxiety disorders was seen in the final model only in the group who had used cannabis use at least five times.

While an independent association between early cannabis use and depression was found in this study, the findings of the previous birth cohort studies addressing this issue have been markedly divided with exactly half reporting a positive finding (Arseneault et al., 2002; Fergusson & Horwood, 1997; Fergusson et al., 2002). Nevertheless, numerous prospective studies utilizing adolescent cohorts of other types have been published, and a meta-analysis assessing this issue reported the presence of a statistically significant association (Gobbi et al., 2019). In contrast to studies with depression outcomes, only a handful of prospective studies of any kind have assessed the association between early cannabis use and subsequent anxiety disorders - and with mixed findings. For example, only two of these studies have reported a statistically significant association. This may be due to a lack of power, as the sample size in our study was three times greater than the largest previously published study with an anxiety outcome (Degenhardt et al., 2013). However, it should be noted that anxiety disorders constitute a group of heterogenic syndromes, ranging from specific phobias to a generalized anxiety disorder.

The association of cannabis use with depression attenuated to non-significance in the group using cannabis at least five times. This might be due to the fact that the incidence of depression was markedly greater in the female than in male participants (65.5% vs 34.5%), and according to the findings of the NFBC86 field study, female participants were at least 5 times less frequently to be located in the category of cannabis users than their male counterparts (Mustonen et al., 2018), which is also in line with the findings from national survey data (EMCDDA, 2019). In contrast, in the sample of this PhD study, lifetime cannabis use was found to be more prevalent among female than male participants (54.5% vs 45.5%). This is slightly inconsistent with values from the ESPAD 2003 report in which lifetime cannabis use was equally prevalent among both sexes (11% for both boys and girls).

Importantly, while a follow-up of 18 years was utilized in this PhD study, some previous investigations assessing the association of early cannabis use and depression or anxiety have utilized short follow-up times of only 2 years, raising concerns pertaining to the possibility of reverse causality (Fergusson & Horwood, 1997; Fergusson et al., 1996; Gage et al., 2015). Lastly, in this PhD study, the cumulative

incidences of depression and anxiety disorder were 9.2% and 10.9%, respectively. These findings are in line with the estimates reported in a Finnish representative population-based survey of a cohort in late adolescence-early adulthood, in which the lifetime prevalence was 13.8% for unipolar depression, and 12.6% for anxiety disorders as assessed by SCID-I for DSM-IV (Suvisaari et al., 2009).

6.1.3 Bipolar disorder

An association was detected between early cannabis exposure and the onset of bipolar disorder after adjusting for sex, emotional and behavioral problems, family structure and parental psychiatric disorders. This association attenuated to non-significance when further adjusted for frequent alcohol intoxications, daily smoking, and use of other illicit drugs.

As far as we are aware, this is only the second study in which a prospective birth cohort data has been exploited to assess the association between adolescent cannabis use and bipolar disorder. Utilizing data from the ALSPAC birth cohort, Marwaha et al. found a significant association between cannabis use at least 2–3 times per week and hypomania (OR=2.21) (Marwaha et al., 2018). The outcome variable was operationalized and based on the self-administered HCL-32 scale. Therefore, the incidence of the bipolar disorder-related outcome defined in this manner was many folds larger than that observed in this PhD study, which utilized data on diagnoses made in clinical practice. It should be noted that the robustness and validity of the HCL-32 as a proxy for bipolar-disorder is somewhat limited, as the specificity of this screening instrument was reported to be 57% in a recent meta-analysis (Wang et al., 2019). Nevertheless, the positive predictive values of clinician-based diagnoses of bipolar disorder have also been found to be modest when compared to gold standard rating methods such as the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (Ghaemi, Boiman, & Goodwin, 2000; Zimmerman, Ruggero, Chelminski, & Young, 2008). However, clinician-made bipolar diagnoses entered in Finnish national registries have been found to be accurate after a reassessment of medical records by applying DSM-IV criteria (Kieseppä, Partonen, Kaprio, & Lönnqvist, 2000).

Furthermore, it should also be noted that the duration of follow-up in the study of Marwaha et al. was only five years. This issue is crucial as cannabis intoxication can itself cause significant mental disturbances that may mimic functional symptomatology (D'Souza et al., 2005), and the average treatment delay from onset of symptoms to an established bipolar disorder diagnosis has been estimated to be eight years (Mantere et al., 2004), introducing the possibility of self-medication by cannabis of an already established disorder. In another population-based study, self-reported mania symptoms as assessed by the CIDI were used as the outcome measure

with a follow-up of 8.3 years (Tijssen et al., 2010). In conclusion, the use of a register-based outcome measure and the exceptionally long duration of follow-up are considered to be unique features that significantly enhance the validity of the results reported in this PhD thesis.

The cumulative incidence of bipolar disorder (1.0%) observed here is similar to reported lifetime prevalence values in the literature (Moreira, Van Meter, Genzlinger, & Youngstrom, 2017; Suvisaari et al., 2009). Although our study is the largest one in terms of sample size to assess the association of early cannabis exposure and the subsequent onset of a bipolar disorder, it still might have been underpowered to detect an independent association with such an infrequent outcome. Perhaps many folds larger cohorts, e.g. that available in the Swedish conscript cohort (Zammit et al., 2002), would be needed to truly evaluate the association of cannabis use with rare outcomes such as a bipolar disorder. In the same vein, when assessing associations between cannabis use and rare outcomes such as schizophrenia, even adequately powered studies with exceptionally large cohort samples have found independent associations only when examining those participants with very heavy cannabis use (e.g., at least 50 times by the age of 18) (Zammit et al., 2002). In contrast, in our study, of those diagnosed with a bipolar disorder, only three out of 66 participants reported having used cannabis at least five times with merely 5.6% of all participants presenting with lifetime cannabis use. Thus, our study population might not have been sufficiently exposed to cannabis for it to confer significant vulnerability to the onset of a bipolar disorder. Nevertheless, the crude association observed still suggests early cannabis exposure to be an adverse clinical marker for the onset of a bipolar disorder. On the other hand, while possibly conferring risk to other adverse psychiatric outcomes, cannabis use might not prove to be independently associated with subsequent bipolar disorder.

Lastly, in our study, only 23% of the subjects who were diagnosed as having a bipolar disorder were male. Although higher prevalence estimates have been reported in type 2 bipolar disorder for females (Merikangas et al., 2011), a bipolar disorder is thought to be equally prevalent in both sexes (Tsuchiya, Byrne, & Mortensen, 2003). However, register-based psychiatric outcomes, as utilized in our study, reflect help-seeking behavior, with females more likely to seek treatment for a bipolar disorder (Humpston, Bebbington, & Marwaha, 2020).

6.2 Impact of cannabis exposure on mental-health trajectories of psychotic-like experiences

In this prognostic study, those participants presenting with both psychotic-like experiences and cannabis exposure at baseline were at a greater odds for each outcome studied than the group presenting with psychotic-like experiences only.

These findings were robust in terms of the sensitivity analyses from which participants presenting with baseline psychiatric diagnoses were excluded.

This is believed to be the first general population-based study assessing the trajectories of psychotic-like experiences and early cannabis exposure with respect to psychotic as well as non-psychotic outcomes. As the objective was to examine prognosis rather than to infer causality, the additional risk of subsequent psychiatric disorders conferred by cannabis exposure to PLE-experiencing adolescents was not estimated. This would have required conducting separate analyses with the subpopulation of PLE-experiencing adolescents, which was precluded by power issues. Even so, early cannabis exposure has been found to increase the risk of conversion from a range of high-risk states to the respective adverse outcomes, e.g., from non-suicidal self-injury to an actual suicide attempt (Mars et al., 2019), from respective prodromal phases to psychosis (Valmaggia et al., 2014), and to a true bipolar disorder (Ratheesh et al., 2015). Thus, it is reasonable to believe that cannabis use may complicate the prognosis of PLE-experiencing adolescents. Moreover, due to the prognostic nature of this study, participants with psychiatric disorders at baseline were not excluded from the main analyses. However, the findings remained robust when sensitivity analyses were conducted by omitting this group.

The association between cannabis use and psychotic disorders was examined in a previous study by Mustonen et al. using the NFBC1986 data (Mustonen et al., 2018). In that study, cannabis use of 5 times or more was associated with any psychotic disorder until the age of 30 years even after adjusting for baseline PLEs, sociodemographic factors and other forms of substance use. In addition, cumulative incidences of psychotic disorders were reported with the sample stratified according to baseline PLEs and cannabis exposure. However, in the present study with its longer follow-up, the sample was stratified by PLE/CE status also for multivariable analyses.

Notably, the prevalence of PLEs defined as a score of at least 3 points on the PROD-screen was very high (30.5%). However, other population-based prospective studies have also reported high prevalence figures for PLEs at baseline. For example, in the school-based study of Bechtold et al., the prevalence of any subclinical psychotic symptom at baseline was 45.5% (Bechtold et al., 2016). Similarly, in the study of Dominguez assessing the prognosis of PLEs utilizing the Munich-based EDSP cohort, the prevalence of PLEs was 21.2% (Dominguez, Wichers, Lieb, Wittchen, & Van Os, 2011). The validity of measures based on self-report is probably also limited. For example, in the ALSPAC cohort, the prevalence of self-reported prodromal symptoms was notably higher than those detected by a clinical interview (37.8% vs 13.7%) (Horwood et al., 2008). On the other hand, the more prevalent PLEs are in the general adolescent population, the more crucial it is to gain an accurate understanding of the risk posed by environmental factors such as

cannabis use as harbingers of future mental health problems in young people with these experiences.

6.3 Accounting for confounding bias when examining sequelae of early cannabis use

Multiple sources of confounding bias were taken to account in each study. First, sex has been found to be independently associated with self-injurious behaviors (Gillies et al., 2018; Miranda-Mendizabal et al., 2019). However, as the frequencies of self-harm were rather similar (55.7% male and 44.3% female) for both sexes in Study I, no association between sex and self-harm was evident either in the preliminary univariable analysis or in the fully adjusted multivariable model. This may be due to the fact that this gender difference is probably less pronounced for severe self-harm requiring medical attention in young adulthood (Geulayov et al., 2019; Goldman-Mellor et al., 2019). In accordance with epidemiologic evidence (Fullana et al., 2020; Van de Velde, Bracke, & Levecque, 2010), sex was associated with mood disorders, depressive disorders and anxiety disorders in Study IV. Unexpectedly, due to the reasons discussed in section 6.2.3, sex was independently associated with the onset of a bipolar disorder, although this disease has been found to be equally prevalent among both sexes in the literature (Tsuchiya et al., 2003).

Baseline psychopathology as adjusted for by ICD-10 diagnoses made in clinical practice in Study I or the YSR subscale or total scores in studies II and III retained its prognostic value for each respective outcome studied. Accounting for baseline psychopathology is important when studying the associations of environmental risk factors with psychiatric disorders, as the time from symptom onset to the establishment of diagnosis might be considerably protracted (Mantere et al., 2004), leading to questions concerning reverse causality. Thus, it is concerning that only one prospective study assessing the association of early cannabis use with bipolar disorder included any variable for baseline psychopathology in their multivariable model (Marwaha et al., 2018). Early psychiatric morbidity has been associated with severe self-harm as well (Christoffersen et al., 2003). However, as Carvalho et al. recently pointed out, a psychiatric disorder emerging after onset of cannabis use may also be seen as part of a mediation pathway between this exposure and self-harm rather than as a source of confounding bias (Carvalho, Souza, & Moreira, 2022). Most of the studies assessing the association between early cannabis use and self-harm (Moran et al., 2012; Spears et al., 2014), depression or anxiety disorders (Fergusson et al., 2002; Gage et al., 2015; Silins et al., 2014) and psychosis (Antti Mustonen et al., 2018) have included a symptom scale or an interview-based variable accounting for baseline psychopathology in their multivariable models. Taking a different approach, as in study I of this thesis, Fontanella exploited a register-based

variable to account for psychiatric comorbidities (Fontanella et al., 2021). To account further for the confounding bias introduced by early psychopathology, those individuals with baseline ICD-10 psychiatric disorders were excluded from studies II and III as well as from the sensitivity analyses of study IV.

Here, the possibility to include register-based information on parental psychiatric diagnoses is unique, as parental psychiatric disorders are known to significantly predispose to the onset of a psychiatric disorder in their offspring, most notably a bipolar disorder (Kieseppä, Partonen, Haukka, Kaprio, & Lönnqvist, 2004; Mullins et al., 2021), and have also been found to associate with self-harm (Christoffersen et al., 2003). In accordance with previous findings, parental psychiatric disorders retained their prognostic significance in all final models in Studies I-IV. However, very few prospective studies focusing on early cannabis use and depression or anxiety (Gage et al., 2015) or psychotic disorders (McGrath et al., 2010; Mustonen et al., 2018) have included any measure of parental psychopathology.

Exploring the possibility of confounding bias by adjusting for other substance use is crucially important, as polysubstance use is common in adolescence (Halladay et al., 2020). Importantly in Study III, the association of cannabis use with bipolar disorder attenuated to non-significance after adjusting for other forms of substance use. However, only one previous adolescent study with a bipolar disorder-related outcome controlled for other substance use (Marwaha et al. 2018). In contrast, all prospective birth cohort studies assessing cannabis use and depression have controlled for other types of substance use (Arseneault et al., 2002; Fergusson et al., 2002, 1996; Gage et al., 2015; Silins et al., 2014).

All three previously published studies examining adolescent cannabis use and subsequent self-harm (Fontanella et al., 2021; Moran et al., 2012; Spears et al., 2014) adjusted for other forms of substance use in their multivariable models. Notably, the association between cannabis use and self-harm attenuated in Study I by 46% when adjusted for frequent alcohol intoxications and the use of other illicit drugs. Furthermore, alcohol use retained statistical significance in the fully adjusted model (HR 2.46, 95%CI 1.49–4.04). This is in line with previous research indicating alcohol use as being an established risk factor for self-injurious behaviors including suicide (Amiri & Behnezhad, 2020; G. Borges et al., 2017; Darvishi, Farhadi, Haghtalab, & Poorolajal, 2015; Rossow & Norström, 2014). However, while early alcohol use has been associated with subsequent psychiatric disorders (Cairns et al., 2014), alcohol use retained its prognostic value only for the substance use disorder outcome in Study IV. This result is similar to findings from a previous study utilizing this birth cohort (Sarala et al., 2020). It should be noted that female sex was associated with mood and anxiety disorders in Study IV, and female adolescents reported alcohol intoxications less frequently than their male counterparts in the field study of the NFBC86 (Sarala et al., 2020).

The use of other illicit drugs was non-significant in most full models of the outcomes examined in Studies I-IV, probably since it was reported very infrequently. However associations between illicit drug use and self-harm (Christoffersen et al., 2003; Mars et al., 2019) and depression (Cairns et al., 2014) have been reported in the published literature.

Studies with prospective data have reported positive associations between smoking and depression (Cairns et al., 2014), bipolar disorder studies (Bach et al., 2021; Martínez-Ortega et al., 2013), and psychosis (Mustonen et al., 2018). However, while daily smoking was associated with an increased risk for all but one outcome in study IV, daily smoking was not associated with depressive disorders, anxiety disorders (Study II) or a bipolar disorder (Study III) in the final models. Perhaps the association should have been studied with smoking evaluated as a continuous variable, e.g. number of cigarettes smoked per day, to determine if there was a possible dose-response relationship. However the different options to account for baseline psychopathology, i.e. stratification by a PROD screen result in Study IV or adjusting for YSR total score as conducted in studies II and III might have influenced these results. Moreover, the primary aim of our study was not to examine the sequelae of diverse forms of substance use other than cannabis, so these analyses should be considered as exploratory.

Lastly, family structure was included in the final models of studies II-IV as a measure of early-life adversities, which have been found to be associated with depression, anxiety and illicit drug use (Hughes et al., 2017). Importantly, this covariate retained statistical significance in all but one model (psychosis) of Study IV and for depression and anxiety disorders in Study II. Many reports assessing psychiatric sequelae of early cannabis use have included some measure of early life social risk factors such as family structure (Degenhardt et al., 2013; Moran et al., 2012)), insurance status and residence (Fontanella et al., 2021), family functioning (Fergusson & Horwood, 1997; Fergusson et al., 1996), early life adversity (Suzanne H. Gage et al., 2015) and family adversity or child abuse (Marwaha et al., 2018).

In summary, the findings of Studies I and III point to substance use as being an important source of confounding bias. Furthermore, early life social risk factors including parental psychiatric disorders and family structure are factors that could potentially confound the association between cannabis use and psychiatric outcomes. The results from these studies also strongly highlighted the necessity to take into account the baseline psychiatric symptoms when assessing the temporality of the associations.

6.4 Summary of the findings

A major aim of this thesis was to examine the nature of the association of adolescent cannabis use with psychiatric sequelae beyond psychotic disorders. While the existing evidence base on the association between cannabis use and psychosis is robust enough to support some criteria of causality (D'Souza et al., 2022), it is far from established whether or not early cannabis use could be a component cause of severe self-harm, depressive disorders, anxiety disorders or bipolar disorder. Key considerations when studying causality (i.e. the Bradford-Hill Criteria) include the plausibility of the association and complementary lines of evidence, consistency of findings, evidence of dose-response, temporality of the association and issues pertaining to confounding bias (Van Reekum, Streiner, & Conn, 2001). First an association of cannabis use with mood and anxiety disorders is *biologically plausible*, as imaging studies point to cannabinoid receptors being highly expressed in brain areas involved in affective disorders such as the hippocampus, cerebellum, basal ganglia, and cortex (Curran et al., 2016) as well as to early cannabis use being associated with structural brain alterations (Albaugh et al., 2021; Jacobus et al., 2019; Lichenstein et al., 2021). Moreover, the endocannabinoid system is thought to fine-tune the activity of other major neurotransmitter systems, including the serotonergic and dopaminergic systems, the function of which are thought to be perturbed in these psychiatric disorders (Arjmand et al., 2019). Putative pathways through which cannabis exposure could be linked to self-harm have also been described, possibly involving associations of cannabis use with both impulse control functions and depressive or psychotic psychopathology (Francesco Bartoli, Lev-Ran, Crocamo, & Carrà, 2018).

There is also *complementary evidence* in the form experimental studies indicating that orally ingested THC has the capacity to induce euphoria (D'Souza et al., 2004) symptoms of depressive and anxiety (Hindley et al., 2020) and suicidal ideation (Koppel et al., 2014). Moreover, cannabis withdrawal syndrome is characterized by depressive and anxiety symptoms (Bahji et al., 2020).

The *consistency of findings* in previously published studies examining the psychiatric sequelae of adolescent cannabis use has varied according to the outcome under focus. Studies examining the association between early cannabis exposure and subsequent self-harm, bipolar disorder or anxiety disorders are rare and the findings have been mixed. In the present PhD work, an independent association was found between early cannabis use and depressive and anxiety disorders as well as severe self-harm requiring medical attention. However, the association of early cannabis use and bipolar disorder attenuated to non-significance after controlling for confounders.

In this thesis, *a dose-response effect* was seen in trend tests conducted in studies I–III for cannabis use and severe self-harm, depression, anxiety disorders, and

bipolar disorder. However, not in accordance with this dose-response effect, the association of cannabis use and depression retained significance in the group exposed to cannabis 1–4 times but not in the group reporting having used cannabis at least 5 times at the age of 15–16 years. In the previous literature, there seems to be some evidence of a dose-response effect for cannabis use and subsequent depression, as Lev Ran et al. found heavy cannabis use to be associated with a greater risk of subsequent depression (Lev-Ran et al., 2014). There is also limited cross-sectional evidence for an association between high potency cannabis use and depression and anxiety disorder (Hines et al., 2020; Petrilli et al., 2022). To date, meta-analyses assessing specifically the association of heavy cannabis use and subsequent bipolar disorder have not been published. In the same vein, while a dose-response effect for cannabis use and subsequent suicide attempt has been reported (Borges et al., 2016), there is insufficient evidence to link early cannabis use and severe self-harm. Furthermore, when assessing dose response, it should be noted that the potency of cannabis has increased steadily during the last three decades (Freeman et al., 2021), and thus the risks for adverse mental health outcomes at present might be higher than when the field study of the NFBC1986 was conducted in 2001–02.

Temporality was taken into account in my PhD studies by excluding participants who had experienced a self-harm outcome at baseline (Study I) or had been diagnosed with a psychiatric disorder at baseline (Study II and III). This source of bias was also controlled for by adjusting for psychopathology at baseline (Studies II and III) and by sensitivity analyses excluding those participants with baseline psychiatric disorders from the analysis (Study IV). Importantly, the long duration of follow-up of Studies I–IV mitigates concern for the possibility of reverse causality. The utility of sufficient length of follow-up was underscored by the fact that the delay between symptom onset to the actual diagnosis of a bipolar disorder has been found to be eight years on average (Mantere et al., 2004). If the duration of follow-up is insufficient, there is the real possibility that individuals with an already established bipolar disorder who are self-medicating its symptoms with cannabis would be unintentionally included in the sample.

Residual confounding is always a concern in observational studies. Particularly, addressing a *confounding bias* introduced by other forms of substance use is of significance, as polysubstance use is common in adolescence (Halladay et al., 2020), and all substance use including cannabis use did indeed cluster in the same participants in our study sample. The importance of this source of bias is highlighted by the fact that the association between cannabis use and a bipolar disorder attenuated to non-significance after controlling for other forms of substance use in study III and the association between cannabis use and self-harm attenuated by 46% when controlling for different forms of substance use other than cannabis. It does seem that only one previously published longitudinal study assessing the association

between early cannabis use and bipolar disorder controlled for other forms of substance use in their final multivariable model (Marwaha et al., 2018). It is also crucial to take into consideration the confounding effect of psychiatric disorders preceding cannabis use, as early psychopathology has been associated with subsequent cannabis use (Miettunen et al., 2014). This source of bias was accounted for as described in the preceding paragraph. Lastly, it may be that due to the rarity of bipolar disorders and suicide death in the general population, larger cohorts would be needed to detect possible independent associations between cannabis exposure and these outcomes. Nonetheless, no association between cannabis use and suicide death was detected even in the very large Swedish conscript cohort study with detailed information on fairly heavy use of cannabis (lifetime use of up to at least fifty times) (Price et al., 2009).

Another major aim of this study was to evaluate the prognosis of adolescents with PLEs with or without cannabis use. Participants with both PLEs and cannabis use were at an increased risk for multiple psychiatric disorders beyond psychotic disorders. This underscores the importance of screening for cannabis use in adolescents experiencing PLEs.

To conclude, there is limited evidence to support the concept that there is causality behind the relationships of early cannabis use with depressive disorders, anxiety disorders or self-harm. Nonetheless, analogously with the multiple hit hypothesis of psychosis, it is plausible that cannabis use could prove to be a so-called insufficient but necessary part of an unnecessary but sufficient condition (INUS) for these non-psychotic psychiatric outcomes (Davis et al., 2016; Susser, Schwartz, Morabia, & Bromet, 2006). This means that one could argue that cannabis exposure could participate in triggering these adverse sequelae in the presence of, or in concert with, other constitutional or acquired risk factors such as a genetic vulnerability or some preceding psychopathology. This thesis does not support the hypothesis of cannabis use as being independently associated with the appearance of a bipolar disorder. However, a factor that is not part of a causal pathway for a given outcome might prove to be its clinical risk factor (Herbert, 2014). Thus, even though cannabis use might not in fact be a component cause of affective disorders or self-harm, the findings of this thesis imply that early cannabis exposure might prove to be an adverse prognostic marker for many psychiatric outcomes and not simply psychosis.

6.5 Strengths and limitations

6.5.1 Strengths

As discussed in this thesis, prospective observational studies assessing the association of adolescent cannabis use with self-harm, anxiety disorder and bipolar

disorder are especially scarce. This was the first birth cohort study and the second general population-based study to assess the association of early cannabis use and self-harm. Furthermore, this was the largest population-based study to assess the association of cannabis use and a bipolar disorder-related outcome, and the first such study in which daily cigarette smoking was included as a source of confounding bias along with other substance use covariates. Moreover, this was the second birth cohort study to assess the association between cannabis use and anxiety disorder and it represents a significant contribution to the current birth cohort literature assessing depressive disorder outcomes. Importantly, no previous population-based study has examined the prognosis of PLE-experiencing adolescents with or without cannabis exposure with respect to psychotic and non-psychotic outcomes. Using register-based data for outcomes ensures minimal loss at follow-up thus limiting concerns for attrition bias. The sample is exceptionally representative and population-based thus enhancing the generalizability of the results.

In all of the studies included in this thesis, a special emphasis was placed on disentangling the effects on the mental health trajectories exerted by cannabis use from those attributable to the use of other substances. This is to be regarded as a strength, as polysubstance use among adolescents is common (Halladay et al., 2020), introducing a significant potential source of confounding. Moreover, as the psychiatric disorders examined here emerge most frequently by late adolescence or early adulthood, (Solmi, Radua, et al., 2021), the studies are well poised to assess hypotheses pertaining to the onset of these disorders. Having detailed information on parental psychiatric disorders is also a unique feature of this thesis work. Lastly, the particularly long duration of follow-up of 18 years mitigates concerns for the possibility of reverse causality.

6.5.2 Limitations

However, there are also limitations. Firstly, power issues precluded using a multi-class cannabis use variable when studying the association of early cannabis use with self-harm and bipolar disorder. This is a significant limitation as lifetime cannabis use might vary from a single exposure to heavy use and it is not plausible to expect that a single event of exposure would contribute to the onset of a bipolar disorder or trigger an event of self-harm many years later. Moreover, even larger cohorts with detailed information on much heavier cannabis consumption than that which was available to us might be required to detect independent associations of cannabis use and very rare outcomes such as a bipolar disorder (Zammit et al., 2002). In addition, information on the potency of cannabis consumed was unavailable for analysis. This is to be regarded as a limitation as recent research findings indicate that especially high-potency cannabis use predisposes not only to psychosis (Di Forti et al., 2019),

but perhaps also to non-psychotic outcomes such as anxiety disorders (Hines et al., 2020). In the same vein, as the potency of both herbal cannabis and cannabis resin has steadily increased (Freeman et al., 2021), adolescents consuming cannabis today might be at a greater risk of cannabis-related harm than 20 years ago when this field study was conducted. Moreover, only 5.6 to 5.7% of the samples utilized in the studies reported a lifetime cannabis use, introducing power issues and increasing the risk of a type II error. In the ESPAD 2003 survey, the lifetime prevalence of cannabis use at the age of 15/16 in Finland was 11%, which suggests that under-reporting might be an issue with our data (49). This source of bias might have weakened the observed associations of early cannabis use with depression, anxiety and a bipolar disorder. Information on cannabis use was collected at one time point only precluding the analysis of the effects of persistence of cannabis use, thus limiting the analysis of a dose-response. Moreover, more detailed information on the specific age of first cannabis exposure was not available for analysis. Also, the cannabis exposure variable utilized did not allow for discerning between current and former use. As the YSR was conducted when participants were aged 15–16 years, it is possible that some participants might have experienced psychiatric symptoms at an earlier time point, thus introducing the possibility of reverse causality. However, to mitigate concerns for this type of bias, those with baseline psychiatric diagnoses recorded in national registries were excluded from the main analyses in studies II and III.

7 Conclusions and future implications

Findings in this thesis indicate that cannabis use is associated with severe self-harm independently of other substance use as well as baseline and parental psychopathology. In addition, an independent association was observed between early cannabis use and anxiety and depressive disorders. In contrast, the association between early cannabis exposure and the onset of a bipolar disorder attenuated to non-significance after adjusting for diverse forms of substance use other than cannabis. Although an independent association was not seen in the full model with a range of confounding factors, the findings imply that cannabis use is an adverse clinical marker for the onset of a bipolar disorder. Furthermore, our findings imply that the prognosis of adolescents with both PLEs and early cannabis exposure might be more complicated than that of adolescents with PLEs only, a result with evident clinical implications. In summary, we conclude that early cannabis use seems to be an adverse prognostic marker for future psychiatric disorders and self-harm. Thus, screening for and delaying the onset of cannabis use of adolescents is an important public health priority.

Future studies are needed to clarify whether or not early cannabis use is independently associated with the onset of a bipolar disorder. The application of a register-based outcome measure provides the obtained results with unparalleled validity but yields a small cumulative incidence, due to the rarity of the outcome. Thus, many folds larger sample sizes than that utilized here would be needed to examine this association. Access to more detailed information on the frequency of cannabis use and the potency of cannabis consumed would also be crucial, not only to detect associations but also to examine if there is a dose-response, an important factor when attempting to infer causality. In particular, it should be noted that only very heavy cannabis use has been associated with pathological outcomes such as schizophrenia in studies utilizing very large population based cohorts (Zammit et al., 2002). Evidently, more studies specifically focusing on the association of high-potency cannabis use and non-psychotic sequelae are needed to determine if there is a dose-response with respect to these outcomes.

Furthermore, more adequately powered and population-based prospective studies are needed to establish whether early cannabis use is truly associated with

self-harm and anxiety disorders, as the findings of the current studies have been inconsistent. In the same vein, the question of whether cannabis exposure poses an additional risk of adverse outcomes in non-help seeking adolescents with PLEs should be addressed by examining sufficiently large samples with prospective data. Similarly, studies adopting a within-subjects design may expand our knowledge regarding these associations by mitigating concerns of bias due to confounding (Van Os et al., 2021). Cannabis use should preferably be measured at multiple time points with complementary measures such as urine drug assays to gain an accurate understanding of the burden of exposure**.** Ideally, cumulative exposure should be measured in standard THC units (Freeman & Lorenzetti, 2020).

Furthermore, as the THC content and the THC:CBD ratio of cannabis has steadily increased during the last few decades, the cannabis consumed by adolescents today might pose a significantly greater risk for adverse psychiatric sequelae than the products ingested by adolescents in Finland in 2001-02, when the field study of the NFBC86 was conducted (Freeman et al., 2021) . It is reasonable to believe that high potency cannabis, cannabis extracts with very high THC contents, and the synthetic cannabinoids that are currently available might pose much higher risks for psychiatric disorders than regular herbal cannabis or cannabis resin (Castaneto et al., 2014; Di Forti et al., 2019; Pierre, Gandal, & Son, 2016). Moreover, concerns have been raised about the cannabis consumption habits of young people as a consequence of recent permissive changes in legislation in some countries (Cerdá et al., 2020; Hinckley, Bhatia, Ellingson, Molinero, & Hopfer, 2022). It seems evident that deepening our knowledge on the sequelae of adolescent cannabis use should be viewed as a timely public health priority.

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